

Markus Ullsperger: Functional Neuroanatomy of Performance
Monitoring: FMRI,ERP, and Patient Studies. Leipzig: Max Planck
Institute for Human Cognitive and Brain Sciences, 2007 (MPI Series in
Human Cognitive and Brain Sciences; 87)

Functional Neuroanatomy of Performance Monitoring: fMRI, ERP, and Patient Studies

Von der Medizinischen Fakultät
der Universität Leipzig
genehmigte

H A B I L I T A T I O N S S C H R I F T

zur Erlangung des akademischen Grades
Doctor medicinae habilitatus
(Dr. med. habil.)

vorgelegt
von Dr. med. Markus Ullsperger,
geboren am 22.04.1970 in Berlin

Tag der Verleihung: 20. 03. 2007

Gutachter:

Prof. Dr. med. Gereon R. Fink
Klinik und Poliklinik für Neurologie, Uniklinik Köln &
Institut für Neurowissenschaften und Biophysik, Medizin (INB3)
Forschungszentrum Jülich

Prof Dr Axel Mecklinger
Experimental Neuropsychology Unit
Universität des Saarlandes

Prof. Dr. Thomas F. Münte,
Lehrstuhl für Neuropsychologie
Otto-von-Guericke-Universität Magdeburg

Bibliographische Beschreibung

Markus Ullsperger, *Functional Neuroanatomy of Performance Monitoring: fMRI, ERP, and Patient Studies [Die funktionelle Neuroanatomie der Handlungsüberwachung: fMRT-, EKP-, und Patientenstudien]*. VIII + 207 Seiten, 61 Abbildungen, 27 Tabellen.

Die vorliegende Schrift zur kumulativen Habilitation beschreibt eine Serie von Studien zur Implementierung der Handlungsüberwachung im menschlichen Gehirn. Es wurden Experimente an gesunden Versuchspersonen und ausgewählten Patienten durchgeführt; dabei wurden Verhaltensdaten erhoben, und es kam die funktionelle Magnetresonanztomographie (fMRT) sowie die Elektroenzephalographie (EEG) zum Einsatz.

Der erste Teil der Arbeit bietet einen Überblick über die messbaren Korrelate der Handlungsüberwachung bei Menschen und nichtmenschlichen Primaten. Auf der Verhaltensebene lassen sich die Verhaltensanpassungen nach Fehlern (Korrekturen, Selektion alternativer Handlungen, Verlangsamung) messen. Den Überwachungsprozess selbst kann man mittels EEG und fMRT abbilden. Im ereigniskorrelierten Potential (EKP) bezogen auf eine fehlerhafte Reaktion findet sich die *error-related negativity* (ERN). Im fMRT wird eine Aktivitätszunahme im posterioren frontomedianen Kortex (pFMC), speziell in der *rostral cingulate zone* (RCZ) bei Fehlern und unerwartet schlechten Handlungsergebnissen beobachtet. Teil I gibt des Weiteren einen Überblick über die aktuellen Theorien zur Handlungsüberwachung und –steuerung. Dabei wird besonders auf die Rolle von Handlungskonflikten und der Belohnungsvorhersage eingegangen.

Teil II widmet sich detailliert der Rolle des pFMC bei der Handlungsüberwachung. Auf der Basis der dargestellten fMRT- und EEG-Ergebnisse, welche sowohl in getrennten Sitzungen als auch simultan erhoben wurden, wird die Hypothese formuliert, dass erhöhte pFMC-Aktivität die Notwendigkeit von Anpassungen zur Optimierung des Handlungsergebnisses signalisiert. Wenn ein Handlungsergebnis nicht erreicht wird (z.B. bei Fehlern und negativen Rückmeldungen) oder wenn die Wahrscheinlichkeit, das Handlungsziel zu erreichen, gering ist (z.B. bei Handlungskonflikten und Entscheidungsunsicherheit) sind Anpassungen erforderlich, die häufig beobachtet werden können. Diese Anpassungen betreffen motorische, kognitive, emotionale und vegetative Prozesse.

In Teil III wird in mehreren Patientenstudien untersucht, welche kortikalen und subkortikalen Hirnareale zusätzlich zum pFMC für die Handlungsüberwachung notwendig sind. Unilaterale Läsionen des lateralen frontalen Kortex und der Basalganglien führen beide zu einer Beeinträchtigung der Handlungsüberwachung. Die ERN ist bei beiden Patientengruppen reduziert. Wenn zusätzlich die Faserverbindungen zwischen pFMC, lateralem frontalem Kortex und Basalganglien durch in das frontale Marklager reichende Läsionen geschädigt sind, sind auch Verhaltensmaße, z.B. die Sofortkorrektur von Fehlern, im Vergleich zu Gesunden beeinträchtigt. Die Spezifität der Befunde wird untermauert durch die Untersuchung von Patienten mit Läsionen des frontopolaren und anterioren orbitofrontalen Kortex und des temporalen Kortex, die keine pathologischen Veränderungen der ERN oder des Verhaltens zeigten.

Teil IV berichtet eine Serie von fMRT- und EEG-Experimenten zur Untersuchung der sofortigen Fehlerkorrektur. Dabei werden vor allem intentionale und spontane

Fehlerkorrekturen charakterisiert. Die fMRT-Daten zeigen, dass die RCZ nicht nur an der Fehlererkennung sondern auch an der Fehlerkorrektur beteiligt ist. Die Befunde zur ERN stehen weitgehend im Einklang mit der Handlungskonflikttheorie. Zusätzlich identifizierten wir eine neue EKP-Komponente, die an die Sofortkorrektur gebunden ist, die *correction-related negativity*. Die anschließende Studie vergleicht Fehlerkorrektur und Fehlersignalisierung. Sie legt nahe, dass die Fehlersignalisierung durch zusätzlichen Tastendruck sensibler und spezifischer Handlungsüberwachungsprozesse abbildet und somit besser für Patientenstudien geeignet ist als die sofortige Fehlerkorrektur. Schließlich zeigt eine Verhaltensstudie weitere, auf der Erkennung von Handlungskonflikt basierende Anpassungsprozesse, die zur Optimierung der Aufgabenbearbeitung führen.

In Teil V werden modulierende Faktoren charakterisiert, die die Aktivität des Handlungsüberwachungssystems beeinflussen. Sowohl fMRT- als auch EEG-Daten zeigen, dass die subjektive Fehlerbedeutung die Handlungsüberwachung moduliert. Je bedeutsamer potentielle Fehler für das Individuum sind, desto mehr wird auch die Erreichung der Handlungsziele überwacht.

Teil VI diskutiert die Fragestellungen und Herausforderungen für die zukünftige Forschung auf dem Gebiet der Handlungsüberwachung und -steuerung. Besonderes Augenmerk wird auf eine Integration der verschiedenen Untersuchungsansätze gelegt. Um neurobiologisch plausible Theorien zur Handlungsüberwachung zu entwickeln, müssen neben EEG und fMRT auch molekulare Befunde herangezogen werden. Somit gewinnen pharmakologische, genetische und nuklearmedizinische Studien massiv an Bedeutung.

Contents

| | | |
|------------|--|------------|
| I | Introduction | 1 |
| 1 | Performance Monitoring | 2 |
| 1.1 | Correlates of Performance Monitoring | 4 |
| 2 | Current Models of Performance Monitoring | 11 |
| 2.1 | The Mismatch Theory | 11 |
| 2.2 | The Reinforcement Learning Theory | 12 |
| 2.3 | The Response Conflict Monitoring Theory | 13 |
| 2.4 | Other models of performance monitoring | 15 |
| II | The Role of the Posterior Frontomedian Cortex | 17 |
| 3 | Subprocesses of performance monitoring: A dissociation of error processing and response competition revealed by event-related fMRI and ERPs | 18 |
| 4 | Error monitoring using external feedback: Specific roles of the habenular complex, the reward system, and the cingulate motor area revealed by fMRI | 35 |
| 5 | Trial-by-trial coupling of concurrent EEG and fMRI identifies the dynamics of performance monitoring | 43 |
| 6 | The role of the medial frontal cortex in cognitive control | 57 |
| III | The Performance Monitoring Network and its Dysfunction after Localized Brain Lesions | 69 |
| 7 | Interactions of focal cortical lesions with error processing: evidence from event-related potentials | 70 |
| 8 | The role of intact frontostriatal circuits in error processing | 86 |
| 9 | Performance monitoring in neurological and psychiatric patients | 101 |
| IV | Adjustments and Remedial Actions Based on Performance Monitoring | 113 |
| 10 | Neural correlates of error detection and error correction: is there a common anatomical substrate? | 114 |
| 11 | Electrophysiological correlates of error correction | 122 |
| 12 | How does error correction differ from error signaling? An event-related potential study | 135 |
| 13 | The conflict-adaptation effect: it's not just priming. | 144 |
| V | Factors Modulating Performance Monitoring | 151 |
| 14 | ERP correlates of error relevance | 152 |

| | |
|--|------------|
| 15 Neuroimaging of performance monitoring: Error detection and beyond | 159 |
| VI Future Directions | 173 |
| 16 Outlook | 174 |
| 16.1 Spatiotemporal dynamics of performance monitoring | 174 |
| 16.2 Molecular bases of performance monitoring | 175 |
| 16.3 Individual differences and development | 176 |
| 16.4 Diagnostics of performance monitoring deficits | 177 |
| References | 179 |
| Abbreviations | 185 |
| <i>Deutschsprachige Zusammenfassung</i> | 186 |
| <i>Erklärung über die selbständige Abfassung der Arbeit</i> | 201 |
| <i>Lebenslauf (CV)</i> | 202 |
| <i>Thesen</i> | 204 |
| <i>Danksagung</i> | 207 |

Part I

Introduction

Chapter 1

Performance Monitoring

"Cuiusvis hominis est errare, nullius nisi insipientis in errore perseverare."

(Everybody may err, but only fools persevere in error)

Marcus Tullius Cicero

One of the most prominent abilities of humans is to flexibly adjust to a continuously changing environment and to pursue individual goals. Often goal-directed actions do not immediately result in the achievement of the goals but lead to errors. Detection of errors, however, enables the individual to implement compensatory actions that remediate the failures and eventually result in goal achievement. Moreover, error detection may serve as the basis for learning and skill acquisition. The individual gradually adjusts his/her behavior such that similar errors can be avoided in the future. Hence, continuous monitoring whether the action goals have been reached is crucial for adjustments and action outcome optimization. In other words, successful goal-directed behavior depends on continuous *performance monitoring*. Its impairment can result in major problems in daily live activities. For example, problems with the implementation of alternative and compensatory actions may be expected, generally reflected in perseveration. In contrast, dysfunctional performance monitoring could also lead to spontaneous switches from successful to less appropriate actions. Moreover, lower performance in complex and new tasks can be expected.

In everyday life, errors and error-prone situations are very common. What is an error and how can it be detected? Errors are inappropriate actions – or the omission of an appropriate action – that result in different effects than the desired ones. In other words, the goals are not achieved. Reason (1990) distinguished several primary types of errors according to the cognitive stages at which they occur. Errors arising while an action is planned are classified as *mistakes* and refer to a failure in identifying and/or in deciding upon the means to achieve it. Another error type emerging during the actual implementation of the action is termed *action slip*. Action slips occur, when the correct response is known, but the individual failed in its execution. One major characteristic of errors relevant to the present work is their detectability. Only detected errors can be compensated. Action slips can be easily detected, whereas mistakes are often difficult to detect and require external feedback. Two examples shall illustrate the different error types further. Action slips typically occur when a prepotent but incorrect response tendency is executed. Imagine, for instance, a person who just bought a new mobile phone. Often button assignment on the new phone is different than on the previous one. When one receives a call, one has the response tendency to press – for example – the left button, which was assigned to accepting calls on the previous phone. But on the new phone this button may have the function to suppress the call. Thus, the overlearned, prepotent response tendency may cause an error. In such cases, the cognitive system

has all information available to detect the error. The performance monitoring system only needs to monitor for a discrepancy between executed and intended response tendencies.

In contrast, in underdetermined situations information is insufficient to determine the correct response. In such situations mistakes are common. To detect a mistake, one needs to watch the effects of the action and monitor for discrepancies between the observed effect and the intended effect of the action. Thus, additional external information, i.e., external feedback is required to detect errors. For example, imagine someone in a supermarket and who wants to pay. Imagine further that there are several lines of people at the cashiers. The lines are of about the same length, and the goal is to wait as little as possible. However, beforehand it is impossible to determine the correct (fastest) line. The only option is to wait at one queue and to watch whether the chosen one is faster than other queues or not. Thus, one needs additional external information to determine whether the choice was correct or wrong.

Performance monitoring and error processing have been studied since the sixties of last century. At the beginning, behavioral studies have dominated the field (Rabbitt, 1966a; Laming, 1968), demonstrating that humans are able to adjust behavior after errors. Further, invasive recordings in non-human primates (Niki and Watanabe, 1979) as well as in humans (Bechtereva, 1971) revealed neurons responsive to errors and unexpected omissions of rewards. Research in the field was considerably accelerated by the discovery of an event-related brain potential (ERP) associated with errors in forced-choice reaction time tasks, the *error-related negativity* (ERN; Falkenstein et al., 1990; Gehring et al., 1993). Originally Michael Falkenstein has termed this component *error negativity* (*Ne*), but the later-introduced term ERN has become more widely used. This finding of a scalp-recorded ERP associated with errors has opened the opportunity to non-invasively study the neural processes involved in performance monitoring. Over the last ten years neuroimaging, particularly functional magnetic resonance imaging (fMRI), has become widely available to study cognitive functions. A considerable number of studies has investigated the brain's response to errors and situations in which errors are likely to occur, thus revealing the brain areas involved in performance monitoring. Furthermore, studies in patients as well as pharmacological challenges have helped to elucidate the neurobiological basis of performance monitoring.

Part I of this volume shall give an introduction into the topic of performance monitoring. In the following section (Chapter 1.1) I will present the correlates of performance monitoring usually observed with non-invasive and invasive measures. Chapter 2 is dedicated to the most prominent functional models of performance monitoring which are currently debated in the field. Part II addresses the role of the posterior frontomedian cortex (pFMC), a region consistently implicated in performance monitoring. In Part III a set of studies in patients with focal brain lesions is presented to elucidate the functional network in which the pFMC is integrated. The studies reveal brain regions that are necessary for optimal performance monitoring and those which are not. Experiments presented in Part IV concern the adjustments and remedial actions based on performance monitoring. Chapters 11-13 focus on immediate error corrections; sequential trial-by-trial adjustments are addressed in Chapter 14. The modulation of the performance monitoring system by factors such as error relevance and instruction is addressed in Part V. Finally, Part VI provides an outlook on future research directions and open questions that remain to be addressed.

1.1 Correlates of Performance Monitoring

Behavioral correlates

At the behavioral level, performance monitoring is reflected in the consequences resulting from errors, contextual feedback evaluation, and situations in which action outcome is at risk (e.g., decision uncertainty, response conflict). Performance-monitoring-induced behavioral adjustments are most obvious after error commission. As a first sign of error processing the error is sometimes accompanied by verbal and emotional responses (swearing, grimacing etc.). In experimental situations, even if not instructed, participants often immediately correct errors by a second key press (Rabbitt, 1966a, 1966b). The characteristics and the underlying neural processes of these *immediate corrections* are addressed in Chapters 11-13 (Part IV).

On trials subsequent to an erroneous response, behavioral adjustments can occur, such as *post-error slowing* (Rabbitt, 1966b). In a number of experiments it has been observed that reaction times are prolonged on correct trials which were preceded by an error as compared to correct trials preceded by correct responses (Figure I-01). This post-error slowing effect has been interpreted as reflecting a change towards a more cautious response strategy: more time is used for stimulus processing, thus responses are slowed down. However, it cannot be ruled out with absolute certainty that post-error slowing in fact results from the persistence of the problem that caused the error on the previous trial rather than reflecting an adjustment resulting from performance monitoring (Gehring et al., 1993). It should also be noted that post-error slowing is often a small effect (below 10 ms) and may not be found to be statistically significant, particularly in tasks with high time pressure

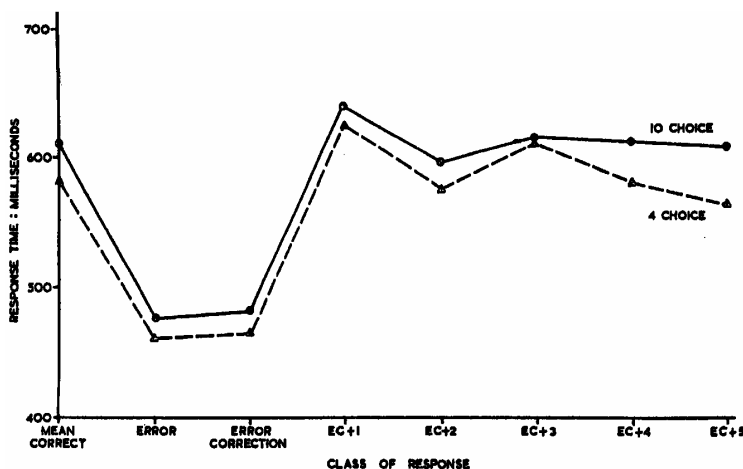


Figure I-01.

Reaction times of correct responses, errors, error corrections, and responses following error correction in a four-alternative and in a ten-alternative self-paced, choice-response task. Note that reaction times for responses following an error (EC+1) are longer than the mean correct reaction time. From Rabbitt, 1966b.

A further adjustment that has been found subsequent to errors is *post-error reduction of interference* (Ridderinkhof et al., 2002). This can result in lower error rates subsequent to an error. In some instances, e.g., with short inter-trial intervals, however, error detection can also interfere with performance on subsequent trials thus increasing error rates after errors (Rabbitt and Rodgers, 1977).

Finally, to test whether an error has become consciously aware the *error signaling* procedure has been introduced (Nieuwenhuis et al., 2001; Rabbitt, 2002). Participants are instructed to press a signaling button which is unrelated to the primary task whenever they encounter an error (cf. Chapter 13).

Intracranial recordings

About 35 years ago, early electrophysiological recordings using depth electrodes in humans gave rise to the notion that the brain contains structures that specifically respond to errors – an "error detector" system (Bechtereva, 1971; Bechtereva et al., 1990, 2005; Bechtereva and Abdullaev, 2000). This notion was corroborated by the discovery that a subset of neurons in the anterior cingulate cortex (ACC) of monkeys specifically increased firing rate after incorrect responses in a differential reinforcement of long latencies task (Niki and Watanabe, 1979). These neurons were also responsive to omission of reinforcement on correct trials. Similarly, a study on motor learning identified transcortical field potential changes in ACC area 24 at the ventral bank of the cingulate sulcus that were associated with inappropriate, i.e., erroneous and unrewarded, movements (Gemba et al., 1986). In a set of experiments using a saccade countermanding task in macaques performed in the group around Jeffrey Schall, these findings were corroborated and extended (Stuphorn et al., 2000; Schall et al., 2002; Ito et al., 2003). In this task, monkeys had to make a prosaccade towards a visual target after a delay in the majority of trials. In a subset of trials, however, a stop signal instructed the monkeys to withhold the prosaccade. This allowed to record single-unit activity on correctly withheld as well as erroneously performed saccades. Moreover, *response conflict* is higher on correct stop-signal trials than on trials in which a saccade was required. Response conflict means the simultaneous activation of two response channels (see Section 2.2). Here, response conflict was operationalized as the coactivation of movement and fixation neurons in the frontal eye fields and superior colliculus, as there was a conflict between performing the prosaccade and withholding it. It was shown that neurons in the dorsal bank of the anterior cingulate sulcus responded to errors in eye movements (Ito et al., 2003). Half of these neurons were also responsive to omission of rewards. A different subset of neurons in this area specifically responded to earned and unexpected reward. Importantly, none of the recorded units in the ACC showed activity related to response conflict. In contrast, the supplementary eye fields in the dorsal premotor cortex were shown to contain distinct neuronal populations that were responsive to errors, reinforcement, or response conflict, respectively (Stuphorn et al., 2000). In contrast to the findings by Ito et al. (2003), a recent study in humans undergoing cingulotomy for medically intractable, severe obsessive-compulsive disorder reported neurons in the caudal ACC sensitive to response conflict (Davis et al., 2005).

A combined single-unit recording and inactivation study in the rostral and caudal cingulate motor areas (CMA) has strongly influenced current theories of performance monitoring (Shima and Tanji, 1998). In this study, macaques were trained to respond to a visual stimulus by two different arm movements (either pushing or turning a handle). The monkeys voluntarily selected one of the two movements based on the amount of reward. In a series of trials in which the reward subsequent to the response was constant, they kept selecting a particular movement. When the reward was reduced, the monkeys chose to select the alternate movement on the subsequent trial. Interestingly, a subset of neurons specific to the rostral CMA (37% of the recorded units in the rostral CMA) showed an increase in activity only when two conditions were met in conjunction: (1) the reward was reduced and (2) the monkey selected an alternative response on the subsequent trial. This increased activity occurred after the reduced reward and before the monkey initiated the alternate movement for the next trial. Importantly, these neurons did not respond to mere reward reductions that were not followed by a change in the monkey's behavior.

They were also unresponsive to movement alternations that were instructed by an external tone signal. When the rostral CMA was reversibly inactivated by the injection of muscimol, a GABA agonist, the monkeys began to fail selecting the correct movement. They often showed perseveration, i.e., they kept selecting the previously performed movement, even when the reward was considerably reduced. In addition, in trial series with constant maximal reward they spontaneously selected the alternative response. Nearly identical results have been found in humans undergoing surgical cingulotomy (Williams et al., 2004). Intraoperative single-unit recordings from the rostral cingulate zone (RCZ) revealed increased activity in response to diminished reward that was predictive of subsequent changes in behavior. After ablation of the RCZ, participants selectively failed to change behavior in response to reward reduction.

A close relationship between reward expectancy and performance monitoring was also suggested by a single-unit recording study in monkeys (Shidara and Richmond, 2002). Cells in the rostral CMA increased their activity with increasing reward expectancy. At the same time, error rate decreased, suggesting an interaction of reward expectancy and motivation. It has been argued that some of the rostral CMA neurons are involved in “goal-based action selection”, that is, selecting between competing actions in view of the anticipated reward associated with each of these actions (Matsumoto et al., 2003; Matsumoto and Tanaka, 2004). Thus, there is evidence for a monitoring and – at least in some cases – also a more executive role of the rostral CMA.

Finally, recordings from depth electrodes in patients suffering from epilepsy revealed biphasic potential changes locked to erroneous responses in a target detection (oddball) task (Brázdil et al., 2002). Interestingly, in addition to recording sites in the ACC, error-related biphasic potentials were recorded at mesiotemporal and lateral frontal intracortical electrodes. In a similar study using a Go/NoGo task a latency shift of different sources in the frontomedian cortex was found (Brázdil et al., 2005). Regions in the pregenual paracingulate gyrus responded to errors about 20 ms later than the RCZ (Figure I-02).

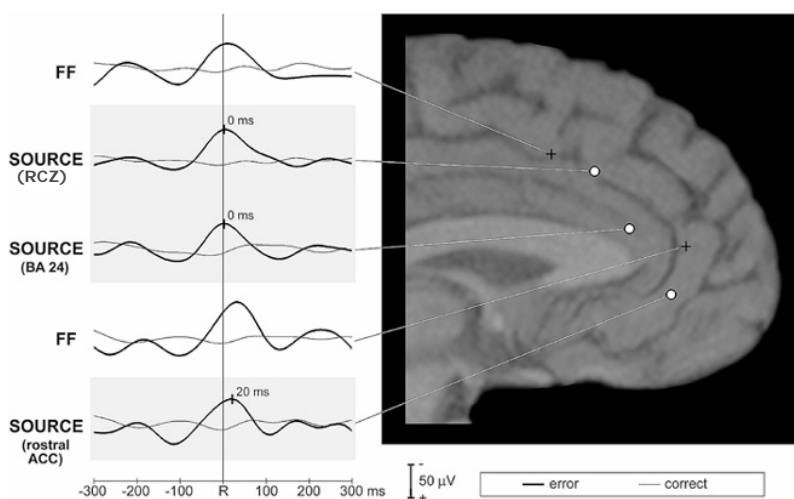


Figure I-02.

A time delay between intracerebral error-related potentials generated within different sub-areas of the frontomedian wall (response-triggered averages from the rostral cingulate zone [RCZ]: -7, 20, 30; latency = 0 ms; cingulate gyrus [BA 24]: -2, 31, 14; latency = 0 ms; rostral anterior (para)cingulate cortex [ACC]: -5, 34, -5; latency = +20 ms). The position of the recording sites (right) is precisely indicated on the subject's MRI scan (verified using postplacement MRI). FF - far field (spreading of the activity). Modified from Brázdil et al., 2005.

A study using arrays of microelectrodes (Wang et al., 2005) in the human ACC showed larger source currents with inhibited firing (in superficial layers) for errors vs. correct responses and for negative vs. positive feedback. Interestingly, source currents were also increased for novel stimuli and with increasing task difficulty. The authors suggest active inhibition in superficial cingulate layers based on these findings. The neuronal activity from deep layers where the efferents of the ACC arise was not recorded, however. Moreover, a

transient phase-locking of task-related theta activity of the superficial cingulate layers and lateral frontal and temporal recording sites was found, suggesting an interaction of these regions during performance monitoring.

Event-related potentials

Since the early nineties scalp-recorded error-related ERPs have been in the focus of performance monitoring research. The *ERN* is elicited by executing prepotent but incorrect responses in choice reaction time tasks, peaks about 50 to 100 ms after the erroneous button press, and has a frontocentral scalp distribution (Falkenstein et al., 1990, 2000; Gehring et al., 1993; Figures I-03, I-04). When referenced to linked mastoids or earlobes, ERN amplitudes up to 15 μV have been observed at the electrodes FCz and Cz. Recent studies suggested that the ERN is in fact embedded a sequence of deflections. It is preceded and followed by positive deflections with maximal amplitudes at frontocentral electrodes. The preceding positive deflection usually peaks 50 to 0 ms before the response, whereas the subsequent positive deflection peaks 100 to 200 ms after the response. This sequence of deflections has raised the idea of an oscillation time-locked to the erroneous response. Power increases in the theta band (5-7 Hz) have been observed at the time of the response. This theta power increase is larger for errors than for correct responses (Luu and Tucker, 2001; Luu et al., 2004; Yordanova et al., 2004; Yordanova and Kolev, 2004; see also Chapter 6). The subsequent frontal positive deflection seems to be more sustained in time than the ERN, which is consistent with the finding of an error-specific increase in delta power (1.5–3.5 Hz; Yordanova et al., 2004). The ERN is independent of stimulus modality and effector (Falkenstein et al., 1997, 2000; Falkenstein, 2004). It has been observed after manual, foot, eye- movement, and vocal responses (Holroyd et al., 1998; Van 't Ent and Apkarian, 1999; Masaki et al., 2001; Nieuwenhuis et al., 2001; De Bruijn et al., 2003).

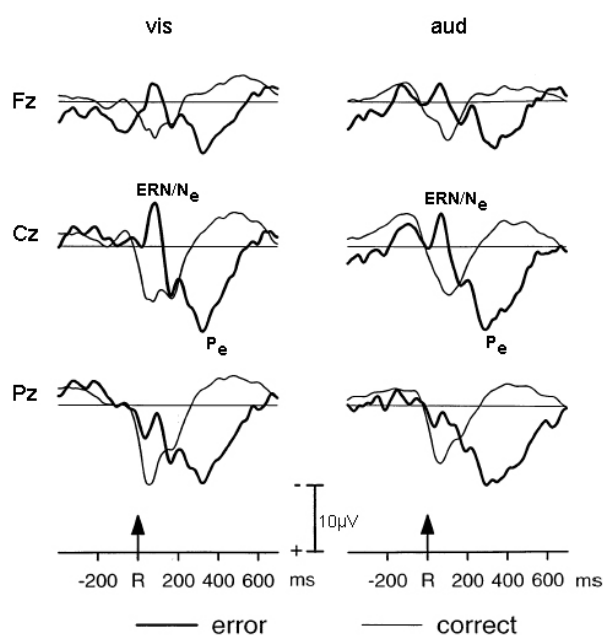


Figure I-03.

Response-locked grand mean average waveforms for errors (bold lines) and correct trials (light lines) after visual (vis) and auditory letter stimuli (aud) in a two-choice reaction task. The error-related negativity ('ERN/Ne') is seen as a sharp negative deflection with central maximum peaking at about 80 ms after the incorrect key press (R). The error positivity ('Pe') is seen as a late parietal positivity with Cz maximum peaking at about 300 ms after the incorrect key press. On correct trials a positive complex with Pz maximum is seen. Modified, from Falkenstein et al., 2000.

Source localization studies suggest that the ERN is generated in the posterior fronto-median cortex (pFMC), specifically in the rostral cingulate zone (RCZ) which is located in caudal anterior cingulate gyrus and sulcus (ACC) (Dehaene et al., 1994; Holroyd et al., 1998; Miltner et al., 2003; see also Chapters 4 and 6).

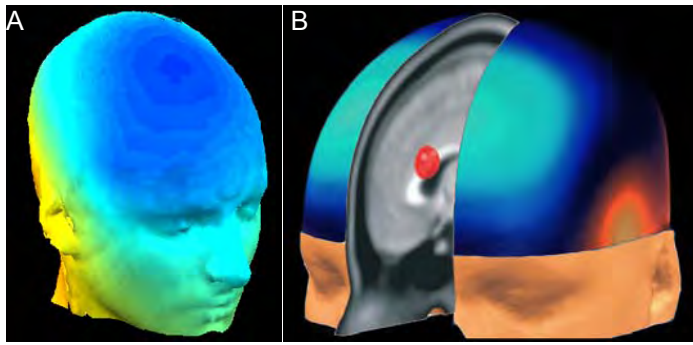


Figure I-04.

A. Topographical distribution of the error-related negativity across the scalp. The maximum of the negativity is located at FCz. The midline component is not lateralized to either hemisphere. Blue colors depict negative amplitudes, yellow and red colors depict positive amplitudes. B. Solution of one-dipole source localization of the ERN (modified from Gehring and Willoughby, 2002)

A second error-related ERP, the *error positivity (Pe)* has a centroparietal distribution and occurs about 300 to 500 ms after the erroneous response (Falkenstein et al., 1990, 2000; Falkenstein, 2004; Figure I-03). It is important to note the difference to the above-mentioned frontocentral positive deflection subsequent to the ERN. In contrast to the frontocentral positivity, the Pe has a parietal maximum and rather a sustained time course over several 100 ms than a clear peak. Some authors have called the frontocentral sharp positive deflection "early Pe" and the classical sustained parietal positivity "late Pe" (van Veen and Carter, 2002). In my opinion, these terms are potentially misleading, as the frontocentral positivity seems to be much more closely related to the ERN than to the parietal Pe. This view is supported by findings using Independent Component Analysis, integration of ERP and fMRI (see Chapter 6), and dipole localization studies (van Veen and Carter, 2002) suggesting that ERN and subsequent frontocentral positivity origin in the same region whereas the parietal Pe seems to stem from at least partly different generators. Moreover, patient studies have revealed a dissociation between Pe and frontocentral positivity (see Chapter 9). Therefore, I will reserve the term Pe only for the parietal sustained positive deflection as originally described by Falkenstein and colleagues (1990). A recent review investigated the functional significance of the Pe (Overbeek et al., 2005). Interestingly, the knowledge about the Pe is much more limited as compared to the ERN. The review revealed much dissociation between reported effects on the ERN and Pe, suggesting that these components reflect different aspects of performance monitoring. The authors "found little support for the proposed hypotheses that the Pe is associated with the affective processing of errors or with post-error behavioral adaptation" (p. 319). Studies on conscious error awareness suggest that the Pe reflects conscious recognition of an error (Nieuwenhuis et al., 2001; Endrass et al., 2005).

An ERP component of frontocentral scalp topography similar to the ERN was described for external negative feedback on errors in underdetermined situations (Miltner et al., 1997). It has been termed feedback ERN, feedback(-related) negativity (FRN) or medial frontal negativity (Gehring and Willoughby, 2002; Holroyd and Coles, 2002; Yeung and Sanfey, 2004). This negative deflection peaks approximately 250 to 300 ms after a stimulus indicating the action outcome, and is greater in amplitude for negative performance feedback and outcomes indicating monetary losses than for positive feedback and monetary gains (Figure I-05). The initial assumption that the response ERN and the FRN are functionally equivalent (Miltner et al., 1997; Holroyd and Coles, 2002) has recently become a matter of debate (Gehring and Willoughby, 2004). Both the ERN and the FRN have in common that they are associated with worse-than-expected action outcomes. A recent study suggests that the FRN indicates the valence of the action outcome, i.e., it is larger on incorrect outcomes and losses (Yeung and Sanfey, 2004). In

contrast, the magnitude of the outcome (loss or gain) is not coded by the FRN but rather by the P300, a large positive deflection that follows the feedback stimulus. This notion has received further support from a series of experiments suggesting that the FRN follows a binary response mode (Holroyd et al., in press). The performance monitoring system seems to classify outcomes into two categories: (1) when outcomes indicate that the goal was satisfied (small or absent FRN) and (2) when outcomes indicate that the goal was not achieved (large FRN).

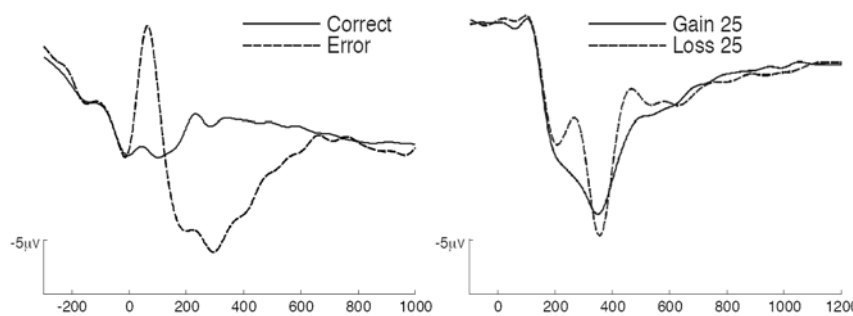


Figure I-05. Response-locked error-related negativity from a flanker task at the FCz electrode (left) and stimulus-locked feedback-related negativity from a gambling task at the Fz electrode (right). Time zero is the moment of response onset in the flanker task and the moment of stimulus onset in the gamble task (from Gehring and Willoughby, 2004).

Recent observations of a negativity associated with correct responses that is similar to the ERN with respect to latency and scalp distribution but of smaller amplitude, sometimes called *correct-related negativity* (CRN; Ford, 1999), led to the notion of a permanently active response evaluation function of the brain structures generating the ERN (Vidal et al., 2000, 2003). This view was supported by recent findings that the CRN amplitude can predict performance on subsequent trials (Ridderinkhof et al., 2003; Allain et al., 2004b). The CRN seems not directly to depend on response conflict but rather on the discrepancy between prepared and implemented strategy to solve the task (Bartholow et al., 2005). It should be noted that the CRN was not found in a substantial number of ERP studies investigating performance monitoring. It is best found after Laplacian transforms of the scalp data (Vidal et al., 2000, 2003; Allain et al., 2004b). This approach favors EEG signals from superficial sources. Therefore, the relation between CRN and ERN with respect to their generators and functional significance is still rather unclear.

Neuroimaging

Over the last decade, functional brain imaging has rapidly developed and become widely accessible. This has opened new avenues for cognitive neuroscience research and enabled to infer about the functional neuroanatomy underlying cognitive functions. Functional magnetic resonance imaging (fMRI) provides a high spatial resolution and has been particularly influential in performance monitoring research. fMRI studies investigating performance monitoring consistently implicate the pFMC in different subprocesses of performance monitoring, such as error processing and response conflict monitoring (Carter et al., 1998; Figure I-06). The role of the pFMC is discussed in Part II of this volume; Chapter 7 provides a comprehensive review of the neuroimaging findings.

In addition to fMRI signal increases in the pFMC, activations of the anterior insula and lateral prefrontal cortex (LPFC) have been observed in the majority of studies. These activations were most consistent in studies investigating error processing. Further activations located, e.g., in the basal ganglia, ventral striatum, thalamus, midbrain etc. were highly dependent on the task and the specific questions that were addressed in the

studies. It is worth mentioning that activations in the orbitofrontal cortex (OFC) were reported only rarely, as this region is likely to show signal losses and distortions resulting from susceptibility artifacts.

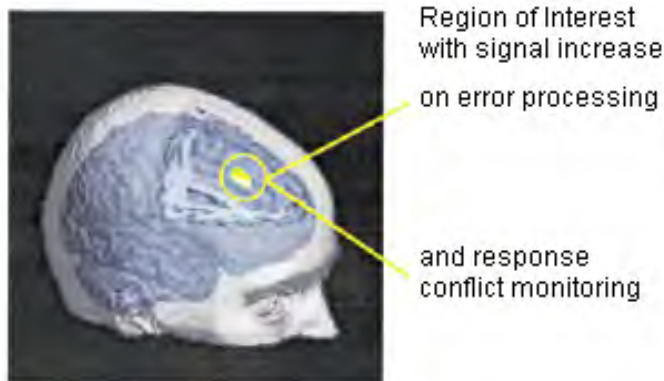


Figure I-06.

Region of interest located in the posterior frontomedian cortex at the border between the rostral cingulate zone, the pre-SMA, and adjacent mesial BA 8, showing fMRI signal increases on erroneous responses as well as on correct trials involving high response conflict. Modified, from Carter et al., 1998.

In summary, correlational studies (ERP, neuroimaging, single- and multiunit recordings) strongly suggest the RCZ, pre-SMA, and mesial cortical area 8 to play key roles in performance monitoring functions. Note that correlational studies, although commonly accepted as providing strong suggestive evidence, by themselves cannot prove the necessity of specific brain regions for specific cognitive functions. Therefore, loss-of-function studies, e.g., in patients are needed for confirmation and hypothesis testing (see Chapters 8-10, Part III).

Chapter 2

Current Models of Performance Monitoring

2.1 The Mismatch Theory

The ability to correct action slips within less than 100 ms and the finding that errors can result in slower but sometimes more accurate responses in subsequent trials has led to the idea of an error detection system (Angel, 1976; Rabbitt and Rodgers, 1977). Cumulating evidence has resulted in the error detection or *mismatch theory* used to explain the behavioral, electrophysiological, and neuroimaging findings (Figure I-07). It assumes that the ERN is a correlate of a mismatch detected by comparing the representations of the intended and the actually performed action (Falkenstein et al., 1990, 2000; Gehring et al., 1993; Coles et al., 2001; Falkenstein, 2004). Behavioral observations (Higgins and Angel, 1970; Angel, 1976) and particularly the early onset of the ERN suggest that the representation of the executed response results from an *efference copy* rather than from proprioceptive feedback. These findings were supported by a single-case study showing a normal ERN in a patient suffering from sensory deafferentation (Allain et al., 2004a). The representation of the intended action is assumed to directly result from complete stimulus processing and application of the task set. It is noteworthy that the ERN is usually found on action slips due to premature responding (i.e., the response was made before stimulus processing and task-related functions were completed). Therefore, the representation of the intended response is still being built up when the erroneous response program is issued. It has been shown that compromising these representations reduces the amplitude difference between the ERN and the negativity occasionally observed on correct responses (i.e., the CRN), reflecting disturbance of the comparison process (Coles et al., 2001). Concerning the timing of the proposed comparison process, the original account suggested that all stimulus processing has to be finished such that the representation of the correct response is complete. Based on continuous flow of information accounts, Coles and colleagues modified the mismatch hypothesis by assuming that the comparison process takes place, when the efference copy of the actual performed response arrives and does not wait "until all possible information about the appropriate response is available. Rather it uses whatever information is available at the time of the response." (p.175; Coles et al., 2001).

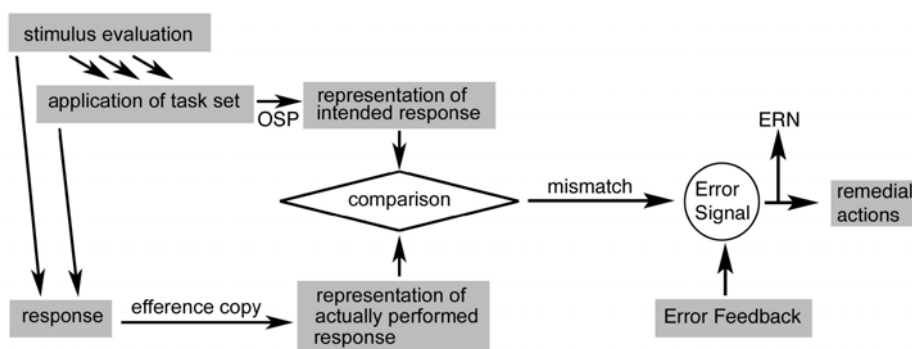


Figure I-07. Schematic illustration of performance monitoring of an erroneous response according to the Mismatch Theory. ERN: error-related negativity, OSP: ongoing stimulus processing.

2.2 The Reinforcement Learning Theory

A neurobiological theory of performance monitoring has been proposed by Holroyd and Coles (2002). This theory is in part based on the mismatch hypothesis, but it also integrates findings on reward processing in primates and reinforcement learning theories. Furthermore, it provides a computational model allowing to compare simulated data based on the theory's predictions with empirical findings.

Prior research in non-human primates indicates that errors in reward prediction are coded by phasic changes in the activity of the midbrain dopamine system: a phasic increase when ongoing events are suddenly better than expected, and a phasic decrease when ongoing events are suddenly worse than expected (Schultz, 2000, 2002). Errors result in the non-achievement of the goals; hence, the detection of an error indicates a worse outcome than the desired one. In other words, an error is associated with the nonoccurrence of an anticipated reward. The detection of an error is an event predicting the nonoccurrence of a reward, i.e., it indicates a negative error in reward prediction which – according to findings in non-human primates – transiently reduces dopaminergic activity. The theory proposes that these phasic dopamine signals are conveyed to the RCZ, where they are used to improve task performance in accordance with the principles of reinforcement learning. Furthermore, it suggests that the phasic dopamine signals modulate the activity of motor neurons in the RCZ. The dopaminergic disinhibition could enable large proportions of apical dendrites of Layer V neurons in the RCZ (which are aligned perpendicularly to the scalp surface) to become depolarized. These postsynaptic potentials sum up and are measurable at the scalp as changes in ERN amplitude (Holroyd and Coles, 2002). In sum, phasic decreases in dopamine activity (indicating a negative reward prediction error) are associated with large ERNs and phasic increases (indicating a positive reward prediction error) with small ERNs.

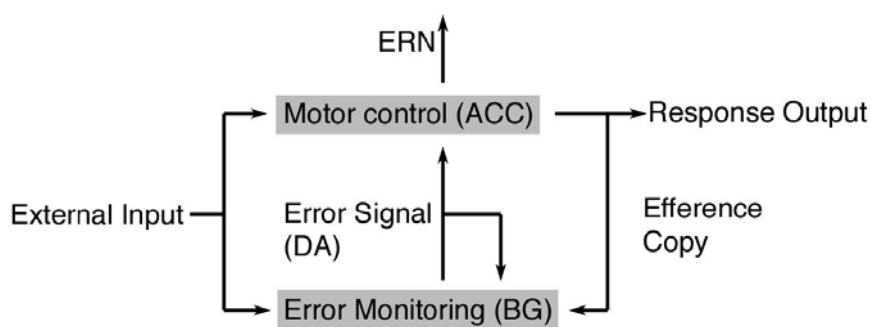


Figure I-08. Schematic illustration of the reinforcement learning theory of the ERN. ERN: error-related negativity; ACC: anterior cingulate cortex; BG: basal ganglia; DA: dopamine.

The reinforcement learning theory of performance monitoring furthermore builds on computational actor-critic models integrating knowledge about anatomy and physiology of the basal ganglia (Barto, 1995; Houk et al., 1995). These models assume that the striatal patch compartments and the mesencephalic dopamine neurons form the basis of the adaptive critic, which is supported by the finding that striatal patch neurons project to the mesencephalic dopamine system (Gerfen, 1992; Graybiel et al., 1994). According to the models, the critic learns to predict rewards from the ongoing actions and information from the environment. Any unexpected discrepancy from outcome prediction results in phasic teaching signals of the dopamine system used by the actor module to optimize behavior and by the critic to optimize prediction. The actor module has been associated with the striatal matrix compartments and with the RCZ (Barto, 1995; Houk et al., 1995; Holroyd and Coles, 2002). A recent fMRI study suggested partly dissociable contributions of the

ventral and dorsal striatum to an actor-critic architecture, with the former corresponding to the critic and the latter to the actor (O'Doherty et al., 2004). The actor (i.e., the RCZ) is using the teaching signal to improve the responses to the task at hand. The reinforcement learning model is schematically illustrated in Figure I-08.

A number of recently published studies tested this theory experimentally. The theory predicts that larger ERNs should be elicited by unexpected unfavorable outcomes than by expected unfavorable outcomes. By varying the frequency of reward occurrence across conditions this was tested, reasoning that the system that produces the ERN would come to expect non-reward when rewards were infrequent (Holroyd et al., 2003). In a reward condition, participants received positive feedback on about three quarters of the trials, and in a non-reward condition, participants received negative feedback on about three quarters of the trials. On each trial the type of feedback stimulus was selected at random. Consistent with the reinforcement learning theory, a larger ERN was elicited by unexpected absence of reward. A subsequent study revealed that the amplitude of the ERN is determined by the value of the eliciting outcome relative to the range of outcomes possible, rather than by the objective value of the outcome (Holroyd et al., 2004). As mentioned in Section 1.1, recent studies suggest that the ERN reflects the valence but not the magnitude of the outcome. Specifically, a large ERN seems to be associated with an outcome indicating that the goal was not satisfied, whereas a small (or no) ERN seems to be elicited when the goal was achieved (Yeung and Sanfey, 2004; Holroyd et al., in press).

2.3 The Response Conflict Monitoring Theory

To characterize the evaluative aspect of cognitive control, which is a prerequisite for adaptive behavior, the response conflict monitoring theory was developed. This model, its theoretical implications and supporting evidence from computational modeling are comprehensively described in (Botvinick et al., 2001, 2004). A series of neuroimaging studies suggests that the pFMC is engaged when response conflict occurs. Response conflict arises when a task concurrently activates more than one response tendency; for example, when the stimulus primes a prepotent but incorrect response or when the correct response is underdetermined. Often, incorrect response tendencies are overridden in time by the overt correct response, resulting in high response conflict before the correct response (pre-response conflict). In contrast, occasional errors resulting from premature responding (typically action slips) are characterized by response conflict after the response: The correct response tendency resulting from continued stimulus processing conflicts with the already executed incorrect response. In underdetermined responding, i.e., under conditions requiring choosing from a multiple equally compelling response alternatives, decision uncertainty occurs. It has been suggested that decision uncertainty involves conflict similar to response conflict observed in tasks in which a prepotent response is overridden (Botvinick et al., 2001; but see Volz et al., 2003, 2004a, 2004b, 2005 for a somewhat different view).

The response conflict monitoring model has been formalized in connectionist parallel-distributed processing models of stimulus-response compatibility tasks. The model for one such task, the Eriksen flanker task (Eriksen and Eriksen, 1974) is illustrated in Figure I-09. The model comprises three layers of units: an input layer consisting of an array of six position-specific letter units; a response layer consisting of a unit for each response; and

an attentional layer with units corresponding to each location in the letter array. The information flow is realized by bi-directional excitatory weights between layers. Competition is elicited by inhibitory links between all of the units within each layer. A conflict monitoring feedback loop simulates the role of the pFMC in performance monitoring and adjustments of control. When an input pattern is applied to the letter units, activations flow through their connections to the response units. According to the task, a biasing input from the attention layer favors the letter in the center of the array and the corresponding response is activated in the response layer. The measured response conflict depends on the relative activation levels of the competing response units and is computed by a multiplication of the response unit activations. When one response unit is active and the other inhibited, conflict is low or zero. When both response units are active, however, the product of their activations is large and hence the degree of response conflict is large. If a response unit crosses an arbitrary response threshold, the corresponding response will be produced (Botvinick et al., 2001; Yeung et al., 2004). Figure I-09B illustrates the findings from the computational simulations for correct and incorrect trials.

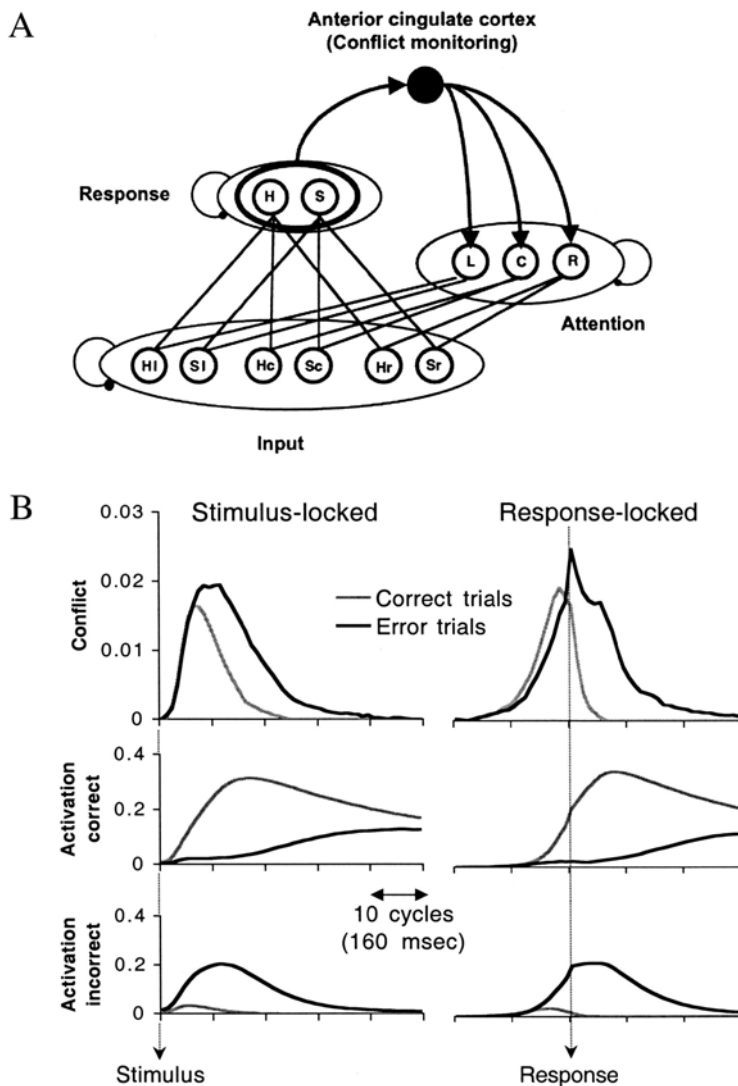


Figure I-09.

A. Illustration of the basic connectionist model of the Eriksen flanker task. The letters H and S designate the stimulus input, which can occur on the left (l/L), in the center (c/C) or on the right (r/R) side of the computer screen. The black lines indicate bidirectional excitatory weights between input, attention and response layers. The arrows represent the conflict monitoring feedback loop. B. Simulated activity on stimulus-locked and response-locked averages of correct and error trials. Response conflict (upper row) is the scaled product of the activity in the correct response unit (middle row) and the incorrect response unit (lower row). From: (Yeung et al., 2004).

Note that the proponents of the response conflict monitoring theory originally focused on the anterior cingulate cortex as the putative conflict monitor. Neuroimaging and animal research, however, suggests a broader cortical involvement in this function, particularly of the posterior frontomedian cortex including isocortical areas 8 and 6.

The theory predicts that the pFMC should be active in correct trials characterized by high pre-response conflict, a prediction that has been confirmed by a large number of studies (reviewed in Part II, Chapter 6). The theory is moreover consistent with the neuroimaging

evidence for pFMC activation in response to errors, and with the timing of the response ERN, indicating post-response conflict. Moreover, the predicted timing of such conflict-related activity is consistent with the occurrence of an ERN-like component, the N2, just before the response (Yeung et al., 2004). Finally, the detection of high post-response conflict may be used as a reliable basis for internal error detection, thereby obviating the need for an explicit error detection mechanism (Yeung et al., 2004). The theory further holds that, upon the detection of response conflict, the pFMC signals other brain structures that the level of cognitive control needs to be increased.

It should be noted that activation of the pFMC is limited specifically to situations of response conflict and does not occur on the occurrence of conflict at non-response levels (Milham et al., 2001). Similarly it was shown that the conflict-related activity varies with the amount of conflict at the response level but not with conflicts at the level of stimulus identification (van Veen et al., 2001).

In a recent study the theory about the pFMC function was extended by suggesting that its activity reflects error likelihood (Brown and Braver, 2005). According to this view, the pFMC is active whenever the task situation involves a high likelihood that an error occurs, which is equivalent to a low probability of reaching the intended outcome (low reward prediction). In this model, both the reinforcement learning as well as the conflict monitoring theories are integrated.

2.4 Other Models of Performance Monitoring

Alternatively to the above-discussed models, it has been suggested that the ERN reflects the activity of a general evaluative system concerned with the motivational significance of errors and emotional reactions to errors (*evaluative monitoring accounts*). Evidence of motivational effects for the ERN was first provided by Gehring and colleagues (Gehring et al., 1993). In one condition, accuracy was emphasized by associating errors with financial penalties. In a second condition, speed was emphasized by offering bonuses for quick responses. In addition, a neutral condition was introduced, where values were altered to produce an intermediate speed-accuracy level. The results showed a larger ERN when accuracy was emphasized relative to the neutral condition and a diminished ERN when instructions emphasized speed. Further evidence for the evaluative monitoring account comes from investigations of individual differences. The ERN amplitude has been shown to vary with negative affect and negative emotionality (Luu et al., 2000) and impulsivity (Pailing et al., 2002; Ruchow et al., 2005; see Chapter 12, however, for an alternative explanation of the findings on response impulsivity). Luu and colleagues (2000) related the ERN to questionnaire scores using the Positive Affect Negative Affect Scale (PANAS; Watson et al., 1988) and the Multidimensional Personality Questionnaire (MPQ; Tellegen and Waller, 1996). In the initial block of the experiment, individuals who scored high on the negative affect scale of the PANAS and the negative emotionality scale of the MPQ showed larger ERN amplitudes than individuals scoring low on these dimensions. In later stages of the experiment, the ERN amplitude decreased for individuals with high negative affect and negative emotionality scores. Based on behavioral data and individuals' self reports, the initial increase of ERN amplitude was attributed to an overengagement in the task and the following decrease of ERN amplitude to a disengagement from that task. Findings by Dikman and Allen (2000) demonstrate that motivational error significance is

affected by personality. Individuals with low scores on a socialization scale showed smaller ERN amplitudes during a punishment task than during a reward task. In contrast, in individuals scoring high on the socialization scale no difference in ERN amplitudes between the conditions was found. A recently published study examined changes in the ERN in relation to motivational incentives and personality traits (Pailing and Segalowitz, 2004). Monetary incentives for finger and hand accuracy were altered across motivational conditions to either be equal or to favor one type of accuracy over the other. A personality questionnaire and a socialization scale were used to measure different personality domains. Individuals who scored high on conscientiousness displayed smaller motivation-related changes to increasing incentives in the ERN than individuals scoring low on this dimension. These data suggest that the ability to selectively invest in error monitoring is modulated by the underlying personality. A drawback of the evaluative monitoring account is that it currently does not provide information on the implementation underlying performance monitoring processes in the human brain.

In the following Part II neuroimaging and EEG studies are presented that specifically address the theories on the pFMC function in performance monitoring, possible functional-anatomical distributions of subprocesses within this framework, and the relationship to the ERN. A review about the current knowledge is provided in Chapter 6, thereby formulating a unified view on the function of the pFMC.

Part II

The Role of the Posterior Frontomedian Cortex

Chapter 3

Subprocesses of performance monitoring: A dissociation of error processing and response competition revealed by event-related fMRI and ERPs

The following chapter reports findings from a study, in which participants performed two separate sessions of a speeded modified flanker task in two separate sessions while fMRI and EEG signals were recorded, respectively. The flanker task is associated with pre-response conflict between the prepotent flanker-induced and the target-induced response tendencies. Moreover, time pressure usually leads to a rather high number of action slips. This error type is easy to detect by the subject (Reason, 1990). As reported in Chapter 12, more than 95% of the errors in flanker tasks are consciously perceived.

The major goals were to test, (1) whether pre-response conflict monitoring and error processing recruit the same networks, and (2) whether the ERN is generated in the structures revealed to be involved in performance monitoring by fMRI. The main finding was that pre-response conflict monitoring and error processing (involving post-response conflict and the initiation subsequent adjustments as well as the appraisal of the error) elicit activity in overlapping networks. At the posterior frontomedian wall, a partial dissociation was observed. Whereas pre-response conflict was associated with a maximal signal increase in the mesial BA 8 and anterior pre-SMA, error processing maximally engaged the RCZ. Both subprocesses led to overlapping activity in the pre-SMA (BA 6). A second finding was that the ERN recorded for errors in the same participants during the EEG session could be explained by a single dipole model placed to the location of the maximal RCZ activity with a goodness of fit of above 90%.

This study has significantly advanced the knowledge about the performance monitoring network including the basal ganglia, the anterior inferior insula, and the lateral frontal cortex, and pinpointed the role of subregions within the pFMC. It was one of the first studies to investigate pre-response conflict and error processing within the same task at a whole brain level. A seminal previous study fostering the response conflict monitoring theory had focused on a region-of-interest analysis (Carter et al., 1998). Furthermore, in contrast to a similar previous study using the Go/NoGo task (Kiehl et al., 2000), inhibitory processes did not confound the results, as in the flanker task both correct and incorrect responses are associated with motor responses.

However, two limitations for the integration of the EEG and fMRI findings should be noted. First, the separate recordings were associated with significantly different performance measures, although task and participants were kept the same. Second, source localization using equivalent dipole modeling poses an ill-defined problem with an indefinite number of solutions. The fact that a single dipole in the RCZ can explain the ERN is thus only weak evidence for the hypothesis that the ERN is generated in the RCZ. A simultaneous recordings study reported in Chapter 5 addresses these points and extends the findings on the dynamics of performance monitoring.

NeuroImage 14, 1387–1401 (2001)

doi:10.1006/nimg.2001.0935, available online at <http://www.idealibrary.com> on IDEAL®

Subprocesses of Performance Monitoring: A Dissociation of Error Processing and Response Competition Revealed by Event-Related fMRI and ERPs

Markus Ullsperger and D. Yves von Cramon

Max Planck Institute of Cognitive Neuroscience, D-04303 Leipzig, Germany

Received February 5, 2001

Performance monitoring can be implemented in the brain by two possible systems, one monitoring for response competition or one detecting errors. Two current models of performance monitoring have different views on these monitoring subsystems. While the error detection model proposes a specific error detection system, the response competition model denies the necessity of a specific error detector and favors a more general unitary system evaluating response conflict. Both models suggest that the frontomedian wall in the vicinity of the anterior cingulate sulcus plays an important role in performance monitoring. The present study investigates the hemodynamic and electrophysiological correlates of response competition and error processing. Twelve young healthy participants performed a speeded, modified flanker task, while fMRI signals and ERPs were measured in separate sessions. The event-related fMRI shows that networks involving the frontomedian wall are activated during both response competition and error processing. However, an anatomical dissociation was found: while error processing preferentially activates the human homologue of the cingulate motor area (CMA, BA 24c') in the depth of the anterior cingulate sulcus, response competition is accompanied by activation of the pre-SMA and mesial BA 8. The ERP waveforms for erroneous trials exhibit a large error-related negativity, which is most likely generated in the CMA. These results suggest that the CMA plays a major role in error processing. Further fMRI activations in the lateral prefrontal and primary motor cortex are discussed with respect to performance monitoring and its influence on task set reconfiguration. © 2001 Academic Press

INTRODUCTION

When humans want to achieve a goal, they need to do two things. First, they have to configure the cognitive system by adopting a task set, which means they must "chain together and configure an appropriate set of processes linking sensory analysis to motor output"

(Rogers and Monsell, 1995, p. 208). A mapping of sensory attributes to a predetermined set of response categories must be established by means of decision criteria. Second, the system must be continuously monitored to determine whether its behavior meets the task goals. Only when the consequences of actions are monitored and errors are detected can behavior be adapted in order to achieve the intended goals. When deviations from these goals are detected, i.e., when errors are made, remedial actions are required. These remedial adjustments can be twofold: immediate corrective actions and more long-term strategic adjustments (task set reconfigurations, e.g., changes in speed and accuracy) that affect future operations of the cognitive system.

It was proposed that not only errors but also the competition of two response programs can lead to strategic adjustments of the task set configuration (e.g., Botvinick *et al.*, 1999, 2001; MacDonald *et al.*, 2000). Currently two models of performance monitoring—one favoring a specific, "genuine" error detection system which is independent on response conflict and one proposing a more general system monitoring for response competition—are discussed.

Among the first researchers to propose an error detection system was Rabbitt (1966), who reported that in psychological experiments participants tended to correct their response immediately after they had committed an error. Moreover, in trials following an erroneous response reaction times were longer and fewer errors occurred, suggesting that participants adopted more conservative strategies after they had detected an error. Around 1990 two groups independently discovered a negative deflection of the event-related potentials (ERPs) which occurred only on incorrect trials (Falkenstein *et al.*, 1990; Gehring *et al.*, 1993). This deflection usually has an amplitude of around 10 μ V, peaks within 80 ms after the erroneous response, and has a focused frontomedian scalp distribution with maximum amplitudes at FCz. It has been termed error negativity or error-related negativity (ERN) for its



specificity to erroneous reactions. Cumulating evidence over the past 10 years suggests that the ERN is a correlate of error processing which is elicited when a comparison between representations of the appropriate (correct, intended) and the actual response yields a mismatch (e.g., Coles *et al.*, 2000; Falkenstein *et al.*, 2000; Gehring *et al.*, 1993). Bernstein and colleagues (1995) could show that ERN amplitudes to similar and dissimilar stimuli did not differ. However, the amplitude was larger when the representations of the correct and the actual response were dissimilar than when the response representations were similar. In other words, the greatest mismatch of response representations elicited the largest ERN, a finding which strongly supports the hypothesis that the ERN reflects a process that compares the correct response with the actual response (Bernstein *et al.*, 1995). Additional evidence for an error detection system based on comparisons comes from the finding that external feedback about errors elicits a negative ERP very similar to the ERN with respect to its amplitude, scalp topography, and source models (Miltner *et al.*, 1997; Holroyd, 2001). Mathalon *et al.* (2000) demonstrated that externally induced errors elicited a ERN-like negative wave of delayed latency.

A current issue in studies of performance monitoring is where and how the proposed error detection system is implemented in the brain. Several source localization studies using dipole models suggest that the ERN is generated in structures of the frontomedian wall, most probably in the anterior cingulate cortex (ACC) or the pre-supplementary motor area (pre-SMA) (Dehaene *et al.*, 1994; Holroyd *et al.*, 1998). These findings were supported by studies using functional magnetic resonance imaging (fMRI) indicating activations of the ACC during erroneous trials (Carter *et al.*, 1998; Kiehl *et al.*, 2000). Holroyd (2001; Holroyd *et al.*, 1999) suggested that particularly the cingulate motor area (CMA, BA 24c) is involved in error detection. Based on anatomical and physiological considerations it seems very plausible that the ERN might be generated by neuronal activity on the ventral bank of the cingulate sulcus, i.e., in the CMA.

The CMA is buried in the cingulate sulcus and consists of several cytoarchitecturally different areas (Luppino *et al.*, 1991; Dum and Strick, 1993). In contrast to the cingulate gyrus itself the CMA has dense interconnections with the primary motor cortex and the spinal cord. Dum and Strick (1993) noted that the cingulate motor areas contain approximately 40% as many direct corticospinal neurons as the primary motor cortex. A major role of the CMA in control of voluntary movements has repeatedly been suggested (Dum and Strick, 1993; Picard and Strick, 1996). Although most studies were performed in monkeys, there is also evidence for a homologue in humans (Picard and Strick, 1996; Diehl *et al.*, 2000).

The error detection model outlined above was challenged by a recent fMRI study which demonstrated activation of the ACC during error trials as well as during correct trials involving high response competition (Carter *et al.*, 1998). These findings led to the view that the ACC detects response competition rather than errors per se. It was assumed that errors occur in trials with very high response competition. According to the response competition model no specific error detection system and no representation of the correct response are required for performance monitoring. A system detecting response competition would initiate adjustments of the task set configuration whenever the conflict of response sets is high. Computational models of several cognitive tasks based on the response competition model supported this view (cf. Botvinick *et al.*, 2001).

However, the experiment presented by Carter and colleagues (1998) does not rule out an additional error detection system. It was implicitly assumed that the fMRI activation found in the ACC correlates with the generation of an ERN. This, however, was not demonstrated by ERP registration. It is conceivable that an ERN would not necessarily be elicited in the experimental design used by Carter *et al.* (1998). In order to increase error rates degraded stimuli were used, but this manipulation has the drawback of high uncertainty about the correct response. In other words, for lack of sufficient information to represent the correct response no comparison could be computed and errors could not be detected. Unfortunately, it was not reported whether participants were aware of their errors and/or showed corrective behavior or strategy adjustments. Further, high uncertainty about the correct response might increase response competition, thus leading to similar activations in correct and incorrect trials. Hence, very crucial for interpretation of the study presented by Carter *et al.* (1998) is whether error processing might have remained unrevealed because participants could not detect most errors for lack of information about the stimuli.

A further question raised by the introduction of the response competition model is how the theoretical construct of response conflict can be described, on which level of cognitive processing it occurs, and how it can be measured independently.

In sum, the two models differ in their view on the processes involved in performance monitoring. Whereas the error detection model proposes a specific comparator system for error detection, the response competition model in its current form denies such a specific system reacting exclusively on errors and suggests a more general, unitary system monitoring for response conflict which signals when several different responses are simultaneously activated.

The purpose of the present study was to disentangle the neural substrates of error processing and response

competition. Here we present data from a study which examined the hemodynamic as well as the electrophysiological response in the same participants while performing the same experiment in two separate sessions. If—as proposed by the error detection model—error detection is solved by a specific system which is independent of response conflict monitoring, then the neural networks activated during errors should differ from those which are active in correct trials involving high response competition. This would lead to different activation patterns in fMRI and to spatiotemporal differences in ERPs during error processing and conflict monitoring. The main focus of investigation was whether and how different structures of the frontomedian wall are differentially involved in performance monitoring. In accordance with Holroyd (2001) we predicted that error-related activity should be found along the cingulate sulcus, i.e., where the CMA in humans is suggested.

Two recent fMRI studies have addressed a related question—error-related brain activity during go/no-go response inhibition tasks (Kiehl *et al.*, 2000; Menon *et al.*, 2001). They reported a dissociation of error-related brain activation from the processes involved in correct no-go trials, namely, response inhibition. It is important to note that response inhibition is a process different from monitoring for response competition as it was formulated previously (e.g., Botvinick *et al.*, 2001). Response conflict arises when more than one preactivated responses compete due to interference of task sets or distracting stimuli. Response inhibition itself can result from detected response conflict as well as after stop cues in a stop-signal task or in the preparation phase of precued task switching. Thus it is conceivable that response inhibition and monitoring for response conflict activate different brain areas. This fact will be taken into account for comparing this study with studies addressing error processing and response inhibition (Kiehl *et al.*, 2000; Menon *et al.*, 2001).

MATERIALS AND METHODS

Participants

Twelve healthy right-handed persons (7 female, age range 21–29 years, mean age 24.9) participated in the study. Informed consent was obtained from each participant before testing. The experiments complied with German legal requirements and were approved by the Ethics Committee of the University of Leipzig. Participants took part in three experimental sessions: training, fMRI data collection, and EEG collection. They were paid for their participation.

Task

A speeded modified flankers task known to produce response conflict and to yield high error rates was

employed (cf. Kopp *et al.*, 1996). The time course of the task is depicted in Fig. 1. Participants had to respond as fast and as accurately as possible on a target arrow briefly presented in the center of the screen. When the target pointed to the right the right button was to be pressed, and when the target pointed to the left,^a response with the left button was required. The target arrow was preceded by irrelevant flanker arrows displayed above and below the screen center. The arrows were 0.46° tall and 1.08° wide, and the four flankers were presented 0.52° and 1.04° above and below the screen center. In onehalf of the trials they pointed in the same (compatible trials) and in the other half of the trials in the opposite direction as the target arrow (incompatible trials). Compatible and incompatible trials appeared in randomized order. When participants did not respond within 450 ms a feedback (“respond faster”) appeared on the screen. Responses were given exclusively with the right hand.

fMRI Data Collection

Imaging was performed at 3 T on a Bruker Medspec 30/100 system equipped with the standard birdcage head coil. Participants were supine on the scanner bed, and cushions were used to reduce head motion. Slices were positioned parallel to the bicommissural plane (AC-PC), with 16 slices (thickness 5 mm, spacing 2 mm) covering the whole brain. Prior to the functional runs, 16 anatomical MDEFT slices and 16 EPI-T1 slices were collected. Functional images in plane with the anatomical images were acquired using a single-shot gradient EPI sequence (TR = 2 s, TE = 30 ms, 64 × 64 pixel matrix, flip angle 90°, field of view 192 mm) sensitive to BOLD contrast. The timing of fMRI data collection relative to the task is shown in Fig. 1. In order to improve temporal resolution for modeling of the hemodynamic response an interleaved design was employed (i.e., trials occurred at multiple, systematically offset time points (± 1 s) in relation to the image acquisition; Josephs *et al.*, 1997; Miezin *et al.*, 2000). In sum, four runs consisting of 64 trials (i.e., 256 scans) each were performed in each session.

In a separate session, high-resolution whole brain images were acquired from each participant to improve the localization of activation foci using a T1-weighted three-dimensional segmented MDEFT sequence covering the whole brain.

fMRI Data Analysis

The fMRI data were processed using the software package LIPSIA (Lohmann *et al.*, 2001). In the preprocessing, artifacts at run borders were removed and a slice-wise movement correction in the transverse direction was applied. Functional data were corrected for slice-time acquisition differences using sinc-interpolation. Spatial smoothing was performed using a Gauss-

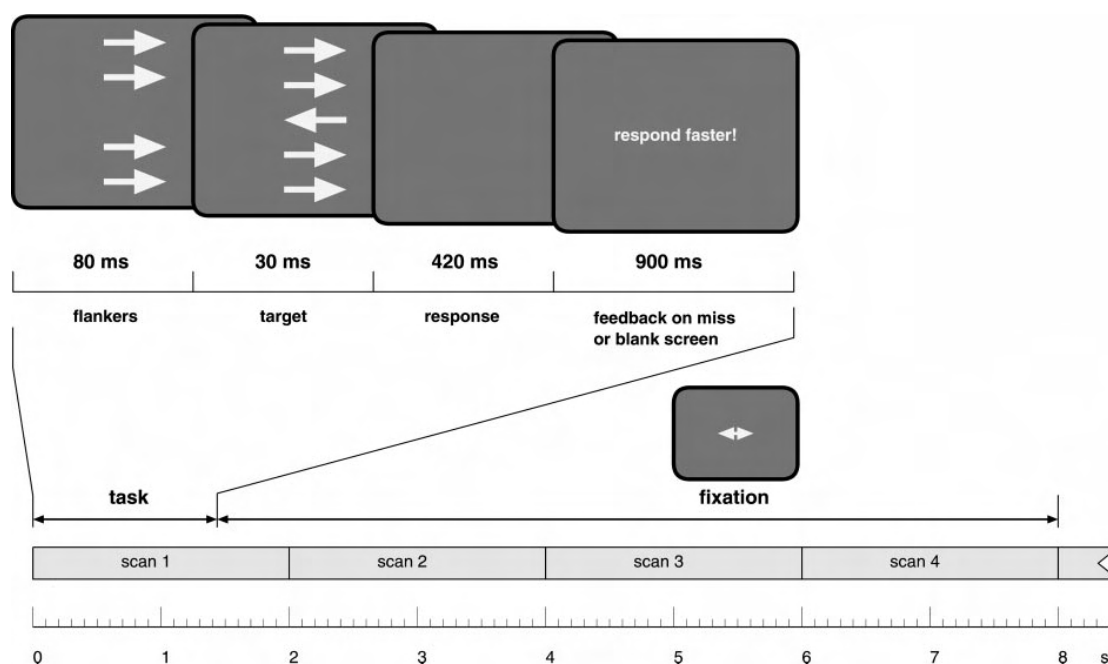


FIG. 1. Time course of the flankers task as used in both sessions and of scan acquisition in the fMRI session. An incompatible trial is shown.

ian filter kernel with a $\sigma = 0.8$. Coregistration of the anatomical and functional data was done in three steps. First, the MDEFT and EPI-T1 slices geometrically aligned with the functional slices were coregistered with the high-resolution 3D reference T1 data set of each participant. Rotational and translational parameters computed for this registration were stored in individual transformation matrices. Second, each individual transformation matrix was scaled to the standard Talairach brain size ($x = 135$, $y = 175$, $z = 120$ mm; Talairach and Tournoux, 1988) by applying linear scaling. Finally, these normalized transformation matrices were applied to the individual functional MRI data. Slice gaps were scaled using a trilinear interpolation, generating output data with a spatial resolution of 3 mm^3 .

The statistical analysis was based on a least-squares estimation using the general linear model for serially autocorrelated observations (Aquirre *et al.*, 1997; Friston *et al.*, 1995; Worsley and Friston, 1995; Zarahn *et al.*, 1997). The design matrix was generated with a synthetic hemodynamic response function and a response delay of 6 s (Friston *et al.*, 1998). The model equation, including the observation data, the design matrix, and the error term, was convolved with a Gaussian kernel of dispersion of 4 s FWHM. The model includes an estimate of temporal autocorrelation that is used to estimate the effective degrees of freedom

(Worsley and Friston, 1995). Low-frequency signal drifts (due to global signal changes like respiration) were suppressed by applying a high-pass filter. The filter length was calculated as twice the length of one complete oscillation, i.e., maximal gap between two trials of the same experimental condition. Because the distance between two erroneous trials varied across participants, individual cut-off frequencies were chosen (range 1/160–1/98 Hz). The increased autocorrelation caused by filtering was taken into account during statistical evaluation by adjustment of the degrees of freedom (Worsley and Friston, 1995). The contrasts between the different conditions were calculated using the t statistic. Subsequently, t values were converted to Z scores. As the individual functional data sets were all aligned to the same stereotactic reference space a group analysis of fMRI data was performed by a voxel-wise t test (see Bosch, 2000, for a detailed description of the method). Resulting Z maps were thresholded at $Z > 3.09$, uncorrected.

The following contrasts were calculated: (1) brain activity related to response competition is reflected by the contrast incompatible correct vs compatible correct trials, (2) error-related brain activity is reflected by the contrast incompatible errors vs incompatible correct trials. Trials in which no response was generated within the 450 ms time window were excluded from analysis.

ERP Data Collection

For collection of the EEG the same participants were seated in a dimly lit, electrically shielded chamber. The EEG activity was recorded with Ag/AgCl electrodes mounted in an elastic cap (Electrocap International) from 61 scalp sites of the extended 10–20 system. Electrode labeling is based on the standard nomenclature described in Sharbrough *et al.* (1990). The ground electrode was positioned 10% of the distance between the two preocular points right to Cz. The vertical electrooculogram (EOG) was recorded from electrodes located above and below the right eye. The horizontal EOG was collected from electrodes positioned at the outer canthus of each eye. Electrode impedance was kept below 5 kohm. The right mastoid was recorded as an additional channel. All scalp electrodes were referenced to the left mastoid and were offline rereferenced to linked mastoids. The EEG and EOG were recorded continuously with a band pass from DC to 30 Hz and were A-D converted with 16-bit resolution at a sampling rate of 250 Hz and stored on hard disc and CD-ROM for offline analysis.

ERP Data Analysis

In the first step, the EEG epochs were scanned for muscular and large EOG artifacts. Whenever the standard deviation in a 200-ms interval exceeded 50 μ V, the epoch was rejected. In the second step, small horizontal and vertical EOG artifacts which were still present in the EEG signal were corrected by an eye movement correction procedure (Pfeifer, 1993) based on a linear regression method described by Gratton *et al.* (1983). Finally, ERPs were separately averaged for compatible correct, incompatible correct, and incompatible erroneous trials. The epochs were response-locked and lasted from 600 ms before to 500 ms after the response button press. The average voltage in the 100 ms preceding the flankers onset served as a baseline, i.e., the mean value was subtracted from each data point in the waveforms. Because some of the ERP components were not clearly visible as peaks at all electrode sites, mean amplitude measures in a given time window were considered more reliable for component scoring than peak measures. In order to avoid the loss of statistical power that occurs when repeated-measures ANOVAs are used to quantify multichannel and multitime window data (Gevins *et al.*, 1996; Oken and Chiappa, 1986), electrode sites were pooled to form nine topographical regions. The following regions of interest were defined: left frontal (AF7, F5, F7, F9), medial frontal (AFz, Fz, F3, F4), right frontal (AF8, F6, F8, F10), left central/temporal (FT7, T7, TP7, C5), medial central (FCz, CPz, C3, C4), right central/temporal (FT8, T8, TP8, C6), left parietal (P5, P7, P9, PO7), medial parietal (P7, PO7, PO3, PO4), and right parietal (P6, P8, P10, PO8). By subjecting the data to a

three-way repeated-measures ANOVA with the factors response type (two levels), anterior–posterior dimension (three levels), and lateral dimension (three levels) it was tested whether the ERP amplitudes differed between correct and erroneous incompatible trials. Finally, in order to test whether the ERPs were topographically different, the same ANOVA was conducted after rescaling such that amplitude differences between the two contrasted conditions were removed (McCarthy and Wood, 1985). All effects with more than 1 degree of freedom in the numerator were adjusted for violations of sphericity according to the formula of Greenhouse and Geisser (1959). In order to avoid reporting large amounts of statistical results not relevant for the issues under investigation, only main effects or interactions including the stimulus/response type factor will be reported. Scalp potential topographic maps were generated using a two-dimensional spherical spline interpolation (Perrin *et al.*, 1989) and a radial projection from Cz, which respects the length of the median arcs. Finally, in order to investigate the relationship between the ERP and the fMRI data sets, source localization procedures were performed using the multimodal neuroimaging tool CURRY 4.5 (Neurosoft, Inc.). Strength and orientation of a single dipole were fitted in the grand average waveform for the erroneous trials. The CURRY Warped Brain (an average brain obtained from more than 100 participants; Neuroscan Laboratories, Sterling, VA) was used to construct a realistically shaped volume conductor model with three volumes employing the Boundary Element Method (Fuchs *et al.*, 1998). The dipole seed point was placed at the Talairach coordinates of an activation maximum in fMRI; the dipole was allowed to vary in location within a sphere with 5 mm radius.

RESULTS

fMRI Session

Three participants were excluded from analysis due to chance-level performance even when late responses were taken into account. Accuracy and reaction times of the remaining participants are documented in Table 1. Accuracy was significantly lower ($t(8) = 7.61$, $P < 0.001$) and reaction times were longer ($t(8) = -12.03$, $P < 0.0001$) for incompatible trials, suggesting a higher response conflict for incompatible trials. In fact, performance for incompatible trials was very low. However, when data for all response types (in time, late, miss) were collapsed it became obvious that the participants included in analysis followed the instructions (cf. Table 1, right columns).

Complete lists of activations exceeding the Z threshold of 3.09 in a volume of at least 150 mm³ in the two contrasts of interest can be found in Tables 2 and 3. The bottom of Fig. 2 depicts the activation foci associ-

TABLE 1
Behavioral Data Collected in the fMRI Session

| | Compatible trials | | Incompatible trials | |
|----------------------|------------------------|-------------|------------------------|-------------|
| | Response within 450 ms | Total | Response within 450 ms | Total |
| Accuracy | | | | |
| Percentage correct | 92.1 (2.19) | 97.1 (1.12) | 49.8 (5.51) | 73.1 (2.76) |
| Percentage incorrect | 2.1 (0.80) | 2.6 (1.07) | 24.9 (2.61) | 26.1 (2.7) |
| Reaction times | | | | |
| Correct | 360 (5.0) | | 421 (6.4) | |
| Incorrect | — ^a | | 342 (4.5) | |

Note. The left columns display the accuracy for trials in which responses were given within the 450-ms time window, the right columns depict the accuracy for all trials collapsed (timely and late responses and misses).

^a Too few errors were generated in this condition to determine error reaction time.

TABLE 2
Response Competition (Incompatible Correct vs Compatible Correct)

| Brain region (Brodmann area) | Volume (mm ³) | Z score local maximum | Talairach coordinates | | |
|---|---------------------------|-----------------------|-----------------------|-----|-----|
| | | | x | y | z |
| R mesial SFG, pre-SMA (8) | 3835 | 4.92** | 4 | 28 | 42 |
| R pre-SMA (6/32) | | 4.70** | 4 | 19 | 41 |
| L SMA (6/23) | | 3.77* | -5 | -3 | 43 |
| R anterior insula | 8287 | 5.35** | 29 | 17 | 10 |
| R precentral gyrus (6) | | 4.08** | 44 | -5 | 32 |
| R precentral sulcus (6) | | 3.94** | 49 | 5 | 35 |
| R precentral sulcus (9/6) | | 3.76* | 37 | 2 | 36 |
| R inferior frontal/precentral sulcus (44) | | 3.87* | 46 | 9 | 29 |
| R IFG, opercular part (44/45) | | 4.73** | 41 | 12 | 14 |
| R IFG, opercular part (44/45) | | 4.75** | 50 | 12 | 11 |
| R IFG, triangular part (45) | | 4.84** | 29 | 15 | -1 |
| R IFG, triangular part (45) | 281 | 4.14** | 44 | 34 | 0 |
| L anterior insula | 2335 | 4.51** | -34 | 17 | 10 |
| L anterior insula | | 4.14** | -35 | 9 | 0 |
| L insula | 202 | 3.79* | -31 | -3 | 2 |
| R MFG (9/46) | 180 | 3.53* | 22 | 43 | 27 |
| R MFG (9/46) | 356 | 3.58* | 46 | 25 | 28 |
| R MFG (9/46) | | 3.42* | 38 | 33 | 24 |
| L MFG (9/46) | 154 | 3.54* | -37 | 39 | 25 |
| L central sulcus | 4657 | 5.30** | -35 | -27 | 45 |
| R IPS (40) | 4529 | 4.96** | 41 | -47 | 49 |
| R PCC (31) | 695 | 4.43** | 4 | -25 | 27 |
| R caudate nucleus (head) | 1751 | 4.85** | 10 | 13 | 2 |
| R colliculus superior | 2601 | 4.54** | 8 | -31 | 0 |
| R lateral geniculate body | | 3.86* | 25 | -31 | 0 |
| L thalamus | | 3.57* | -14 | -20 | 9 |
| L mesencephalon/thalamus | | 4.10** | -11 | -22 | -2 |
| R medial occipital gyrus (19) | 322 | 3.91** | 46 | -70 | 19 |
| R cerebellum | 4316 | 4.70** | 13 | -58 | -9 |
| R cerebellum | | 4.10** | 2 | -56 | -3 |
| R cerebellum | | 4.51** | 23 | -47 | -17 |
| L cerebellum | | 3.61* | -10 | -60 | -6 |
| L cerebellum | 821 | 3.93** | -32 | -64 | -22 |
| L fusiform gyrus (19) | 713 | 3.58* | -25 | -80 | -13 |

Note. ACC, anterior cingulate cortex; IFG, inferior frontal gyrus; IPS, intraparietal sulcus; MFG, middle frontal gyrus; PCC, posterior cingulate cortex; SMA, supplementary motor area.

* $P < 0.0005$ uncorrected.

** $P < 0.00005$ uncorrected.

TABLE 3
Error-Related Activations (Incompatible Incorrect vs Incompatible Correct)

| Brain region (Brodmann area) | Volume (mm ³) | Z score local maximum | Talairach coordinates | | |
|------------------------------|---------------------------|-----------------------|-----------------------|-----|-----|
| | | | x | y | z |
| R pre-SMA (6/31) | 399 | 3.84* | 2 | 13 | 42 |
| L pre-SMA (6/32) | | 3.36* | -2 | 5 | 47 |
| R ACC (rostral CMA: 24c') | 810 | 4.36** | 7 | 19 | 30 |
| L anterior insula | 2510 | 4.58** | -35 | 14 | 8 |
| L anterior insula | | 4.31** | -40 | 4 | 4 |
| L anterior insula | | 4.25** | -40 | 15 | -1 |
| L IFG (pars orbitalis, 47) | | 4.33** | -32 | 15 | -13 |
| R anterior insula | 2584 | 4.78** | 41 | 7 | 6 |
| R anterior insula | | 4.65** | 32 | 11 | 8 |
| R anterior insula | | 3.90** | 32 | 21 | 0 |
| R IPS (40) | 705 | 4.18** | 58 | -46 | 29 |
| R IPS (40) | 407 | 4.62** | 61 | -33 | 29 |
| L IPS (40) | 294 | 3.40* | -41 | -51 | 44 |
| L SMG (39/40) | 801 | 4.28* | -58 | -54 | 22 |

Note. ACC, anterior cingulate cortex; CMA, cingulate motor area; IFG, inferior frontal gyrus; IPS, intraparietal sulcus; MFG, middle frontal gyrus; PCC, posterior cingulate cortex; SMA, supplementary motor area; SMG, supramarginal gyrus.

* $P < 0.0005$ uncorrected.

** $P < 0.00005$ uncorrected.

ated with response competition (left) and error processing (right) on the median wall of the right hemisphere. During incompatible correct trials involving high *response competition* the mesial superior frontal gyrus, in particular the pre-SMA, was more activated than during compatible correct trials which involve less response conflict. This activation had two local maxima (posterior, BA 6; anterior and superior, BA 8) and extended in inferior and anterior direction to the banks of the anterior cingulate sulcus (BA 32/24c'). An additional activation focus was visible in the posterior cingulate cortex (BA 31). The contrast reflecting *error processing* revealed activation foci in the pre-SMA (BA 6) and on the banks of the anterior cingulate sulcus (BA 32/24c'). These foci partially overlap with the activations found during response competition. However, there are clear subregional differences between the two contrasts. This is most obvious when trial averages of the registered BOLD response at two regions of interest are considered (see top of Fig. 2): The mesial BA 8 responded selectively to response competition. In contrast, the cingulate motor area (BA 32/24c') was activated by error processing and not by response competition.¹

¹ In the time courses of the hemodynamic responses activity related to response competition is reflected by the difference between the curves for incompatible correct and compatible correct trials. Error-related activity is reflected by the difference between the BOLD responses for erroneous and correct incompatible trials. An inspection of the time courses (Fig. 2) suggests that the CMA was also activated during correct responses. However, the amplitude of the BOLD response was lower than that during errors, and it did not differ between compatible and incompatible correct trials. This latter

More lateral foci of the hemodynamic response are shown in Fig. 3. In the *response competition* contrast activations were found along the anterior bank of the right superior and inferior precentral sulcus (lateral premotor cortex, BA 6), on the right inferior frontal gyrus (IFG; opercular and triangular divisions, BA 44/45), in the vicinity of the right intraparietal sulcus (horizontal branch, BA 40), in the left sensorimotor cortex (central sulcus, left-hand field), and bilaterally in the anterior superior insula and on the middle frontal gyrus (BA 46).

In the contrast reflecting *error processing* only the anterior insula and intraparietal sulcus (horizontal branch, BA 40) were activated bilaterally. In addition, a small activation was found in the left posterior orbitofrontal cortex (BA 47). This latter activation has to be interpreted with caution, because it also might be spurious due to susceptibility artifacts.

ERP Session

The behavioral data collected during the ERP session are displayed in Table 4. Although overall performance was better than during the fMRI session,² the

fact makes it clear that the activation of the CMA during correct trials cannot be attributed to response conflict. As known from several imaging studies (cf. Picard and Strick, 1996) this region seems to be also involved in complex motor behavior and motor preparation. This may account for the activation during correct trials. The amplitude increase during erroneous trials, however, is error related.

² Although the ERP session was always performed after the fMRI session, we do not attribute these performance differences to learn-

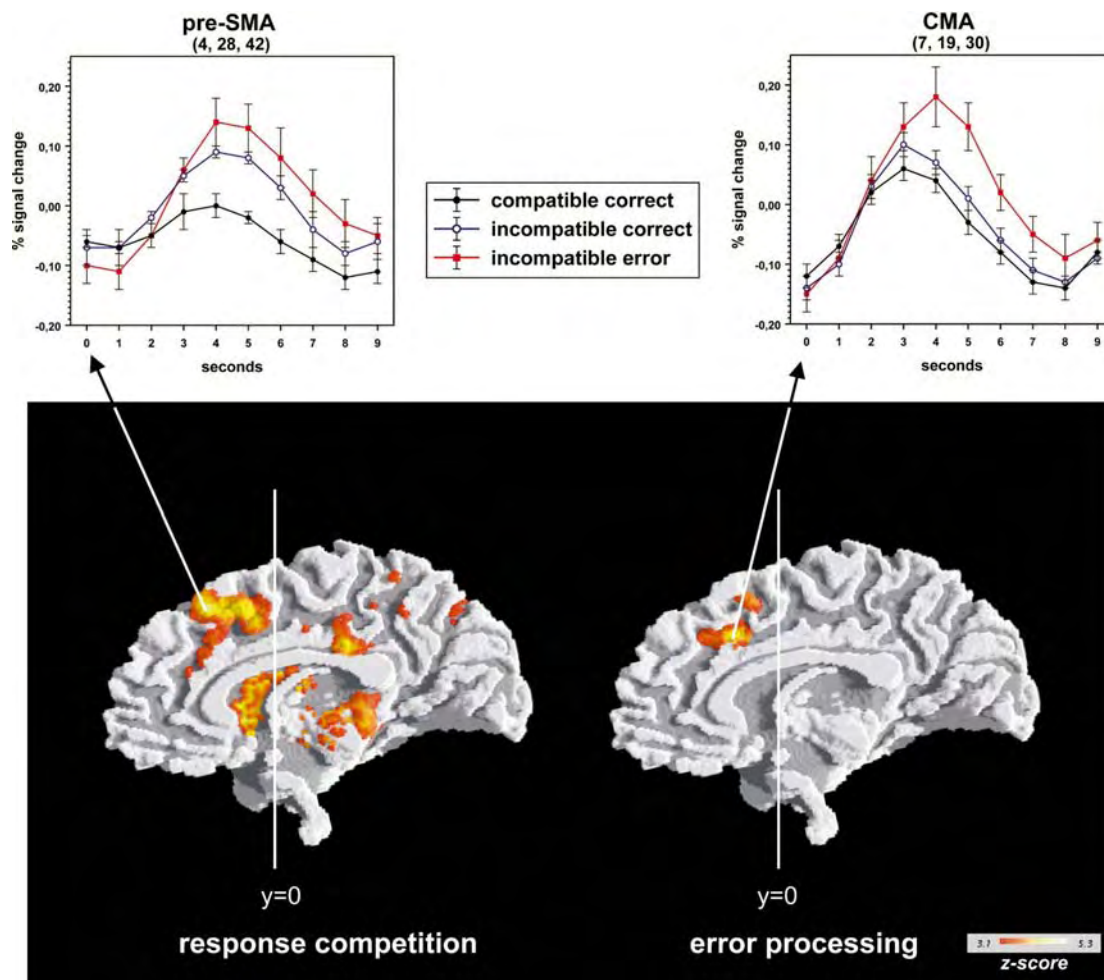


FIG. 2. fMRI activations at $Z > 3.09$ for the response competition (left) and error processing contrasts (right). Activations within a depth of 7 mm were projected onto the median surface of a white matter segmented image of the right brain hemisphere, which had been normalized and aligned to the Talairach stereotactic space. Top: Time courses of the BOLD responses to the three stimulus/response types in two regions of interest (left, pre-SMA; right, CMA).

typical effects of incompatibility were found: error rates were higher ($t(11) = 3.86$; $P < 0.005$) and reaction times longer ($t(11) = 11.24$; $P < 0.001$) for incompatible trials, suggesting that response conflict was higher during incompatible trials compared to compatible ones. Figure 4 depicts the response-locked ERP waveforms at two midline electrodes for compatible correct, incompatible correct, and incompatible erroneous trials. A clear ERN was identified on erroneous incompatible trials. At FCz its average latency after the

response button press was 56 ms ($SE = 0.4$) and the average amplitude amounted to $-9.6 \mu V$ ($SE = 1.4$). Interestingly, no negative deflection of similar latency and topography was present in the waveforms for the correct trials. This was confirmed by an ANOVA of the ERPs for correct and incorrect incompatible trials in a time window from 30 to 100 ms. Significant interactions response type \times anterior-posterior dimension ($F(2, 22) = 11.8$, $P < 0.005$) and response type \times anterior-posterior dimension \times lateral dimension ($F(4, 44) = 4.61$, $P < 0.01$) were revealed. The same interactions were significant ($F(2, 22) = 17.38$, $P < 0.0001$; $F(4, 44) = 3.84$, $P < 0.05$, respectively) when the ANOVA was performed on amplitude-normalized data (McCarthy and Wood, 1985). The findings suggest that

ing. In a behavioral pretest performed before the fMRI study in order to test whether enough errors would be committed with the given response deadline participants' performance was comparable to the behavioral results from the ERP session.

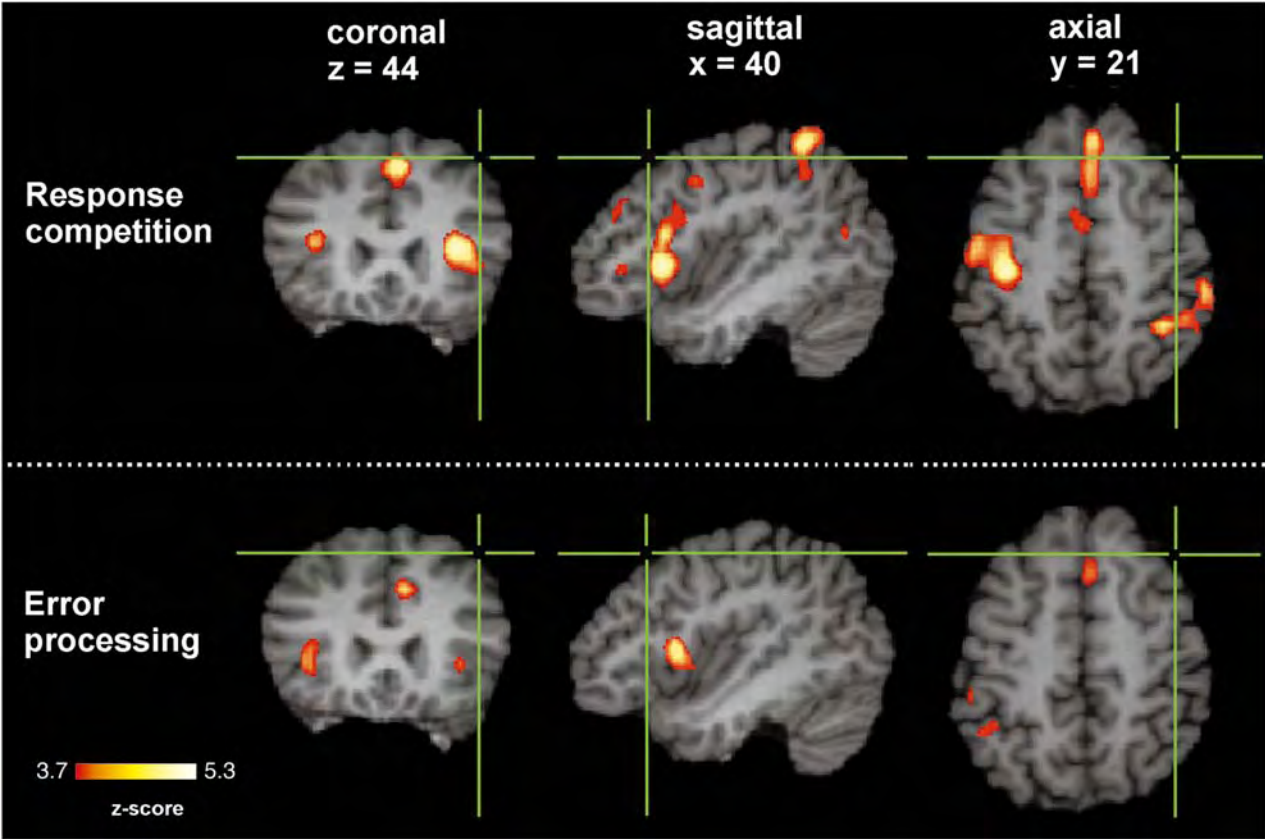


FIG. 3. FMRI foci on coronal ($y = 21$), right lateral sagittal ($x = 40$), and axial ($z = 44$) slices of a 3D structural MRI normalized and aligned to the Talairach stereotactic space. Upper row: Response competition contrast. Lower row: Error contrast.

error processing and performance monitoring involve different processes and generators during correct trials with high response conflict.

After the ERN an additional parietal positive deflection peaking around 370 ms after the response was present in the waveforms for erroneous trials. This

wave was previously described by Falkenstein and colleagues (2000, 1990) as the error positivity (Pe). ERPs for correct and erroneous incompatible trials in a time window 300–400 ms after response were subjected to an ANOVA. Significant interactions of response type \times lateral dimension ($F(2, 22) = 7.92, P < 0.005$), response

TABLE 4
Behavioral Data Collected in the ERP Session

| | Compatible trials | | Incompatible trials | |
|----------------------|------------------------|-------------|------------------------|-------------|
| | Response within 450 ms | Total | Response within 450 ms | Total |
| Accuracy | | | | |
| Percentage correct | 95.8 (0.86) | 98.4 (0.36) | 85.7 (2.42) | 91.0 (2.24) |
| Percentage incorrect | 1.1 (0.32) | 1.3 (0.37) | 7.7 (1.90) | 8.4 (2.03) |
| Reaction times | | | | |
| Correct | 323 (6.8) | | 378 (6.1) | |
| Incorrect | — ^a | | 283 (7.9) | |

Note. The left columns display the accuracy for trials in which responses were given within the 450-ms time window, the right columns depict the accuracy for all trials collapsed (timely and late responses and misses).

^a Too few errors were generated in this condition to determine error reaction time.

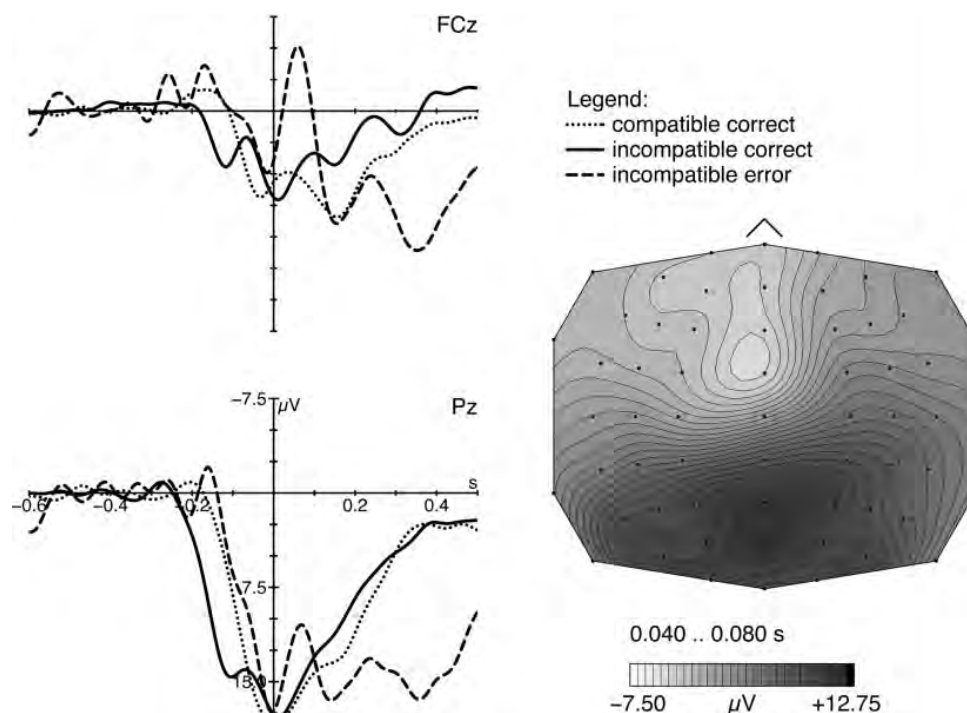


FIG. 4. Left: ERP waveforms averaged across participants for compatible correct, incompatible correct, and incompatible erroneous trials at two midline electrodes. Response was given at $t = 0$. Right: Isopotential maps showing the scalp topography of the ERPs in a time window from 40 to 80 ms after the erroneous response on incompatible trials. The negative voltages (unshaded) of the ERN are most pronounced around FCz.

type \times anterior dimension ($F(2, 22) = 5.64, P < 0.05$), as well as the triple interaction response type \times lateral dimension \times anterior dimension ($F(4, 44) = 5.00, P < 0.01$) were revealed. This difference was most prominent at central midline electrodes as revealed by post hoc tests. Subjecting amplitude-normalized data to the same ANOVA gave rise to the same interactions—response type \times lateral dimension ($F(2, 22) = 3.55, P < 0.05$), response type \times anterior dimension ($F(2, 22) = 10.00, P < 0.001$), and response type \times lateral dimension \times anterior dimension ($F(4, 44) = 4.34, P < 0.05$). This suggests that scalp topographies differed also in the late time window between correct and incorrect responses.

DISCUSSION

The Frontomedian Wall: Pre-SMA and Cingulate Motor Areas

Taken together, both error processing and response competition activated networks involving the fronto-medial cortex. However, important subregional and extent differences of the hemodynamic responses were found. The activations showed only partial overlap at the border of SMA and pre-SMA, but a clear anatomi-

cal dissociation at more rostral regions: The pre-SMA was activated by response competition to a much higher extent than during errors. The activation involved the mesial BA 8, which selectively responded to response competition. A recent study investigating response conflict in a Stroop task (Zysset *et al.*, 2001) reported a very similar focus of brain activity. The present findings are also in line with a recent study by Hazeltine *et al.* (2000), who failed to find ACC activation during response competition but demonstrated activation of the SMA. In contrast, the cortex along the ACC (BA 24c'/32) was selectively activated by error processing and not by response competition. Examination of single-participant data revealed that this error-related activation of the ACC was always centered to the rostral CMA ("rostral cingulate zone" according to Picard and Strick, 1996). It could be argued, however, that activations found in the error-related contrast may involve more processes than error processing alone. In addition, it could entangle those processes which led to an incorrect resolution of the response conflict imposed by the incompatible trial.

The dissociation described here contrasts with the findings reported by Carter *et al.* (1998), who reported activations of the ACC by both response competition

and errors. This may be due to the fact that the centroid of the activation reported by Carter and colleagues is located more superiorly, at the border between BA 32 and BA 8. Thus, hemodynamic responses of the pre-SMA as well as the CMA could have contributed to this finding. The pre-SMA belongs to the mesial premotor cortex and is located anterior to the vertical line transversing the anterior commissure (Picard and Strick, 1996; Vorobiev *et al.*, 1998). Evidence from electrophysiological, brain imaging, and lesion studies indicate that the pre-SMA and the more posteriorly located SMA play a major role in preparation and processing of motor activity (for reviews see Picard and Strick, 1996; Rizzolatti *et al.*, 1996; Tanji, 1994). In contrast to the SMA, which is more closely related to movement execution and effector-specific modulations, the pre-SMA seems to be involved in higher hierarchical roles of motor control (Matsuzaka *et al.*, 1992; Tanji, 1994; Picard and Strick, 1996; Lee *et al.*, 1999; Schubotz and von Cramon, 2001). According to Rizzolatti and colleagues (1996; Vorobiev *et al.*, 1998) the pre-SMA is important for the transmission of cognitive and motivational information to the premotor areas. The strong interconnections with prefrontal cortex on one hand and the lateral premotor areas and the SMA on the other could enable this region to monitor for conflicting intentions to act. In contrast to the CMA, the anterior pre-SMA and the adjacent mesial BA 8 contain (almost) no corticospinal neurons (Tanji, 1994; Picard and Strick, 1996).

As noted above, the activation observed during errors occurred in what we think is the homologue of the rostral part of the CMA (BA 24c') in humans. Relatively few physiological studies have specifically investigated the cingulate motor areas, thus little is known about its specific functions in motor control. Several studies reviewed in Picard and Strick (1996) indicate that the rostral CMA is related to complex movements, learning of new movement sequences, and internal selection of movements. Based on anatomical and physiological considerations Holroyd (2001) suggested that the ERN is elicited by activity of neurons located within the ventral bank of the anterior cingulate sulcus where the CMA is located. The activations during errors in the present study are consistent with this view. The ERP results demonstrate that the task was sufficient to elicit an ERN on incorrect trials. In order to examine whether this ERN may have been generated by the CMA a single dipole was placed at the Talairach coordinates of the error-related ACC activity found in the fMRI experiment ($x = 7$, $y = 19$, $z = 30$). Dipole orientation and strength were fitted in the grand mean waveform for the incorrect responses using a realistic boundary elements head model. The dipole model accounted for 90.7% of the variance at

peak latency of the ERN, supporting the view that the CMA is involved in the generation of this component.³

Two recent studies reported an anatomical dissociation of activations reflecting error processing and response inhibition in a go/no-go task (Kiehl *et al.*, 2000; Menon *et al.*, 2001). These studies show similarities and differences compared to the present experiment which require further discussion. The error-related activation found in the go/no-go study involves the caudal ACC (CMA) but in contrast to our data the activation extends into the rostral cingulate cortex. The rostral cingulate cortex is known to be involved in processing of emotional information (e.g., Bush *et al.*, 2000). In contrast to errors in flanker tasks, errors of commission in go/no-go tasks cannot be corrected by a second key press. This fact may have led to a more negative affective valence of errors for the participants. In addition, error rates were significantly lower in the study reported by Menon *et al.* (2001) than in the present one (6.25% vs 24.9%),⁴ which might also influence the affective valence of errors. This may hint on the functional significance of the error-related activity in the rostral ACC. An interesting question for future research would be how much the perception and emotional valence of errors is influenced by their overall frequency during psychological tasks and whether this is reflected in the activity of the emotional subdivision of the ACC.

The comparison of activations related to response competition in the current study and to response inhibition and execution in the go/no-go papers (Kiehl *et al.*, 2000; Menon *et al.*, 2001) provides insights into the brain areas involved in these processes. As already pointed out in the Introduction, response conflict monitoring and response inhibition are not the same but are often coincident processes. It is conceivable that in go/no-go tasks only one response is activated. This response tendency has to be inhibited on no-go trials. Thus, correct no-go trials should activate networks involved in response inhibition. In contrast, incompatible trials in flanker tasks lead to preactivation of two (the correct and the incorrect) responses even in correct trials (e.g., Gratton *et al.*, 1988, 1992). This results in response conflict. The incorrect response must be inhibited in order to resolve this conflict. It is therefore conceivable that in the response competition two processes are reflected: monitoring for response conflict and the resulting inhibition of the incorrect

³ The resulting dipole was slightly displaced compared to the maximal fMRI activation, but this displacement was lower than the allowed 5 mm. The dipole location with the lowest residual variance was still within the CMA, but slightly more posterior at $y = 14.2$.

⁴ In fact, overall error rates were also lower in the study reported by Kiehl and colleagues (2000). In their experiment, errors occurred on 23.7% of the nontargets, which appeared with a probability of 20%. Thus, the overall frequency of errors was much lower than in the present study.

response when the conflict was detected. Interestingly, the frontomedian activations found in this contrast show partial overlap with those reported for response inhibition by Menon *et al.* (2001) and Kiehl *et al.* (2000). However, in the present study, the activation had its maximum more anteriorly and superiorly (it extended into mesial BA 8), while the main focus in the go/no-go studies was more in the posterior pre-SMA (BA 6), which is also known to be involved in the preparation of motor processes (Vorobiev *et al.*, 1998; Picard and Strick, 1996). The response execution contrast reported by Menon and colleagues (2001) showed an even more posterior frontomedian focus, the SMA. Taking these findings together, one might speculate that—on a very simplified description level—the anterior pre-SMA including mesial BA 8 could be involved in the detection of “action obstacles” reflected by response conflict, whereas the posterior pre-SMA could be preferentially engaged in removing these obstacles by inhibiting the wrong response.

Further Correlates of Response Competition

In the response competition contrast additional activations were found in the lateral premotor cortex and even in the left sensorimotor cortex (left-hand field; note that participants responded with the right hand). It can be assumed that these premotor and motor activations are a correlate of response competition. Studies investigating lateralized readiness potentials (LRPs) in tasks involving high response competition demonstrated activations of the premotor and motor cortex corresponding to the incorrect response prior to the correct response (e.g., Gratton *et al.*, 1988, 1992; Osman *et al.*, 1992; De Jong *et al.*, 1994). Therefore, it is conceivable that on incompatible correct trials both the correct and the incorrect responses were activated in the left-hand field while on compatible trials only one (the correct) response was activated. In other words, motor cortex activity was larger on correct incompatible trials. We suggest that this residual motor cortex activation in the response competition contrast can serve as a measure of response conflict. Interestingly, no residual motor cortex activation was found in the error contrast, suggesting that response competition was not higher in erroneous than in correct incompatible trials. This finding is inconsistent with the response competition model, which assumes higher response conflict in erroneous trials compared to correct ones (Botvinick *et al.*, 2001).

The ERP data are in congruence with these fMRI findings on larger activation of the primary motor cortex during trials involving high response competition. We calculated response-locked lateralized electrical activity over the primary motor cortex by subtracting the

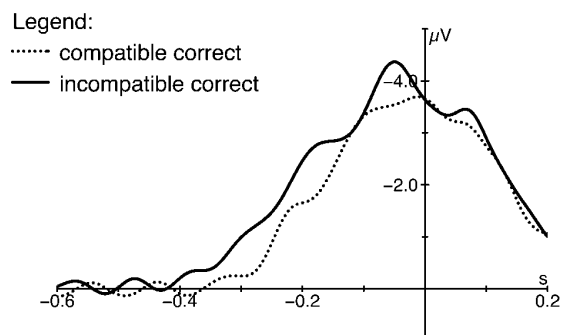


FIG. 5. Response-locked lateralized potentials recorded over central areas (C3–C4, see text) averaged across participants for correct compatible and incompatible trials.

ERP waveforms at C4 from those at C3.⁵ Due to the fact that participants responded with their right hands the difference waves for both compatible and incompatible trials show a negative deviation as a correlate of response activation in the left primary motor cortex. As can be seen in Fig. 5, the lateralization of the electrical activity was significantly larger for correct incompatible trials than for correct compatible trials in a time window from 350 to 0 ms prior to the response ($t(11) = 2.71$; $P < 0.05$), suggesting that the left motor cortex has been more activated by the incompatible trials. We propose that a comparison of primary motor cortex activation in two different task conditions involving the same motor response using either fMRI or LRPs can serve as a measure of response competition.

Lateral Prefrontal Activations

In contrast to our expectations, no lateral prefrontal activations during errors were found, which is in contrast to previous studies (Carter *et al.*, 1998; Kiehl *et al.*, 2000). This is surprising because the lateral prefrontal cortex has been shown to be involved in performance monitoring (Gehring and Knight, 2000). However, we did find an activation of the left and right middle frontal gyri in the contrast reflecting response competition. The left MFG activation was very close to the focus described by Kiehl *et al.* (2000) in the error condition. This similarity suggests that the prefrontal activation might not be specific for error processing but rather for the implementation of control (i.e., task set management) when either response conflict or errors are detected (Zysset *et al.*, 2001; Mac Donald *et al.*, 2000; Botvinick *et al.*, 2001).

In the response competition contrast, activations of the opercular part of the right IFG were observed.

⁵ Note that the unimanual responses (right hand only) did not allow the calculation of conventional lateralized readiness potentials.

These findings are consistent with findings reported by Hazeltine *et al.* (2000) and Zysset *et al.* (2001). Similar activations have been found in neuroimaging studies examining set shifting and task switching (e.g., Konishi *et al.*, 1998; Dove *et al.*, 2000) and go/no-go tasks (Konishi *et al.*, 1999). It has been suggested that the IFG in the vicinity of the inferior precentral sulcus is involved in producing goal-oriented sequences of actions (e.g., Fuster, 1995; Schubotz *et al.*, 2000) and in inhibition of latent response tendencies (Konishi *et al.*, 1999). In other words, the posterior IFG may play a specialized role in the resolution of response competition and task set management (Hazeltine *et al.*, 2000; Zysset *et al.*, 2001).

The Error Positivity

As noted under Results, the ERN in the ERPs for erroneous trials was followed by a positivity peaking around 370 ms after the response. A significant topographical difference from the waveform following correct responses was revealed, thus replicating earlier reports of the Pe (e.g., Falkenstein, 2000). A recent paper suggests that the Pe may be associated with conscious error recognition and/or task set adjustments after errors (Nieuwenhuis *et al.*, 2001). Estimation of possible generators of the Pe by dipole modeling was tried. One to three dipoles were placed at the coordinates of the CMA and/or the lateral temporal fMRI activations. None of these models yielded acceptable solutions (explained variance was below 80%). This negative finding may be due to the fact that electrical activity reflected in ERPs does not necessarily have similar correlates in fMRI and vice versa (cf. Rugg, 1998). Future research investigating the awareness of errors by means of hemodynamic measures will be necessary to elucidate the functional neuroanatomy of the Pe.

CONCLUSIONS

In sum, the present study suggests that performance monitoring involves two functionally and anatomically different systems—one monitoring for response conflict and one detecting erroneous actions. As noted by Botvinick and colleagues (2001), the processes proposed to be involved in detection of either response conflict or errors might be quite closely related. Both systems of performance monitoring have influence on cognitive control (i.e., adjustments of the task sets), reflected by activations of the dorsolateral prefrontal cortex. One important difference between the two systems is timing relative to the potential problem requiring cognitive control: while the error detection system allows remedial actions after the error had been committed and later adjustments of the cognitive system only, monitoring of response conflict can prevent the

occurrence of errors before they occur by triggering online adaptive behavior. The data presented here suggest that the CMA plays a major role in error detection, while response conflict monitoring appears to be implemented in a larger area of the frontomedian wall—predominantly in the pre-SMA. Considering the current knowledge about interconnections of these areas, one might speculate that the pre-SMA is more generally involved in overcoming obstacles on the way between planning and execution of a motor action before the actual action occurs. These “obstacles” could be reflected in response conflict. In contrast, the CMA with its dense connections to the spinal cord could be involved not only in error processing but also in using this information for immediate corrective behavior. This latter notion will be tested in future experiments.

ACKNOWLEDGMENTS

We thank M. Falkenstein and N. G. Müller, for constructive suggestions on this study, and P. Ullsperger and two anonymous reviewers for valuable comments on an earlier version of the manuscript.

REFERENCES

- Aguirre, G. K., Zarahn, E., and D'Esposito, M. 1997. Empirical analysis of BOLD fMRI statistics. II. Spatially smoothed data collected under null-hypothesis and experimental conditions. *NeuroImage* **5**: 199–212.
- Bernstein, P. S., Scheffers, M. K., and Coles, M. G. H. 1995. “Where did I go wrong?” A psychophysiological analysis of error detection. *J. Exp. Psychol.: Hum. Percept. Perform.* **21**: 1312–1322.
- Bosch, V. 2000. Statistical analysis of multi-subject fMRI data: The assessment of focal activations. *J. Magn. Reson. Imaging* **11**: 61–64.
- Botvinick, M., Nystrom, L. E., Fissell, K., Carter, C. S., and Cohen, J. D. 1999. Conflict monitoring versus selection-for-action in the anterior cingulate cortex. *Nature* **402**: 179–181.
- Botvinick, M. M., Braver, T. S., Barch, D. M., Carter, C. S., and Cohen, J. D. 2001. Conflict monitoring and cognitive control. *Psychol. Rev.*, **108**: 624–652.
- Bush, G., Luu, P., and Posner, M. I. 2000. Cognitive and emotional influences in anterior cingulate cortex. *Trends Cognit. Sci.* **4**: 215–222.
- Carter, C. S., Braver, T. S., Barch, D. M., Botvinick, M. M., Noll, D., and Cohen, J. D. 1998. Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science* **280**: 747–749.
- Coles, M. G. H., Scheffers, M. K., and Holroyd, C. 2000. Why is there an ERN or Ne on correct trials? *Psychophysiology* **37**: S9.
- De Jong, R., Liang, C. C., and Lauber, E. 1994. Conditional and unconditional automaticity: A dual-process model of effects of spatial stimulus–response correspondence. *J. Exp. Psychol.: Hum. Percept. Perform.* **20**: 721–750.
- Dehaene, S., Posner, M. I., and Tucker, D. M. 1994. Localization of a neural system for error detection and compensation. *Psychol. Sci.* **5**: 303–305.
- Diehl, B., Dinner, D. S., Mohamed, A., Najm, I., Klem, G., LaPresto, E., Bingaman, W., and Lüders, H. O. 2000. Evidence of cingulate motor representations in humans. *Neurology* **55**: 725–728.

- Dove, A., Pollmann, S., Schubert, T., Wiggins, C. J., and von Cramon, D. Y. 2000. Prefrontal cortex activation in task switching: An event-related fMRI study. *Cognit. Brain Res.* **9**: 103–109.
- Dum, R. P., and Strick, P. L. 1993. Cingulate motor areas. In *Neurobiology of Cingulate Cortex and Limbic Thalamus* (B. A. Vogt and M. Gabriel, Eds.), pp. 415–441. Birkhäuser, Boston.
- Falkenstein, M., Hohnsbein, J., Hoormann, J., and Blanke, L. 1990. Effects of errors in choice reaction tasks on the ERP under focused and divided attention. In *Psychophysiological Brain Research* (C. H. M. Brunia, A. W. K. Gaillard, and A. Kok, Eds.), pp. 192–195. Tilburg Univ. Press, Tilburg, The Netherlands.
- Falkenstein, M., Hoormann, J., Christ, S., and Hohnsbein, J. 2000. ERP components on reaction errors and their functional significance: A tutorial. *Biol. Psychol.* **51**: 87–107.
- Friston, K., Holmes, A. P., Worsley, K. J., Poline, J.-P., Frith, C. D., and Frackowiak, R. S. J. 1995. Statistical parametric maps in functional imaging: A general linear approach. *Hum. Brain Mapp.* **2**: 189–210.
- Friston, K., Fletcher, P., Josephs, O., Holmes, A., Rugg, M. D., and Turner, R. 1998. Event-related fMRI: Characterizing differential responses. *NeuroImage* **7**: 30–40.
- Fuchs, M., Drenckhahn, R., Wischmann, H. A., and Wagner, A. 1998. An improved boundary element model for realistic volume conductor modeling. *IEEE Transact. Biomed. Eng.* **45**: 980–997.
- Gehring, W. J., Goss, B., Coles, M. G. H., Meyer, D. E., and Donchin, E. 1993. A neural system for error detection and compensation. *Psychol. Sci.* **4**: 385–390.
- Gehring, W. J., and Knight, R. T. 2000. Prefrontal-cingulate interactions in performance monitoring. *Nat. Neurosci.* **3**: 516–520.
- Gevens, A., Smith, M. E., Le, J., Leong, H., Bennett, J., Martin, M., McEvoy, L., Du, R., and Whitfield, S. 1996. High resolution evoked potential imaging of the cortical dynamics of human working memory. *Electroencephalogr. Clin. Neurophysiol.* **98**: 327–348.
- Gratton, G., Coles, M. G. H., and Donchin, E. 1983. A new method for off-line removal of ocular artifact. *Electroencephalogr. Clin. Neurophysiol.* **55**: 468–484.
- Gratton, G., Coles, M. G. H., and Donchin, E. 1992. Optimizing the use of information: Strategic control of activation and responses. *J. Exp. Psychol.: Gen.* **121**: 480–506.
- Gratton, G., Coles, M. G. H., Sirevaag, E. J., Eriksen, C. W., and Donchin, E. 1988. Pre- and post-stimulus activation of response channels: A psychophysiological analysis. *J. Exp. Psychol.: Hum. Percept. Perform.* **14**: 331–344.
- Greenhouse, S., and Geisser, S. 1959. On methods in the analysis of profile data. *Psychometrika* **24**: 95–112.
- Hazeltine, E., Poldrack, R., and Gabrieli, J. D. E. 2000. Neural activation during response competition. *J. Cognit. Neurosci.* **12**(Suppl. 2): 118–129.
- Holroyd, C. B. 2001. *Reinforcement Learning and the Error-Related Negativity: A Computational and Neurophysiological Investigation*. Univ. of Illinois, Urbana-Champaign. [Ph.D. dissertation]
- Holroyd, C. B., Dien, J., and Coles, M. G. H. 1998. Error-related scalp potentials elicited by hand and foot movements: Evidence for an output-independent error-processing system in humans. *Neurosci. Lett.* **242**: 65–68.
- Holroyd, C. B., Reichler, J., and Coles, M. G. H. 1999. Is the error-related negativity generated by a dopaminergic error signal for reinforcement learning? Hypothesis and model. *J. Cognit. Neurosci.* **11**: 45.
- Josephs, O., Turner, R., and Friston, K. 1997. Event-related fMRI. *Hum. Brain Mapp.* **5**: 243–248.
- Kiehl, K. A., Liddle, P. F., and Hopfinger, J. B. 2000. Error processing and the rostral anterior cingulate: An event-related fMRI study. *Psychophysiology* **37**: 216–223.
- Konishi, S., Nakajima, K., Uchida, I., Kameyama, M., Nakahara, K., Sekihara, K., and Miyashita, Y. 1998. Transient activation of inferior prefrontal cortex during cognitive set shifting. *Nat. Neurosci.* **1**: 80–84.
- Konishi, S., Nakajima, K., Uchida, I., Kikyo, H., Kameyama, M., and Miyashita, Y. 1999. Common inhibitory mechanism in human inferior prefrontal cortex revealed by event-related functional MRI. *Brain* **122**: 981–991.
- Kopp, B., Rist, F., and Mattler, U. 1996. N200 in the flanker task as a neurobehavioral tool for investigating executive control. *Psychophysiology* **33**: 282–294.
- Lee, K.-M., Chang, K.-H., and Roh, J.-K. 1999. Subregions within the supplementary motor area activated at different stages of movement preparation and execution. *NeuroImage* **9**: 117–123.
- Lohmann, G., Müller, K., Bosch, V., Mentzel, H., Hessler, S., Chen, L., and von Cramon, D. Y. 2001. Lipsia—A new software system for the evaluation of functional magnetic resonance images of the human brain. *Comput. Med. Imaging Graph.*, in press. [See also <http://www.cns.de/lipsia>.]
- Luppino, G., Matelli, M., Camarda, R. M., Gallese, V., and Rizzolatti, G. 1991. Multiple representations of body movements in mesial area 6 and the adjacent cingulate cortex: An intracortical microstimulation study in the macaque monkey. *J. Comp. Neurol.* **311**: 463–482.
- MacDonald, A. W., III, Cohen, J. D., Stenger, V. A., and Carter, C. S. 2000. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science* **288**: 1835–1838.
- Mathalon, D. H., Turken, A. U., Whitfield, S., Gray, M., Kalba, S., Glover, G., Faustman, W. O., Colrain, I., and Ford, J. M. 2000. Anterior cingulate activations to self-made errors and induced errors in schizophrenia during a go/no-go task. Paper presented at Executive Control, Errors, and the Brain. Jena, Germany.
- Matsuzaka, Y., Aizawa, H., and Tanji, J. 1992. A motor area rostral to the supplementary motor area (presupplementary motor area) in the monkey: Neuronal activity during a learned motor task. *J. Neurophysiol.* **68**: 653–662.
- McCarthy, G., and Wood, C. C. 1985. Scalp distributions of event-related potentials: An ambiguity associated with analysis of variance models. *Electroencephalogr. Clin. Neurophysiol.* **62**: 203–208.
- Menon, V., Adelman, N. E., White, C. D., Glover, G. H., and Reiss, A. L. 2001. Error-related activation during a go/nogo response inhibition task. *Hum. Brain Mapp.* **12**: 131–143.
- Miezin, F. M., Maccotta, L., Ollinger, J. M., Petersen, S. E., and Buckner, R. L. 2000. Characterizing the hemodynamic response: Effects of presentation rate, sampling procedure, and the possibility of ordering brain activity based on relative timing. *NeuroImage* **11**: 735–759.
- Miltner, W. H. R., Braun, C. H., and Coles, M. G. H. 1997. Event-related brain potentials following incorrect feedback in a time-estimation task: Evidence for a “generic” neural system for error detection. *J. Cognit. Neurosci.* **9**: 788–798.
- Nieuwenhuis, S., Ridderinkhof, K. R., Blom, J., Band, G. P. H., and Kok, A. 2001. Error-related brain potentials are differentially related to awareness of response errors: Evidence from an antisaccade task. *Psychophysiology*, **38**: 752–760.
- Oken, B. S., and Chiappa, K. H. 1986. Statistical issues concerning computerized analysis of brainwave topography. *Ann. Neurol.* **19**: 493–494.
- Osman, A., Bashore, T. R., Coles, M. G. H., Donchin, E., and Meyer, D. E. 1992. On the transmission of partial information: Inferences from movement-related brain potentials. *J. Exp. Psychol.: Hum. Percept. Perform.* **18**: 217–232.

ERROR PROCESSING AND RESPONSE COMPETITION

1401

- Perrin, F., Pernier, J., Bertrand, O., and Echallier, J. F. 1989. Spherical splines for scalp potential and current density mapping. *Electroencephalogr. Clin. Neurophysiol.* **72**: 184–187.
- Pfeifer, E. 1993. IPCM—Iterative PCA correction method. A new method for the correction of ocular artifacts in ERP-data. *Psychophysiology* **30**: 51.
- Picard, N., and Strick, P. L. 1996. Motor areas of the medial wall: A review of their location and functional activation. *Cereb. Cortex* **6**: 342–353.
- Rabbitt, P. M. A. 1966. Errors and error correction in choice reaction tasks. *J. Exp. Psychol.* **71**: 264–272.
- Rizzolatti, G., Luppino, G., and Matelli, M. 1996. The classic supplementary motor area is formed by two independent areas. In *Advances in Neurology*, Vol. 70, *Supplementary Sensorimotor Area* (H. O. Luders, Ed.), pp. 45–56. Lippincott–Raven, Philadelphia.
- Rugg, M. D. 1998. Convergent approaches to electrophysiological and hemodynamic investigations of memory. *Hum. Brain Mapp.* **6**: 394–398.
- Schubotz, R. I., Friederici, A. D., and von Cramon, D. Y. 2000. Time perception and motor timing: A common cortical and subcortical basis revealed by fMRI. *NeuroImage* **11**: 1–12.
- Schubotz, R. I., and von Cramon, D. Y. 2001. Interval and ordinal properties of sequences are associated with distinct premotor areas. *Cereb. Cortex*, **11**: 210–222.
- Talairach, J., and Tournoux, P. 1988. *Co-planar Stereotaxis Atlas of the Human Brain*. Thieme, New York.
- Tanji, J. 1994. The supplementary motor area in the cerebral cortex. *Neurosci. Res.* **19**: 251–268.
- Vorobiev, V., Govoni, P., Rizzolatti, G., Matelli, M., and Luppino, G. 1998. Parcellation of human mesial area 6: Cytoarchitectonic evidence for three separate areas. *Eur. J. Neurosci.* **10**: 2199–2203.
- Worsley, K., and Friston, K. 1995. Analysis of fMRI time-series revisited—Again. *NeuroImage* **2**: 359–365.
- Zarahn, E., Aguirre, G. K., and D'Esposito, M. 1997. Empirical analysis of BOLD fMRI statistics. I. Spatially smoothed data collected under null-hypothesis and experimental conditions. *NeuroImage* **5**: 179–197.
- Zysset, S., Müller, K., Lohmann, G., and von Cramon, D. Y. 2001. Color-word matching Stroop task: Separating interference and response conflict. *NeuroImage* **13**: 29–36.

Chapter 4

Error monitoring using external feedback: Specific roles of the habenular complex, the reward system, and the cingulate motor area revealed by fMRI

As demonstrated in the previous Chapter, the RCZ plays an important role in monitoring for easily detectable action slips. The reinforcement learning theory (Chapter 2.2) suggests that the same performance monitoring system is active when the error is identified on the basis of external feedback. In other words, when the action outcome is worse than expected and when this is indicated by negative feedback, the RCZ should be activated. Previous research on reward processing suggests furthermore that the ventral striatum should respond to unexpected positive feedback indicating that an action outcome is better than predicted. These hypotheses were addressed in two fMRI studies using a dynamically adaptive motion prediction task. While the first experiment revealed a large overlap of the network engaged in processing negative feedbacks with the one reported on action slips, the second experiment disentangled error-related activity from activity related to decision uncertainty. The major findings were that errors and negative feedback led to specific signal increases in the RCZ and the anterior inferior insula. Positive feedback was associated with activity in the ventral striatum (Nucleus accumbens), and decision uncertainty resulted in signal increases in the anterior pre-SMA.

A further important finding was that the habenular complex seems to play a major role modulating the activity of the mesencephalic monoamine systems, particularly of dopamergic activity. This is plausible given the anatomical connectivity of the habenula, which has been shown to receive afferent fibers from limbic forebrain structures and the prefrontal cortex and to send primarily inhibitory efferent fibers to the midbrain nuclei (Scheibel, 1997; see Figure II-01).

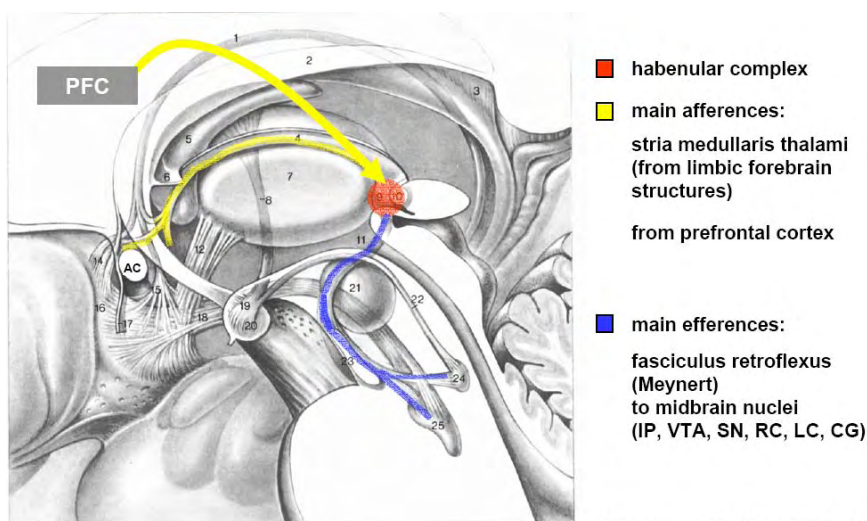


Figure II-01. Main afferent (yellow) and efferent (blue) connections of the habenular complex (red). PFC: prefrontal cortex, IP: interpeduncular nucleus, VTA: ventral tegmental area, SN: substantia nigra, RC: raphe complex, LC: locus coeruleus, CG: central gray.

Sources: Nieuwenhuys et al., 1988, Scheibel, 1997

The habenular complex showed an intriguing pattern of activity suggesting it to be involved in the integration of reward prediction and action outcome, and thus modulating the activity of the reward and performance monitoring systems.

It should also be noted that an unpublished companion ERP study using the same task as in Experiment 2 of this Chapter revealed a medial frontal negativity related to negative feedbacks, the feedback-related negativity FRN (Figure II-02). It was only present when the feedback stimulus carried the information whether the previous response was correct or incorrect. This finding supports the notion that ERN and FRN are functionally equivalent with respect to the fact that they reflect a signal indicating that an error has occurred and requires remediation.

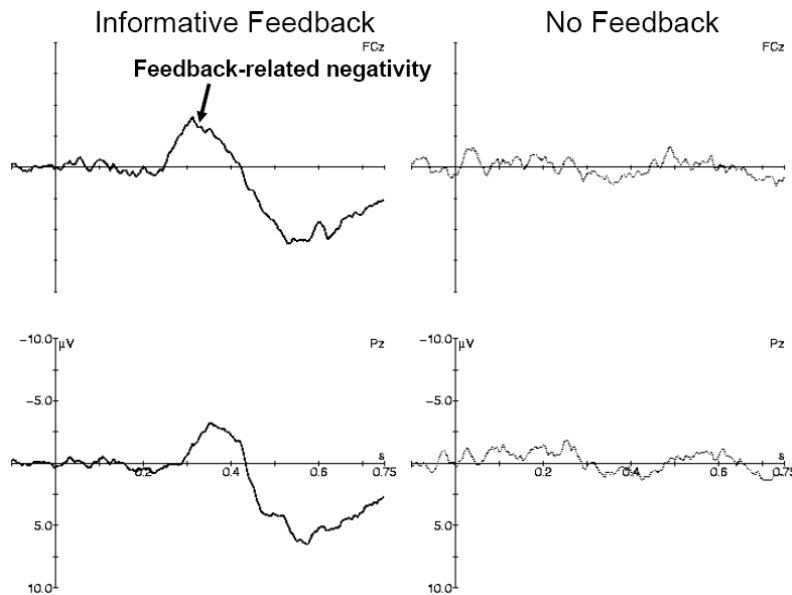


Figure II-02.

ERP findings in the dynamic motion prediction task with informative feedback (left) and non-informative stimuli instead of feedback (right). Difference waves of the feedback-locked ERPs for incorrect and correct responses shown at two midline electrodes. Informative feedback elicited a feedback-related negativity, which was larger for negative feedback. No such negativity was found for non-informative stimuli. Twenty participants. (Ullsperger, unpublished data).

In sum it can be stated that for errors detected internally as well as errors indicated by the action outcome and external feedback the same performance monitoring system is activated. Particularly the RCZ seems to be involved in signaling that an error occurred, irrespective of the way of its detection. This finding has been replicated at a within-subjects level (Holroyd et al., 2004).

Surprisingly, studies using a time estimation task failed to replicate the finding of an involvement of the RCZ in negative feedback processing (van Veen et al., 2004; Nieuwenhuis et al., 2005). One explanation could be that the feedback in a time estimation task merely indicates whether the response was correct or wrong, but does not provide information for adjustment processes that would allow to improve performance (it does not indicate whether the subject's estimate was too long or too short). It can therefore be hypothesized that the pFMC is only involved when the performance monitoring signal can be used for subsequent adjustments. A recent study in which the rare case occurred that positive feedback carried as much information for subsequent adjustments as negative feedback, both feedback types elicited similarly strong performance-monitoring-related activity in the RCZ (Walton et al., 2004). This suggests that the engagement of the pFMC is not only determined by the valence of an action outcome alone, but perhaps even more by the usefulness of information conveyed by an event for subsequent cognitive adjustments.

Error Monitoring Using External Feedback: Specific Roles of the Habenular Complex, the Reward System, and the Cingulate Motor Area Revealed by Functional Magnetic Resonance Imaging

Markus Ullsperger and D. Yves von Cramon

Max Planck Institute of Cognitive Neuroscience, D-04103 Leipzig, Germany

The dopaminergic system has been shown to be involved in the processing of rewarding stimuli, specifically of errors in reward prediction, in animal studies as well as in recent neuroimaging studies in humans. Furthermore, a specific role of dopamine in the human homolog of the rostral cingulate motor area (rCMA) was proposed in a recent model of error detection. Negative feedback as well as self-detected errors elicit a negative event-related brain potential probably generated in the rCMA. We performed two experiments using functional magnetic resonance imaging to investigate the brain activity related to negative and positive feedback in a dynamically adaptive motion prediction task. Whereas positive feedback raised hemodynamic activity in the ventral striatum (nucleus accumbens), negative feedback activated the rCMA, the inferior anterior insula, and the epithalamus (habenular complex). These data demonstrate the role of the habenular complex in the control of the human reward system, a function previously hypothesized on the basis of animal research. The rCMA reacted only to errors with negative feedback but not to errors without feedback, which ruled out an influence of response conflict or uncertainty on its role in error detection by external signals.

Key words: error detection; performance monitoring; reward; feedback; CMA; habenula; fMRI

Introduction

Goal-directed behavior and skill acquisition require continuous performance monitoring. Good performance is reinforced; deviations from the goals (errors) call for remedial actions and strategy adjustments. Although action slips resulting from premature responses can be internally detected by the individual, mistakes attributable to insufficient knowledge are recognized by their consequences (external feedback) (Rabbitt, 1966; Reason, 1990). It has been shown that even abstract positive feedback activates the same brain structures as primary reward, in particular the ventral striatum with the nucleus accumbens (Elliott et al., 2000). Several lines of evidence suggest an important role of the dopaminergic system in reward processing, more specifically in signaling errors in reward prediction (Schultz, 2000, 2002; Schultz and Dickinson, 2000; Pagnoni et al., 2002). Unpredicted primary or conditioned secondary reward stimuli elicit a strong phasic dopaminergic response. In contrast, after omission of expected rewarding stimuli, the basal dopaminergic activity in the ventral tegmental area (VTA) and substantia nigra (SN) temporarily ceases.

Electrophysiological and hemodynamic studies suggest a specific role of the rostral cingulate motor area (rCMA) in error detection and generation of an error-specific event-related brain

potential (ERP), the error-related negativity (ERN) (Falkenstein et al., 1990; Gehring et al., 1993; Carter et al., 1998; Ullsperger and von Cramon, 2001). An ERP component of identical scalp topography was described for external negative feedback on errors undetectable for participants for lack of sufficient information (Miltner et al., 1997). According to a recent model, the ERN results from disinhibited neuronal activity in the rCMA attributable to phasic depression of the dopaminergic activity on errors (Holroyd and Coles, 2002). Self-detection of error, as well as external negative feedback in hard-to-detect errors, predicts the nonoccurrence of reward, which should result in decreased dopamine release.

It is still rather unclear how the mesencephalic dopaminergic neurons are inhibited when expected rewards do not occur. Animal studies provide evidence that the VTA and SN receive inhibiting neurons from a structure of the dorsal medial thalamus (epithalamus) called the habenula, because of its morphological resemblance to a rein. Electrical stimulation of the habenular nuclei causes inhibition of ~85–90% of the dopamine neurons in the VTA and SN in rats (Christoph et al., 1986). In contrast, habenular lesions result in increased dopamine turnover in the nucleus accumbens, striatum, and prefrontal cortex, reflecting an activation of the dopaminergic system (Lisoprawski et al., 1980; Nishikawa et al., 1986). The habenular complex receives fibers from the basal forebrain, medial striatum, and anterior hypothalamus via the stria medullaris thalami. The main efferent pathway is the fasciculus retroflexus of Meynert projecting to the interpeduncular nucleus, VTA and SN, medial raphe complex, locus ceruleus, and central gray (Scheibel, 1997). These anatomical findings suggest high importance of the habenular complex as a

Received Dec. 19, 2002; revised March 5, 2003; accepted March 7, 2003.

This work was supported with help from F. Szymanski, M. Naumann, A. Mempel, and C. Buschendorf in data collection, the contributions of J. Lepsien and A. Szameitat in task development, and the comments of two anonymous reviewers on a previous version of this manuscript.

Correspondence should be addressed to Markus Ullsperger, Max Planck Institute of Cognitive Neuroscience, Stephanstrasse 1a, D-04103 Leipzig, Germany. E-mail: ullsperg@cns.mpg.de.

Copyright © 2003 Society for Neuroscience 0270-6474/03/234308-07\$15.00/0

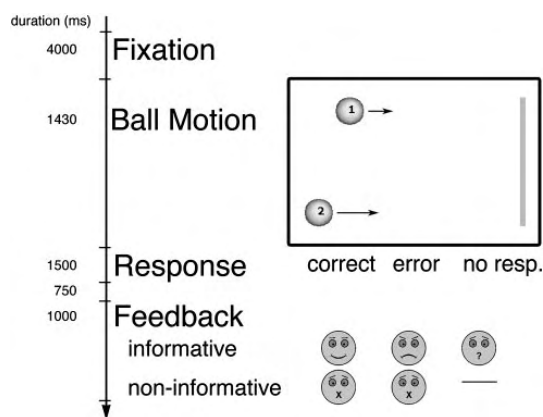


Figure 1. Timing of the dynamically adaptive motion prediction task ("first-over-the-finish-line-task"). Note that the noninformative stimuli instead of feedback were presented only in experiment 2.

critical modulatory relay between the limbic forebrain structures and the midbrain.

Our study aimed at investigating error processing on the basis of external feedback using functional magnetic resonance imaging (fMRI). We hypothesized a larger hemodynamic activity of the epithalamus (habenular complex) on errors with negative feedback and a lower hemodynamic activity on correct responses with positive feedback. Moreover, based on electrophysiological findings (Miltner et al., 1997), we predicted selectively increased rCMA activity for negative feedback on mistakes.

Materials and Methods

Participants and task. Sixteen healthy right-handed volunteers participated in each experiment (experiment 1: nine females, 21–28 years of age, mean age, 24.1; experiment 2: eight females, 20–33 years of age, mean age, 25). Informed consent was obtained from each participant according to the declaration of Helsinki. The experiments were approved by the University of Leipzig Ethics Committee. Stimuli were presented using Presentation 0.45 (Neurobehavioral Systems, San Francisco, CA) and appeared on a back-projection screen mounted inside the scanner bore, which was viewed through mirror glasses. A new dynamically adaptive motion prediction (DAMP) task was applied in both experiments (Fig. 1). During each trial, participants observed a short sequence of the motion of two balls that moved from different respective starting points (in one-half of the screen) and different speeds toward a finish line on the other side. After 1.43 sec, the balls disappeared (still far from the finish line), and the question "which ball?" was presented on the screen. The task was to predict which ball would first cross the finish line and to indicate the decision by a button press. During the experiments, task difficulty (operationalized as the time difference of arrival of the two balls at the finish line) was dynamically adapted to each participant's behavior, such that the error rate was constantly kept at ~37%. Therefore, participants were highly uncertain about whether their prediction was correct. A feedback about correctness of the prediction (a smiley face) was presented 750 msec after the response. The next trial started after a fixation period of at least 4000 msec. To keep the error rate high during the first trials of the experiments, individual difficulty levels were determined in a training session (100 trials and only informative feedback) that was performed during the anatomical scans.

In experiment 1, we investigated the hemodynamic response elicited by feedback stimuli that were informative on all trials (i.e., errors were always followed by negative feedback, and correct responses were followed by positive feedback). In experiment 2, we introduced an additional noninformative stimulus that occurred instead of the informative

feedback with a probability of 26.5% on correct and incorrect responses each. It contained no information on whether the response was correct (i.e., the smiley face had an "x" instead of a mouth) (Fig. 1). Experiment 1 consisted of 120 trials and 12 randomly interspersed nonevents; experiment 2 consisted of 200 trials and 20 nonevents.

Image acquisition and analysis. Imaging was performed at 3 T on a Bruker (Ettlingen, Germany) Medspec 30/100 system equipped with the standard bird cage head coil. Sixteen functional slices were obtained parallel to the anterior commissure–posterior commissure (AC–PC) line (thickness, 5 mm; spacing, 1 mm) using a single-shot gradient echo-planar imaging (EPI) sequence (repetition time, 2 sec; echo time, 30 msec; 64×64 pixel matrix; flip angle, 90° ; field of view, 192 mm) sensitive to blood–oxygen level-dependent contrast. Trials occurred at multiple, systematically offset time points (range, 0–0.5 sec) in relation to the image acquisition to improve temporal resolution (Josephs et al., 1997; Miezin et al., 2000). Before the functional runs, anatomical modified driven equilibrium Fourier transform (MDEFT) and EPI-T1 slices in the plane with functional images were collected. Susceptibility artifacts (image distortion and signal loss) were only present in the orbitofrontal and frontopolar regions, which, therefore, are not discussed in this paper (see Wansapura et al., 1999, for more details regarding susceptibility artifacts at 3 T).

Data processing was performed using the software package Leipzig Image Processing and Statistical Inference Algorithms (Lohmann et al., 2001). Functional data were corrected for motion artifacts and slice time acquisition differences using sinc-interpolation. Signal changes and baseline-drifts were removed by applying a temporal high-pass filter with a cutoff frequency of 1/200 Hz. Spatial smoothing was applied using a Gaussian filter with 5.65 mm full width at half maximum (FWHM).

To align the functional data slices with a three-dimensional stereotactic coordinate reference system, a rigid linear registration with 6 df (three rotational and three translational) was performed. The rotational and translational parameters were acquired on the basis of the MDEFT and EPI-T1 slices to achieve an optimal match between these slices and the individual three-dimensional reference data set that was acquired for each subject during a previous scanning session. The MDEFT volume data set with 160 slices and 1 mm slice thickness was standardized to the Talairach stereotactic space (Talairach and Tournoux, 1988). The rotational and translational parameters were subsequently transformed by linear scaling to a standard size. The resulting parameters were then used to transform the functional slices using trilinear interpolation so that the resulting functional slices were aligned with the stereotactic coordinate system, generating output data with a spatial resolution of 3 mm^3 . The statistical analysis was based on a least squares estimation using the general linear model for serially autocorrelated observations (Friston et al., 1995; Worsley and Friston, 1995; Aguirre et al., 1997; Zarahn et al., 1997). The design matrix was generated with a synthetic hemodynamic response function (Friston et al., 1998). The model equation, including the observation data, the design matrix, and the error term, were convolved with a Gaussian kernel of dispersion of 4 sec FWHM. The effective degrees of freedom were estimated as described by Worsley and Friston (1995). Contrasts between negative and positive feedback conditions were calculated. The resulting contrast images of all participants were subjected to a voxel-wise one-sample *t* test that indicated whether observed differences between conditions were significantly distinct from zero (Holmes and Friston, 1998). Resulting *z*-maps were thresholded at $z > 3.09$, uncorrected. Event-related analysis was performed on the onset of the feedback stimuli. In addition, averaged time courses of the hemodynamic response for all conditions were investigated in experiment 2. The mean amplitudes of the hemodynamic response (percentage signal change related to the mean signal of the entire signal) were submitted to repeated-measures ANOVAs in which all effects with >1 df in the numerator were adjusted according to the formula put forth by Greenhouse and Geisser (1959).

Neuroanatomical criteria. To ensure highest anatomical precision, we independently determined the coordinates of the habenular complex in the individual anatomical data sets (inter-rater reliability, 98.4%). For habenular nuclei, the time courses at those individual coordinates were

computed, and for all other regions under investigation, the coordinates of the maximal z -values in the group statistics were used.

We defined anatomical regions at the frontomedian wall according to the literature on homolog medial premotor areas in human and nonhuman primates (Vogt et al., 1995; Picard and Strick, 1996; Vorobiev et al., 1998). The Talairach coordinates of the regions are depicted in Picard and Strick's (1996) review and served as a reference for localization of the activation in our study. Activation was defined as falling into the pre-supplementary motor area (pre-SMA) when they were located anterior to the coronal plane through the anterior commissure ($y > 0$) (Vorobiev et al., 1998), and >45 mm above the AC-PC plane ($z > 45$). The anterior border of the pre-SMA is less well defined in the literature. Traditionally, it is identified as the border between Brodmann area (BA) 6 and BA 8 (Picard and Strick, 1996). The rCMA or rostral cingulate zone is primarily buried in the cingulate sulcus and located anterior to the coronal plane through the anterior commissure and posterior to the genu of the corpus callosum. It comprises BA 24c' and might extend into BA 32', as indicated by Picard and Strick (1996).

Results

Behavioral data

Reaction times were significantly shorter for correct predictions than for erroneous predictions in both experiments (experiment 1: $M = 633.3$ and 661.2 msec, $F_{(1,15)} = 16.03$, $p < 0.005$; experiment 2: $M = 524.5$ and 557.5 msec, $F_{(1,15)} = 18.81$, $p < 0.001$). Because of dynamic difficulty adjustments, in both experiments, error rates amounted to 36.8% (SEM in experiments 1 and 2, 1.4 and 1.0, respectively).

In the debriefing of experiment 2, participants rated the overall certainty of their responses during the main experiment and training block on a scale ranging from 0 to 4. During training, difficulty was lower and participants' responses were erroneous only 22.8% of the time (SEM, 0.8). In concordance with the higher error rates during the main experiment, the certainty at response was significantly reduced ($p < 0.001$) compared with the training, suggesting that participants' performance monitoring depended on feedback evaluation.

Experiment 1: fMRI data

We investigated the hemodynamic response elicited by feedback stimuli that were informative on all trials (i.e., errors were always followed by negative feedback and hits by positive feedback). Although on negative feedback, hemodynamic activity was higher in the human homolog of the rCMA, pre-SMA, anterior inferior insula, and epithalamus (habenular complex), for positive feedback, the ventral striatum (nucleus accumbens) and the putamen were more activated (see Table 1 for list of activations). Before functional data analysis, the habenular complex was independently identified by the two authors in each subject's anatomical MRI. The habenular negative-feedback-related activation was clearly located within the area resulting from overlapping the single subject coordinates of the habenular nuclei (Fig. 2).

Activity related to negative feedback on errors in experiment 1 could reflect the response of the brain to the omission of reward. However, the reaction times on error trials were significantly longer than those on correct trials, suggesting a higher uncertainty or response conflict during errors. Thus, the activation on negative feedback could also be a correlate of response conflict and uncertainty about which response would be rewarding. Temporal overlap of the hemodynamic response on reaction and feedback does not allow disentanglement of activity related to negative feedback from conflict- and uncertainty-related activations. One way to firmly establish that the feedback-related effects are not attributable to differences in uncertainty or processing

Table 1. List of activations revealed by contrasting errors with negative feedback versus correct trials with positive feedback in experiment 1

| Side | Brain region | Talairach coordinates | | | Z score |
|------------------------------|--------------------------------------|-----------------------|-----|----|---------|
| | | x | y | z | |
| Negative > positive feedback | | | | | |
| R | rCMA (BA 24c') | 6 | 19 | 35 | 3.81 |
| R | Pre-SMA (BA 6)* | 0 | 13 | 53 | 3.89 |
| L | Anterior inferior insula (BA 13/14) | -37 | 10 | -3 | 4.34 |
| R | Anterior inferior insula (BA 13/14) | 42 | 7 | 0 | 4.28 |
| L | Superior bank of IFS (BA 9) | 48 | 19 | 32 | 3.79 |
| L | Inferior precentral sulcus (BA 6) | 54 | 10 | 26 | 3.48 |
| R | Anterior SFS (BA 8) | 15 | 40 | 29 | 3.90 |
| L | Anterior IPS (BA 7/40) | -35 | -46 | 41 | 3.90 |
| R | IPL (BA 40) | 51 | -49 | 32 | 4.75 |
| L/R | Habenular complex (bilateral) | 3/-5 | -25 | 8 | 4.05 |
| L | Thalamus (ventrolateral/anterior Nc) | -11 | -10 | 11 | 4.44 |
| R | Thalamus (ventrolateral/anterior Nc) | 12 | -10 | 14 | 4.08 |
| R | Thalamus (ventrolateral Nc) | 9 | -10 | 5 | 3.86 |
| L | Thalamus (laterodorsal Nc) | -14 | -22 | 21 | 3.89 |
| Positive > negative feedback | | | | | |
| L | Ventral striatum (Nc accumbens) | -17 | 7 | -5 | 4.00 |
| L | Putamen | -22 | -1 | 14 | 3.80 |
| R | Putamen | 24 | -19 | 8 | 4.00 |

IFS, inferior frontal sulcus; IPL, inferior parietal lobule; IPS, intraparietal sulcus; SFS, superior frontal sulcus; Nc, nucleus; L, left; R, right. Asterisk indicates pre-SMA not significantly activated with reaction time as regressor.

time of the task was to reanalyze the data with the reaction time as a regressor. We found the same activation pattern as reported in Table 1, except for the finding that the pre-SMA did not show significant activity in this reanalysis.

Experiment 2: fMRI data

Another way to disentangle feedback-related activity from uncertainty-related activity was chosen in experiment 2, in which a noninformative stimulus occurred with a probability of 26.5% on each correct and incorrect response instead of the informative feedback. Activation related to response conflict or uncertainty should occur independently, regardless of whether feedback or noninformative stimuli were presented (i.e., it should be highest on errors regardless of whether it was followed by a negative feedback). In contrast, brain activity related to negative feedback processing should be highest exclusively on errors followed by informative feedback.

In contrasting errors with informative (negative) feedback versus correct trials with informative (positive) feedback, the results from experiment 1 were replicated (Table 2). In Figure 3, the mean signal changes of the hemodynamic responses for all four conditions (correct and error times presence and absence of feedback) are depicted for several regions of interest (ROIs). Additional analyses revealed that in these ROIs, except for the pre-SMA, there was an interaction between the response type (Resp, two levels) and feedback occurrence (Feedb, two levels) (Table 3) of the factors.

In the ventral striatum (nucleus accumbens) (Fig. 3d), a reliable signal increase was found with positive feedback only on correct trials (i.e., the signal change was significantly larger than zero; $T_{(15)} = 6.38$; $p < 0.0001$).

Mean amplitude data from the rCMA and insula (Fig. 3a,e) were subjected to repeated-measure ANOVAs with the factors Resp and Feedb that revealed main effects of both factors (rCMA Resp, $F_{(1,15)} = 4.87$, $p < 0.05$; rCMA Feedb, $F_{(1,15)} = 7.42$, $p < 0.05$; insula Resp, $F_{(1,15)} = 27.51$, $p < 0.0001$; insula Feedb, $F_{(1,15)} = 4.09$, $p < 0.062$) and a Resp by Feedb interaction (rCMA, $F_{(1,15)} = 4.62$, $p < 0.05$; insula, $F_{(1,15)} = 8.61$, $p < 0.05$). Planned

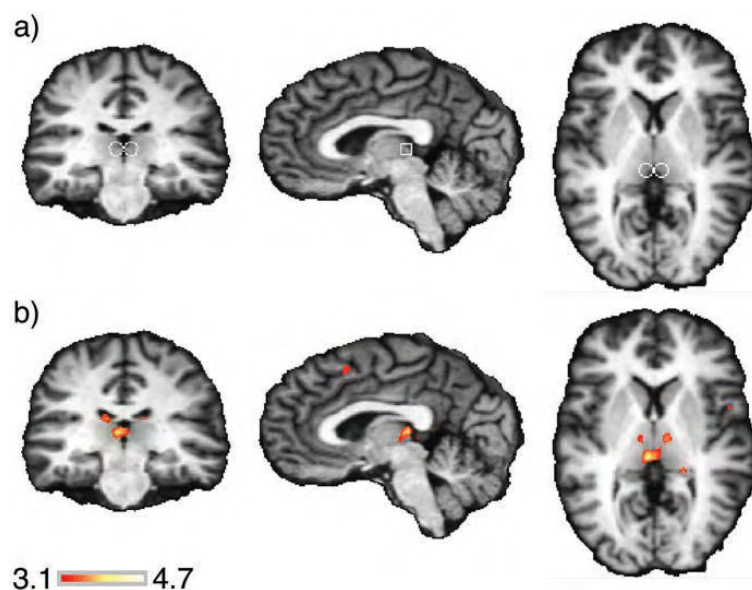


Figure 2. Activation of the epithalamus in experiment 1. *a*, Overlap area resulting from variability of the habenular complex across subjects. *b*, z-map of activation. From left to right: coronal, sagittal, and horizontal slices at $x = -2$, $y = -25$, and $z = 8$.

Table 2. List of activations revealed by contrasting errors with negative feedback versus correct trials with positive feedback in experiment 2

| Side | Brain region | Talairach coordinates | | | Z score |
|------------------------------|-------------------------------------|-----------------------|-----|----|---------|
| | | x | y | z | |
| Negative > positive feedback | | | | | |
| R | rCMA (BA 24c') | 4 | 18 | 35 | 3.69 |
| R | Pre-SMA (BA 6) | 4 | 15 | 53 | 3.79 |
| L | Anterior inferior insula (BA 13/14) | -37 | 15 | -3 | 4.20 |
| R | Superior bank of IFS (BA 9) | 39 | 10 | 29 | 3.75 |
| L/R | Habenular complex | -5/6 | -25 | 8 | 3.66 |
| R | Thalamus (ventrolateral Nc) | 15 | -13 | 14 | 4.10 |
| L | Thalamus (posterolateral Nc) | -12 | -16 | 14 | 3.71 |
| R | Cuneus (BA 18) | -2 | -73 | 20 | 3.65 |
| Positive > negative feedback | | | | | |
| L | Ventral striatum (Nc accumbens) | -13 | 6 | -3 | 4.38 |
| | Ventral striatum (ventral caudate) | -7 | 15 | 0 | 4.13 |
| R | Ventral striatum (Nc accumbens) | 8 | 8 | -3 | 3.87 |
| L | IPS (horizontal branch, BA 7/40) | -29 | -52 | 41 | 3.76 |
| L | Caudate Nc | -14 | -13 | 23 | 4.32 |

IFS, inferior frontal sulcus; IPS, intraparietal sulcus; Nc, nucleus; L, left; R, right.

comparisons confirmed that in both ROIs, errors with informative feedback evoked significantly higher hemodynamic activity than all other conditions. Although the signal for errors with negative feedback was larger than that for errors without feedback (rCMA, $F_{(1,15)} = 8.56$, $p < 0.05$; insula, $F_{(1,15)} = 8.76$, $p < 0.01$) and correct trials with feedback (rCMA, $F_{(1,15)} = 12.41$, $p < 0.005$; insula, $F_{(1,15)} = 29.07$, $p < 0.0001$), no significant signal difference was found between correct trials with and without feedback and errors without feedback ($p > 0.38$).

The data from the pre-SMA (Fig. 3*b*) were subjected to the same ANOVA, which gave rise only to a main effect of Resp ($F_{(1,15)} = 12.25$; $p < 0.005$), reflecting errors leading to higher activation of the pre-SMA than correct responses regardless of the presence or absence of the feedback.

Finally, the same analysis performed on the data from the

habenular complex (Fig. 3*c*) gave rise to a Resp by Feedb interaction ($F_{(1,15)} = 7.29$; $p < 0.05$). Here, single-condition comparisons showed that errors with negative feedback led to significantly higher hemodynamic responses than errors without feedback ($F_{(1,15)} = 6.22$; $p < 0.05$) and correct responses with positive feedback ($F_{(1,15)} = 6.41$; $p < 0.05$). Furthermore, correct trials without feedback showed a tendency to activate the habenular complex more than correct trials with positive feedback ($F_{(1,15)} = 4.00$; $p < 0.064$) and errors without feedback ($F_{(1,15)} = 3.15$; $p < 0.097$).

Discussion

The present two studies aimed at investigating performance monitoring under conditions when the individual cannot detect the errors because of lack of knowledge. The resemblance of the negative ERP on feedback with the ERN (Miltner et al., 1997; Luu et al., 2003) suggests that similar networks are involved in error detection based on external feedback as in self-detection of action slips. We used a DAMP task, making sure that the difficulty

was tailored to each individual such that high uncertainty about whether the response was correct was induced. Hence, for evaluation of the responses and strategy adjustment, participants were dependent on the feedback. Because error trials might also involve a higher degree of uncertainty and response conflict preceding the feedback, and that response conflict may account for similar activation differences (cf. Carter et al., 1998), we performed experiment 2, in which on a proportion of trials, no feedback was given. Those trials would involve uncertainty and response conflict but not the negative-feedback-associated activity.

Interactions with the reward processing system

In summary, the results from the two studies provide several new insights into the mechanisms involved in performance monitoring and reward processing and point at the interfaces between these cognitive functions. The ventral striatum was activated only when positive feedback occurred. This supports the fact that the ventral striatum is engaged when rewards or positive feedback occur (Elliott et al., 2000; Berns et al., 2001; Pagnoni et al., 2002; Volz et al., 2003), probably because of phasic dopamine release (Schultz, 2000, 2002; Schultz and Dickinson, 2000). It is also compatible with the view that the attribution "incentive salience" to the stimuli (i.e., that the stimuli are "wanted") (cf. Berridge and Robinson, 1998) is reflected by dopamine release in the nucleus accumbens. Our results seem to be inconsistent with previous findings (Horvitz et al., 1997; Horvitz, 2000) that nonrewarding salient events may result in dopamine release in the nucleus accumbens, suggesting that less frequent noninformative and negative feedback stimuli might induce higher activity in the ventral striatum, which was not found in our data. An explanation could be that the stimuli in this research are not comparable with nonconditioned stimuli, as used by Horvitz et al. (1997), because their association to reward, nonoccurrence of reward, and uncertainty about reward, respectively, was established by instruction and experienced throughout the experiment.

Furthermore, these data highlight processes in other structures that come into play when expected reward fails to occur (e.g., during negative feedback). They clarify the role of the habenular complex that has primarily been neglected in research in humans (partly because of the fact that it is almost never selectively damaged). When an error was made and negative feedback was received, the habenular nuclei seemed to be activated most. Similar activity was observed when correct responses were not followed by informative (positive) feedback (i.e., there was an interaction of response type and the occurrence of informative feedback). To understand this interaction, one needs to keep in mind that the habenula inhibits the midbrain nuclei. Many neuromodulator systems are influenced by fibers from the habenular complex (Scheibel, 1997). We focus the discussion on the dopamine system, which seems to be the most involved in reward prediction and error processing (Schultz, 2000, 2002; Holroyd and Coles, 2002). It is conceivable that the higher engagement of the habenula observed in the experiment reduces the probability of phasic dopamine release in the reward system. This inhibitory function seems to be based on an integration of reward expectancy and the actual occurrence of reward or punishment. In this experiment, the actual reward relevant for goal-directed behavior is the knowledge that the response was correct, symbolized here by the smiley face. The reward expectancy is not only dependent on the global frequency of positive rewards in the experiment but also on the certainty about the correctness of the current response. The longer reaction times suggested that uncertainty was higher during error trials than correct responses, leading to lower reward expectancy. For trials without feedback information (i.e., without reward or punishment), this could have resulted in lower habenular activity for errors than correct trials (Fig. 3c), such that the VTA and SN are less inhibited (if it occurred, a feedback resulting in a phasic dopamine signal would be highly informative during the uncertain error trials). However, negative feedback on errors assures the participant that no reward (in the form of knowing that the response was correct) can be received in the current trial. Because before the feedback reward prediction was not zero, this reflects a negative error in reward prediction. The accompanying increased habenular activity might indicate an increased inhibition of the dopaminergic midbrain nuclei resulting in decreased dopamine output, as reported for nonoccurring rewards (Schultz and Dickinson, 2000; Schultz, 2002). According to the model proposed by Holroyd and Coles (2002), this decreased dopamine release can result in higher activity in the rCMA, as was the case in this experiment during errors with negative feedback. In contrast, for correct trials, reward expectancy was slightly higher than during errors because of higher certainty. However, the global frequency of positive feedback in experiment 2 was only 45.2%; thus, reward expectancy was not very high, even during correct trials. Therefore, positive feedback would still be informative for the system, but less so than during the error trials involving higher uncertainty (this might explain the relatively high habe-

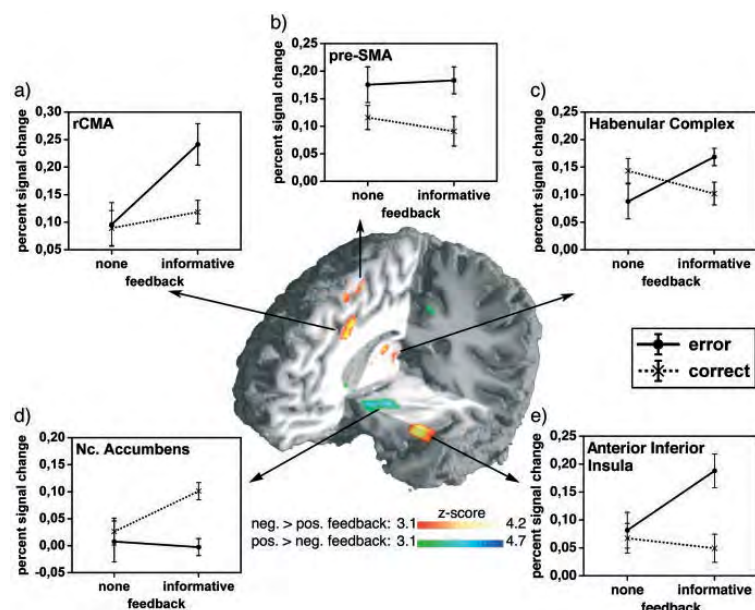


Figure 3. Activations in experiment 2. The central picture shows the z-map resulting from contrasting negative and positive informative feedback. *a–d*, Signal change of the hemodynamic response for correct and error trials with and without informative feedback at the CMA (*a*), pre-SMA (*b*), habenular complex (*c*), ventral striatum (nucleus accumbens) (*d*), and left insula (*e*).

Table 3. Regions of interest showing interactions between feedback presence and response type

| | | Talairach coordinates | | |
|--|---------------------------------|-----------------------|----------|----------|
| Side | Brain region | <i>x</i> | <i>y</i> | <i>z</i> |
| Interaction response type × presence of feedback | | | | |
| R | rCMA | 4 | 18 | 35 |
| L | Anterior inferior insula | −37 | 15 | −3 |
| L | Ventral striatum (Nc accumbens) | −13 | 6 | −3 |
| R | Ventral striatum (Nc accumbens) | 8 | 8 | −3 |
| L/R | Habenular complex | −5/6 | −25 | 8 |

Nc, Nucleus; L, left; R, right.

nular activity during correct trials without feedback). Therefore, positive feedback on correct trials revealed a positive error in reward prediction. This error in reward prediction is reflected in the decrease in the habenular activity when correct trials were followed by positive feedback, thus disinhibiting the dopaminergic midbrain areas. Bearing in mind the anatomical connections of the habenular complex, this interpretation is consistent with the view that the VTA and SN react with phasic changes of dopamine release to errors in reward prediction (i.e., with dopamine release on unexpected rewards and a decrease in activity on non-occurring predicted rewards) (Schultz and Dickinson, 2000; Pagnoni et al., 2002). It seems that the difference in the habenular activity between informative and noninformative activity correlates with the error in reward prediction. However, fMRI is not able to characterize the exact time course of the habenular activity, and in particular, it cannot disentangle phasic and tonic activity. Therefore, electrophysiological studies in primates might be of significant help in understanding the function of the epithalamus.

Areas on the frontomedian wall

In experiment 2, the rCMA seems to specifically react on errors followed by informative (i.e., negative) feedback. It is important to note that the same area has been shown repeatedly to be involved in self-detection of errors (Carter et al., 1998; Ullsperger et al., 2001). It is conceivable that the rCMA is the generator not only of the ERN but also of the feedback-related negativity (Miltner et al., 1997; Luu et al., 2003). Thus, error detection based on the comparison of representations of the intended response and the actual response appears to involve mechanisms very similar to those seen for error detection based on external feedback. In both cases, error detection can lead to remedial actions and skill acquisition (Rabbitt, 1966; Reason, 1990). The role of the rCMA in this function is supported by the findings of Shima and Tanji (1998), demonstrating that CMA neurons respond only when reduced reward leads to a change in behavior (i.e., to remedial actions). A similar finding was reported recently for an fMRI study in humans (Bush et al., 2002). In this context, it would be interesting to investigate whether feedback induced performance gains suggestive of visuomotor learning, and whether this was related to changes in feedback-related brain activity. However, over the given time frame, there was no evidence for performance gains that should be reflected in increasing difficulty or shorter reaction times. Longer experiments with more trials will be needed to investigate this issue.

In contrast to the rCMA, the pre-SMA was activated by errors in general and even without negative feedback (i.e., without the individual's knowledge of a mistake). As mentioned above, erroneous trials seemed to involve higher uncertainty about what response to choose (higher response conflict and lower reward expectancy) than correct trials. This uncertainty persisted even after the response. The activation pattern supports the view that the pre-SMA is preferentially engaged by response conflict and/or uncertainty. The findings from experiment 2 are corroborated by the reanalysis of experiment 1 with reaction time as a regressor, which revealed that the pre-SMA activity correlated with the reaction time and thus with uncertainty. Furthermore, these findings are in accordance with recent studies investigating underdetermined responding (Elliott and Dolan, 1998; Volz et al., 2003). A similar functional dissociation of the rCMA (most activated during errors) and pre-SMA (most engaged by uncertainty and response conflict), as in our data, was shown in studies investigating self-detected errors (Ullsperger and von Cramon, 2001; Garavan et al., 2002).

Similarly, as with the rCMA, the anterior inferior insula was most activated by negative feedback. It could be speculated that this activity is correlated with accompanying autonomic responses to the negative emotional action of the feedback.

Conclusion

Our pair of experiments illustrates the close relationship between performance monitoring and reward processing. It shows that reward and nonoccurrence of reward activate different players in the network (the ventral striatum and the rCMA, respectively). The importance of the habenula complex in reward processing and influencing the dopaminergic system was demonstrated for the first time in humans. It appears that the habenula restrains the midbrain nuclei and plays a role in determining the error in reward prediction. As described previously by Scheibel (1997), the functional integrity of the epithalamus can be assumed to be relevant for psychiatric disturbances and drug abuse. In our opinion, the findings of this study suggest that measurements of single-unit activity in the habenula of primates would reveal in-

teresting results on the tonic and phasic neuronal activity influencing the midbrain nuclei.

References

- Aguirre GK, Zarahn E, D'Esposito M (1997) Empirical analysis of BOLD fMRI statistics, Vol II: spatially smoothed data collected under null-hypothesis and experimental conditions. *NeuroImage* 5:199–212.
- Berns GS, McClure SM, Pagnoni G, Montague PR (2001) Predictability modulates human brain response to reward. *J Neurosci* 21:2793–2798.
- Berridge KC, Robinson TE (1998) What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Res Brain Res Rev* 28:309–369.
- Bush G, Vogt BA, Holmes J, Dale AM, Greve D, Jenike MA, Rosen BR (2002) Dorsal anterior cingulate cortex: a role in reward-based decision making. *Proc Natl Acad Sci USA* 99:523–528.
- Carter CS, Braver TS, Barch DM, Botvinick MM, Noll D, Cohen JD (1998) Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science* 280:747–749.
- Christoph GR, Leonzio RJ, Wilcox KS (1986) Stimulation of the lateral habenula inhibits dopamine-containing neurons in the substantia nigra and ventral tegmental area of the rat. *J Neurosci* 6:613–619.
- Elliott R, Dolan RJ (1998) Activation of different anterior cingulate foci in association with hypothesis testing and response selection. *NeuroImage* 8:17–29.
- Elliott R, Friston KJ, Dolan RJ (2000) Dissociable neural responses in human reward systems. *J Neurosci* 20:6159–6165.
- Falkenstein M, Hohnsbein J, Hoormann J, Blanke L (1990) Effects of errors in choice reaction tasks on the ERP under focused and divided attention. In: *Psychophysiological brain research* (Brunia CHM, Gaillard AWK, Kok A, eds), pp 192–195. Tilburg, The Netherlands: Tilburg UP.
- Friston KJ, Holmes AP, Worsley KJ, Poline JP, Frith CD, Frackowiak RSJ (1995) Statistical parametric maps in functional imaging: a general linear approach. *Hum Brain Mapp* 2:189–210.
- Friston KJ, Fletcher P, Josephs O, Holmes A, Rugg MD, Turner R (1998) Event-related fMRI: characterizing differential responses. *NeuroImage* 7:30–40.
- Garavan H, Ross TJ, Kaufman J, Stein EA (2002) Neuroanatomical dissociation of response conflict from error detection using event-related fMRI. *NeuroImage* 17:1820–1829.
- Gehring WJ, Goss B, Coles MGH, Meyer DE, Donchin E (1993) A neural system for error detection and compensation. *Psychol Sci* 4:385–390.
- Greenhouse S, Geisser S (1959) On methods in the analysis of profile data. *Psychometrika* 24:95–112.
- Holmes AP, Friston KJ (1998) Generalisability, random effects and population inference. *NeuroImage* 7:754.
- Holroyd C, Coles MGH (2002) The neural basis of human error processing: reinforcement learning, dopamine, and the error-related negativity. *Psychol Rev* 109:679–709.
- Horvitz JC (2000) Mesolimbocortical and nigrostriatal dopamine responses to salient non-rewarding events. *Neuroscience* 96:651–656.
- Horvitz JC, Stewart T, Jacobs BL (1997) Burst activity of ventral tegmental neurons is elicited by sensory stimuli in the awake cat. *Brain Res* 759:251–258.
- Josephs O, Turner R, Friston K (1997) Event-related fMRI. *Hum Brain Mapp* 5:243–248.
- Lisoprawski A, Herve D, Blanc G, Glowinski J, Tassin JP (1980) Selective activation of the mesocortico-frontal dopaminergic neurones induced by lesion of the habenula in the rat. *Brain Res* 183:229–234.
- Lohmann G, Müller K, Bosch V, Mentzel H, Hessler S, Chen L (2001) LIP-SIA—a new software system for the evaluation of functional magnetic resonance images of the human brain. *Comput Med Imaging Graph* 25:449–457.
- Luu P, Tucker DM, Derryberry D, Reed M, Poulsen C (2003) Electrophysiological responses to errors and feedback in the process of action regulation. *Psychol Sci* 14:47–53.
- Miezin FM, Maccotta L, Ollinger JM, Petersen SE, Buckner RL (2000) Characterizing the hemodynamic response: effects of presentation rate, sampling procedure, and the possibility of ordering brain activity based on relative timing. *NeuroImage* 11:735–759.
- Miltner WHR, Braun CH, Coles MGH (1997) Event-related brain potentials following incorrect feedback in a time-estimation task: evidence for a “generic” neural system for error detection. *J Cognit Neurosci* 9:788–798.

- Nishikawa T, Fage D, Scatton B (1986) Evidence for and nature of the tonic inhibitory influence of the habenulointerpeduncular pathway upon cerebral dopaminergic transmission in the rat. *Brain Res* 373:324–336.
- Pagnoni G, Zink CF, Montague PR, Berns GS (2002) Activity in the human ventral striatum locked to errors of reward prediction. *Nat Neurosci* 5:97–98.
- Picard N, Strick PL (1996) Motor areas of the medial wall: a review of their location and functional activation. *Cereb Cortex* 6:342–353.
- Rabbitt PMA (1966) Errors and error correction in choice-response tasks. *J Exp Psychol* 71:264–272.
- Reason J (1990) The detection of errors. In: *Human error*, pp 148–172. Cambridge, UK: Cambridge UP.
- Scheibel AB (1997) The thalamus and neuropsychiatric illness. In: *The neuropsychiatry of limbic and subcortical disorders* (Salloway S, Malloy P, Cummings JL, eds), pp 31–40. Washington, DC: American Psychiatry.
- Schultz W (2000) Multiple reward signals in the brain. *Nat Rev Neurosci* 1:199–207.
- Schultz W (2002) Getting formal with dopamine and reward. *Neuron* 36:241–263.
- Schultz W, Dickinson A (2000) Neuronal coding of prediction errors. *Annu Rev Neurosci* 23:473–500.
- Shima K, Tanji J (1998) Role for cingulate motor area cells in voluntary movement selection based on reward. *Science* 282:1335–1338.
- Talairach J, Tournoux P (1988) *Co-planar stereotaxis atlas of the human brain*. New York: Thieme.
- Ullsperger M, von Cramon DY (2001) Subprocesses of performance monitoring: a dissociation of error processing and response competition revealed by event-related fMRI and ERPs. *NeuroImage* 14:1387–1401.
- Vogt BA, Nimchinsky EA, Vogt LJ, Hof PR (1995) Human cingulate cortex: surface features, flat maps, and cytoarchitecture. *J Comp Neurol* 359:490–506.
- Volz KG, Schubotz RI, von Cramon DY (2003) Predicting events of varying probability: uncertainty investigated by fMRI. *NeuroImage*, in press.
- Vorobiev V, Govoni P, Rizzolatti G, Matelli M, Luppino G (1998) Parcellation of human mesial area 6: cytoarchitectonic evidence for three separate areas. *Eur J Neurosci* 10:2199–2203.
- Wansapura JP, Holland SK, Dunn RS, Ball WS (1999) NMR relaxation times in the human brain at 3.0 Tesla. *J Magn Reson Imaging* 9:531–538.
- Worsley KJ, Friston KJ (1995) Analysis of fMRI time-series revisited—again. *NeuroImage* 2:173–181.
- Zarahn E, Aguirre GK, D'Esposito M (1997) Empirical analysis of BOLD fMRI statistics, Vol I: spatially unsmoothed data collected under null-hypothesis conditions. *NeuroImage* 5:179–197.

Chapter 5

Trial-by-trial coupling of concurrent EEG and fMRI identifies the dynamics of performance monitoring

In the previous Chapters the role of the pFMC as a key player in performance monitoring was pin-pointed. The RCZ has been shown to respond to different error types. However, its role for subsequent adjustments is still rather unclear. While an early study provided evidence at the within-subjects level that a stronger ERN is associated with stronger post-error slowing (Gehring et al., 1993), later between-subjects analyses failed to replicate this finding (Falkenstein et al., 2000; Hajcak et al., 2003). To address this point, a single-trial analysis of the performance monitoring signal and its relation to subsequent adjustments is required. This major aim of the study presented in this Chapter was reached by utilizing independent component analysis (ICA) of the EEG data enabling the assessment of the electrophysiological correlate of performance monitoring, the ERN, on a trial-by-trial basis.

A further aim was to non-invasively address the relationship of the fMRI blood oxygen level dependent (BOLD) signal to the electrophysiological activity. Previously, this relationship could only be addressed using invasive recordings in monkeys (Logothetis et al., 2001; Logothetis, 2002, 2003). Thus, combining fMRI and EEG measures would make use of the complementary advantages of the two methods and therefore be of general interest for cognitive neurosciences. For the field of performance monitoring, a simultaneous study could underpin the notion that the ERN is generated in the RCZ.

While EEG and fMRI signals were recorded simultaneously, participants performed the modified flanker task. The EEG-informed fMRI analysis revealed a trial-by-trial coupling of the ERN amplitude and the fMRI signal in the RCZ. Higher ERN amplitudes were associated with stronger BOLD activity. Moreover, the single-trial ERN amplitude predicted the reaction time on the subsequent trial. Higher ERN amplitudes were followed by stronger post-error slowing.

These findings are the first direct evidence that the ERN is generated in the RCZ. Moreover, they show that the performance monitoring signal varies from trial to trial, and that this variation is functionally meaningful. Finally, the ICA-based EEG-informed fMRI analysis opens new avenues for the integration of fMRI and EEG data. A promising way in the future is to identify independent components in the EEG reflecting specific cognitive functions and investigating their relationship to the fMRI signal. Then the mutual temporal relation between the independent component activities allows inferences on the timing within the brain networks whose anatomy was identified by fMRI.

11730 • The Journal of Neuroscience, December 14, 2005 • 25(50):11730–11737

Behavioral/Systems/Cognitive

Trial-by-Trial Coupling of Concurrent Electroencephalogram and Functional Magnetic Resonance Imaging Identifies the Dynamics of Performance Monitoring

Stefan Debener,^{1,2*} Markus Ullsperger,^{3*} Markus Siegel,¹ Katja Fiehler,^{3,4} D. Yves von Cramon,³ and Andreas K. Engel¹

¹Institute of Neurophysiology and Pathophysiology, Center of Experimental Medicine, University Medical Center, Hamburg University, D-20246 Hamburg, Germany, ²Medical Research Council Institute of Hearing Research Southampton, Royal South Hants Hospital, SO 14 0YG Southampton Hants, United Kingdom, ³Department of Cognitive Neurology, Max-Planck Institute for Human Cognitive and Brain Sciences, D-04103 Leipzig, Germany, and ⁴Cognitive Psychophysiology Laboratory, Department of Psychology, Philipps-University Marburg, D-35032 Marburg, Germany

Goal-directed behavior requires the continuous monitoring and dynamic adjustment of ongoing actions. Here, we report a direct coupling between the event-related electroencephalogram (EEG), functional magnetic resonance imaging (fMRI), and behavioral measures of performance monitoring in humans. By applying independent component analysis to EEG signals recorded simultaneously with fMRI, we found the single-trial error-related negativity of the EEG to be systematically related to behavior in the subsequent trial, thereby reflecting immediate behavioral adjustments of a cognitive performance monitoring system. Moreover, this trial-by-trial EEG measure of performance monitoring predicted the fMRI activity in the rostral cingulate zone, a brain region thought to play a key role in processing of response errors. We conclude that investigations of the dynamic coupling between EEG and fMRI provide a powerful approach for the study of higher order brain functions.

Key words: fMRI; EEG; anterior cingulate cortex; performance monitoring; ICA; error processing

Introduction

In a rapidly changing environment, goal-directed behavior requires the monitoring and dynamic adjustment of ongoing actions. Erroneous actions, in particular, are highly informative for successful adjustments of future behavior (Ridderinkhof et al., 2004). Accordingly, neural correlates of performance monitoring have been studied intensively in humans by means of electroencephalogram (EEG) and functional magnetic resonance (MR) imaging (fMRI). One of the EEG signatures is the error-related negativity (ERN), an event-related brain potential (ERP) peaking within 100 ms after erroneous responses (Falkenstein et al., 1990; Gehring et al., 1993). fMRI studies consistently implicate the posterior frontomedian cortex in processing of response errors, negative feedback, response conflict, and decision uncertainty (Ridderinkhof et al., 2004). Informed by both ERN and fMRI research, the current view is that error processing is accomplished by a fundamental performance monitoring system signaling the need for behavioral adjustments in the service of action outcome optimization (Ridderinkhof et al., 2004; Ullsperger and von Cramon, 2004).

A common notion is that performance monitoring is a dynamic process that systematically fluctuates over time. Behavioral adjustments can, for instance, lead to prolonged reaction times (RTs) on trials subsequent to errors, thereby reflecting a more cautious response mode (Rabbitt, 1966; Ridderinkhof et al., 2004). This view is supported by fMRI work showing that enhanced activity in the posterior frontomedian cortex predicts greater subsequent posterror slowing (Garavan et al., 2002; Kerns et al., 2004). For the ERN, this question is difficult to address, because ERPs usually are derived by averaging across trials. To account for this problem, independent component (IC) analysis (ICA) can be applied, a statistical source separation technique suitable for single-trial EEG analysis (Makeig et al., 2002, 2004). If the ERN indeed reflects performance monitoring, ICA-filtered trial-to-trial variations of its amplitude should go along with systematic behavioral changes in the same trial and particularly in subsequent trials. Based on a previous account (Gehring et al., 1993), we predicted greater single-trial ERN amplitudes after errors, reflecting a change to a more conservative response strategy in subsequent trials.

EEG source localization studies (Dehaene et al., 1994; Ullsperger and von Cramon, 2001) have suggested the posterior frontomedian cortex as neural generator of the ERN. However, these analyses do not inform on whether the ERN is related to hemodynamic changes of error monitoring. To date, it remains poorly understood how hemodynamic and electrophysiological correlates of cognitive processes relate to each other. Regarding the relationship between electrophysiological measures and

Received Aug. 5, 2005; revised Sept. 30, 2005; accepted Nov. 6, 2005.

This work was supported by a grant from the Deutsche Forschungsgemeinschaft to M.U. and K.F. We thank R. Niaz, S. Makeig, and A. Delorme for invaluable contributions to this project and S. Zysset and T. Mildner for their help with data recordings.

*S.D. and M.U. contributed equally to this work.

Correspondence should be addressed to Dr. Stefan Debener, Medical Research Council Institute of Hearing Research Southampton, Royal South Hants Hospital, SO 14 0YG Southampton Hants, UK. E-mail: stefan@debener.de.
DOI:10.1523/JNEUROSCI.3286-05.2005

Copyright © 2005 Society for Neuroscience 0270-6474/05/2511730-08\$15.00/0

fMRI, local field potentials recorded in the visual cortex of anesthetized monkeys have been shown to predict the local fMRI blood-oxygen-level-dependent (BOLD) signal (Logothetis et al., 2001). Here, we tested whether the electrophysiological correlate of performance monitoring systematically predicts the BOLD response in the rostral cingulate zone (RCZ) of the posterior frontomedian cortex. To address both the dynamic variability of performance monitoring and the relationship between its hemodynamic and electrical signatures, we performed a single-trial analysis of simultaneous EEG/fMRI measurements. We thereby avoided the usual problem that within-subject behavior fluctuates across separate recording sessions (Ullsperger and von Cramon, 2001).

Materials and Methods

Participants. Eighteen healthy right-handed volunteers participated in the experiment. As a result of technical malfunction and thus incomplete recordings of either EEG or fMRI, data from five subjects had to be discarded. The final sample consisted of eight females and five males (22–29 years of age; mean age, 25.2 years). Written informed consent before the start of the experiment was obtained from each participant according to the declaration of Helsinki.

Behavioral task. Stimuli were presented using Presentation 0.76 (Neurobehavioral Systems, San Francisco, CA) and appeared on a back-projection screen mounted inside the scanner bore behind the participants head. A speeded modified flanker task was used known to yield sufficient error rates to study the ERN (see Fig. 1). Participants were presented with a fixation mark at the center of the screen, after which four horizontal flanker arrows appeared for 110 ms. The arrows were 0.46° tall and 1.08° wide and appeared 0.52° and 1.04° above and below the screen center. The target arrow was presented for 30 ms in the center of the flanker arrows; its onset was delayed by 80 ms from the onset of the flanker. In 50% of the 400 trials, the flankers pointed in the same direction as the target (compatible trials), and in the other half of the trials in the opposite direction (incompatible trials). Compatible and incompatible trials appeared in randomized order. Participants were instructed to respond with maximal speed and accuracy to the target arrow with the response hand indicated by the arrow direction. Whenever participants responded after an individual, dynamically adapting response deadline, a symbolic feedback was presented for 1400 ms after target onset, instructing participants to speed up. The average intertrial interval amounted to 6 s; for the remaining time, the fixation mark was presented. The trials were interspersed with a total of 32 nonevents, during which only the fixation cross was presented and no response was required. Trials occurred at multiple, systematically offset time points (range, 0–1.5 s) in relation to fMRI data acquisition to improve temporal resolution (Josephs et al., 1997; Miezin et al., 2000).

Simultaneous EEG/fMRI recording. Imaging was performed at 3 tesla on a Siemens (Erlangen, Germany) Trio system equipped with the standard bird cage head coil. Twenty-two functional slices were obtained parallel to the anterior commissure–posterior commissure line (thickness, 4 mm; interslice gap, 1 mm) using a gradient-echo echo planar imaging (EPI) sequence with an echo time of 30 ms, a flip angle of 90°, a repetition time (TR) of 2000 ms, and an acquisition bandwidth of 100 kHz. Acquisition of the slices was arranged such that they all were acquired within 1500 ms and were followed by a 500 ms no-acquisition period to complete the TR. This was done to visually monitor proper recording of the EEG signal during MR scanning and to include for each TR a nongradient contaminated baseline period into the EEG recordings (Fig. S1, available at www.jneurosci.org as supplemental material). The fMRI matrix acquired was 64×64 with a field of view of 19.2 cm, resulting in an in-plane resolution of $3 \times 3 \text{ mm}^2$. A total of 1309 volumes was acquired. Functional data were motion-corrected off-line with the Siemens motion correction protocol. Before the functional runs, anatomical modified driven equilibrium Fourier transform (MDEFT) and EPI-T1 slices in the plane with functional images were collected.

Continuous EEG data were collected from 30 standard scalp sites using the BrainAmps MR plus, a high-input impedance amplifier specifically

designed for recordings in high magnetic fields (BrainProducts, Munich, Germany). Sintered Ag/AgCl ring electrodes with built-in 5 k Ω resistors were used and mounted into an electrode cap according to the 10–20 system (Falk Minow Services, Herrsching, Germany). Two additional electrodes were placed below the left eye and on the lower back to monitor eyeblinks and electrocardiograms, respectively. Electrode impedances were maintained below 10 k Ω before recordings. The nonmagnetic EEG amplifier was fixed beside the head coil and powered by a rechargeable power pack placed outside the scanner bore. The subject's head was immobilized using vacuum cushions and sponge pads. The amplified EEG signals were transmitted with a fiber optic cable to a recording personal computer placed outside the scanner room. All 32 channels were recorded with FCz as reference. Although this is an unusual reference site for ERN studies, it allowed us to keep the distance between recording reference and “active” electrodes small, thereby minimizing the chance of amplifier saturation. The data were recorded with a pass-band of 0.016–250 Hz and digitized with 5000 samples per second at 16 bit with 0.5 μV resolution (dynamic range, 16.38 mV).

EEG data analysis. EEG data were corrected for MR gradient and ballistocardiac artifacts by applying modified versions of the algorithms proposed by Allen and colleagues (Allen et al., 1998, 2000). Gradient artifacts were removed as implemented in Vision Analyzer 1.04 software (BrainProducts) by subtracting an artifact template from the 40 Hz low-pass-filtered data, using a baseline-corrected sliding average of 20 consecutive volumes. This resulted in EEGs denoised for MR gradients, as shown for representative 10 s traces in Figure S1 (available at www.jneurosci.org as supplemental material). Further processing of the 250 Hz downsampled data was performed using Matlab 6.5 (MathWorks, Natick, MA) and EEGLAB 4.51 (Delorme and Makeig, 2004), a freely available open source software toolbox (EEGLAB toolbox for single-trial EEG data analysis, Swartz Center for Computational Neurosciences, La Jolla, CA; <http://www.sccn.ucsd.edu/eeeglab>). The EEGLAB plug-in FMRIB 1.0 (Niazy et al., 2005) (FMRIB EEGLAB plug-in for removal of fMRI-related artifacts, Center for functional MRI of the Brain, Oxford, UK; <http://www.fmrrib.ox.ac.uk/~rami/fmrribplugin>) was used for 0.4–35 Hz filtered data to remove ballistocardiac artifacts. Based on the identified heartbeat events, an artifact template was defined as the median across a sliding window of 30 heartbeats centered around the heartbeat event being processed. As a result, EEG data denoised for ballistocardiac artifacts were derived but with common EEG artifacts such as eyeblinks still being present (Fig. S1, available at www.jneurosci.org as supplemental material).

The MR-denoised EEG data were re-referenced to common average, and stimulus- and response-locked ERPs were calculated separately for the experimental conditions of interest. The time-locking event for all stimulus-locked analyses was the target arrow onset, with a baseline set to -200 – 0 ms. For response-locked ERPs, we used a baseline from -600 to -400 ms to avoid contamination of the baseline period with stimulus-evoked potentials. Stimulus-locked ERPs clearly indicated the common ERP morphology (i.e., an N1 at occipital channels, a P300 at parietal channels, and the ERN at frontocentral channels), altogether confirming reasonable data quality (Fig. S2a, available at www.jneurosci.org as supplemental material). Grand mean ERP images were computed by color-coding the single-trial amplitudes aligned to stimulus onset, smoothed with a moving average across 30 adjacent trials (Delorme and Makeig, 2004). Topographical inspection of both scalp ERPs and reaction-time-sorted ERP images clearly indicated a contamination of the event-related portion of the signal with different artifacts (Fig. S2, available at www.jneurosci.org as supplemental material). In addition to the typical eyeblink artifacts, a strong response-locked exogenous artifact was visible at temporal sites, as characterized by a reversed polarity between left and right hemisphere channels. This event-related artifact probably was caused by button-press-related small body movements and related current induction. For this and other reasons, it was inevitable to linearly decompose the response-related process of interest from these and further signal contributions. We performed extended infomax ICA (Bell and Sejnowski, 1995; Lee et al., 1999) on the MR-denoised single-subject continuous EEG data. ICA finds an unmixing square matrix of the size of the number of channels, which, when matrix-multiplied with the raw

data, reveals maximally temporally independent activations. A weight change of 10^{-7} as stop criterion resulted in stable decompositions after <800 iterations. Each IC can be characterized by a time course (IC activation) and a topography (IC map), the latter being given by the inverse weights. The 30 ICs for each subject were screened for maps resembling the typical frontocentral radial ERN topography and a contribution to the ERP difference between incompatible error and incompatible correct trials, that is, a larger negative deflection at the response interval for erroneous trials. This resulted in identification of one IC for each subject, presumably reflecting the contribution of the neural correlate of performance monitoring to the scalp EEG. Figure S3 (available at www.jneurosci.org as supplemental material) shows the individual IC maps identified along with the average map, after root mean square normalization of individual maps (see Fig. 2*a*). For each subject, the selected IC was then back-projected to the scalp to reveal unique polarity information and microvolt scaling. Figure S4 (available at www.jneurosci.org as supplemental material) shows the resulting ERPs and ERP images. Compared with the original scalp data (Fig. S2, available at www.jneurosci.org as supplemental material), spatiotemporally overlapping contributions were now absent in the IC ERPs and ERP images.

To model the neural source of the selected ICs, the grand average IC map was submitted to BESA 2000, version 4.2 (MEGIS, Graefeling, Germany). A standardized finite element model (FEM), as provided by BESA, was used. It was created from an averaged head of 24 individual MRIs in Talairach space, and this head was also used for display purposes (Fig. 2*c*). The BESA FEM provides a realistic approximation of three compartments (brain/CSF, skull, scalp) and was applied with default conductivity parameters. An informed dipole seeding approach was used by placing an equivalent current dipole into the RCZ. The location [Talairach coordinates (x, y, z) = 0, 20, 30] was derived from the second-level fMRI result from the same subjects in the same recording session, with the x -axis value set to zero.

Time–frequency analysis of single-trial IC activations was performed for data collapsed across three frontocentral channels (FC1, FC2, Cz) by convolving the data with a complex Morlet wavelet $w(t/f_0)$ having a Gaussian shape in the time (σ_t) and frequency (σ_f) domain around the center frequency f_0 . A constant wavelet is characterized by a constant ratio $Q = (f_0/\sigma_f)$. We used nonconstant wavelets with Q increasing linearly from five to eight for frequencies from 3.5 to 35 Hz (step size, 0.5 Hz), which results in an increase in spectral versus temporal resolution with increasing frequency. The Q at 5 Hz was characterized by a frequency resolution of $\sigma_f = 0.97$ Hz and a temporal resolution of $\sigma_t = 165$ ms. For every single trial, the norm of the complex result of the convolution was computed, scaled to decibels ($10 \times \log_{10}$), and normalized by subtracting for each frequency the mean value of the -500 to -200 ms prestimulus interval from the poststimulus values. The epoch length for the single-trial analysis was set to 3 s to ensure that the interval of interest (-500 – 1500 ms relative to target onset) did not interfere with invalid edge effects, as indicated by the half length of the wavelet scales.

Based on the results of the time–frequency analysis, which suggested a low β increase at about the response interval, the back-projected IC activations were 2–10 Hz bandpass filtered to unveil a cleaner single-trial estimate of the ERN-related theta response. A parametric vector for each subject was then computed as follows. First, the minimum value in the interval 15–85 ms after each button-press was determined, and the mean of the preceding (-80 – 0 ms) and succeeding (85–240 ms) positivity was subtracted (see Fig. 3*a*). These latency windows were determined based on the grand average IC ERP (see Fig. 2*b*) and also were compatible with the time–frequency results confirming a prominent theta activity (see Fig. 2*e*). The resulting single-trial amplitudes vector (see Fig. 3*b*) was then convolved with the canonical hemodynamic response function and used as parametric regressor for fMRI analysis (see below).

fMRI data analysis. MR data processing was performed using the software package LIPSLA (Lohmann et al., 2001). Functional data were corrected for slice-time acquisition differences using sinc-interpolation. Signal changes and baseline drifts were removed by applying a temporal high-pass filter with a cutoff frequency of 1/120 Hz. Spatial smoothing was applied using a Gaussian filter with 5.65 mm full width at half maximum (FWHM). To align the functional data slices with a three-

dimensional stereotactic coordinate reference system, a rigid linear registration with six degrees of freedom (three rotational and three translational) was performed. The rotational and translational parameters were acquired on the basis of the MDEFT and EPI-T1 slices to achieve an optimal match between these slices and the individual three-dimensional reference data set [MDEFT volume data set with 160 slices and 1 mm slice thickness standardized to the Talairach stereotactic space (Talairach and Tournoux, 1988)] that was acquired for each subject during a previous scanning session. The rotational and translational parameters were subsequently transformed by linear scaling to a standard size. The resulting parameters were then used to transform the functional slices using trilinear interpolation so that the resulting functional slices were aligned with the stereotactic coordinate system, generating output data with a spatial resolution of 3 mm³.

Statistical analysis. Randomization statistics based on 1000 repetitions were performed to identify significant power changes in the time–frequency plane relative to baseline activity in the EEG. This analysis was applied separately to each subject and each condition. In addition, randomization statistics on the time–frequency power differences between incompatible error and incompatible correct conditions were performed. To summarize these results for the group of 13 subjects, binomial statistical analysis was applied.

Statistical analysis of the association between single-trial EEG amplitudes and reaction times was achieved by determining the linear regression slopes between single-trial amplitudes and reaction time values (see Fig. 3*c*). Separate analyses were performed for the current trial, that is, single-trial amplitudes were related to reaction times of the same trial and to the following trial. In the latter case, single-trial amplitude values were associated to reaction times whenever the following trial belonged to the same stimulus condition. For group analysis, the resulting individual slopes were tested against zero (see Fig. 3*d*) by applying one-sided t tests for conditions in which a prediction could be made on the basis of the performance monitoring model.

The statistical analysis of fMRI data was based on a least squares estimation using the general linear model for serially autocorrelated observations (random effects model) (Friston et al., 1995; Worsley and Friston, 1995; Aguirre et al., 1997; Zarahn et al., 1997). Event-related designs were implemented, that is, the hemodynamic response function was modeled by the experimental conditions for each stimulus (event = onset of stimulus presentation). The measured signal was described by a convolution of the temporal stimulus distribution and the hemodynamic response function. The design matrix was generated using a synthetic hemodynamic response function and its first and second derivative and a response delay of 6 s (Friston et al., 1998). The model equation, including the observation data, the design matrix, and the error term, was convolved with a Gaussian kernel with a dispersion of 4 s FWHM. The effective degrees of freedom were estimated as described by Worsley and Friston (1995). In the following, contrast maps, that is, estimates of the raw-score differences among specified conditions, were generated for each subject. The individual functional datasets were all aligned to the same stereotactic reference space, and a group analysis was performed. For multisession analysis, the random-effects analysis can be effected as a one-sample t test on the resulting contrast images across subjects and sessions (Worsley and Friston, 1995; Holmes and Friston, 1998). Subsequently, t values were transformed into z scores. The design matrix consisted of onset vectors for compatible correct, incompatible correct, and incompatible erroneous trials. Trials involving late response feedbacks and nonevents formed two additional onset vectors. The six translational and rotational motion correction parameters provided by the Siemens motion correction protocol were included as regressors. As in previous studies (Ullsperger and von Cramon, 2001, 2004), analysis of error-related brain activity was performed by contrasting incompatible erroneous with incompatible correct trials, thus extracting specific signal increases on errors. Conflict-related activity should cancel out, because response conflict occurs on both incompatible correct and erroneous trials. To minimize the probability of false positives (type I error), only voxels with a z score > 3.09 ($p < 0.001$, uncorrected) and with a volume > 180 mm³ (five voxels) were considered as activated voxels (Braver et al., 2001).

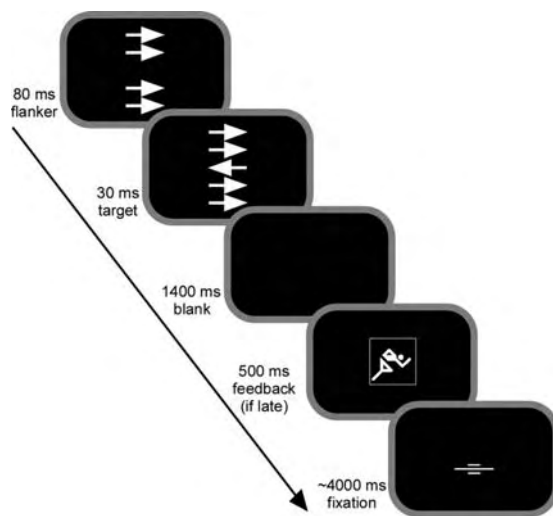


Figure 1. Sequence of stimulus events in the speeded flanker task. Participants viewed four task-irrelevant flanker arrows, followed by a central arrow that indicated the response direction and pointed to the same or opposite direction as flanker arrows. Compatible (same direction) and incompatible (opposite direction) trials appeared in randomized order and with the same probability. For trials in which subjects responded slower than a dynamically adapting individual response deadline, a symbolic feedback occurred urging the subject to speed up in consecutive trials.

In a second analysis testing whether the single-trial ERN measure covaries with the fMRI signal, a parametric design was used (Büchel et al., 1996, 1998). The single-trial amplitudes vector was used as a parameter referring to the onsets of all responses in the task, regardless of their accuracy and speed. The design matrix furthermore contained two onset vectors for late-response feedbacks and nonevents. The six translational and rotational motion correction parameters were included as additional regressors.

Results

Behavioral results

While participants underwent concurrent EEG and fMRI data acquisition, they performed a speeded flanker task. They were required to respond with button-presses according to the direction indicated by a centrally presented target arrow, which was surrounded by irrelevant but distracting flanker arrows (Fig. 1). Participants made errors on 0.58% (SEM, 0.16) of compatible and 17.23% (SEM, 2.17) of incompatible trials (significant difference; $t_{(12)} = 7.75$; $p < 0.0001$). The number of compatible errors was insufficient for meaningful statistical analyses, such that this stimulus–response type was excluded from further analysis. Hit reaction times were 380.8 ms (SEM, 7.9) for compatible and 445.0 ms (SEM, 8.1) for incompatible trials (significant difference; $t_{(12)} = 21.26$; $p < 0.0001$). The mean deadline was 475.7 ms (SEM, 17.7). It was missed in 9.46% (SEM, 1.8) of compatible and in 27.69% (SEM, 3.50) of incompatible trials. Error reaction times for incompatible trials were 388.2 ms (SEM, 9.8), thus being significantly shorter than for incompatible correct trials ($t_{(12)} = 4.41$; $p < 0.001$). In sum, these behavioral results are consistent with previous findings for flanker tasks (Eriksen and Eriksen, 1974; Ullsperger and von Cramon, 2001). Importantly, there was a sufficient numbers of errors for incompatible trials to allow meaningful data analyses.

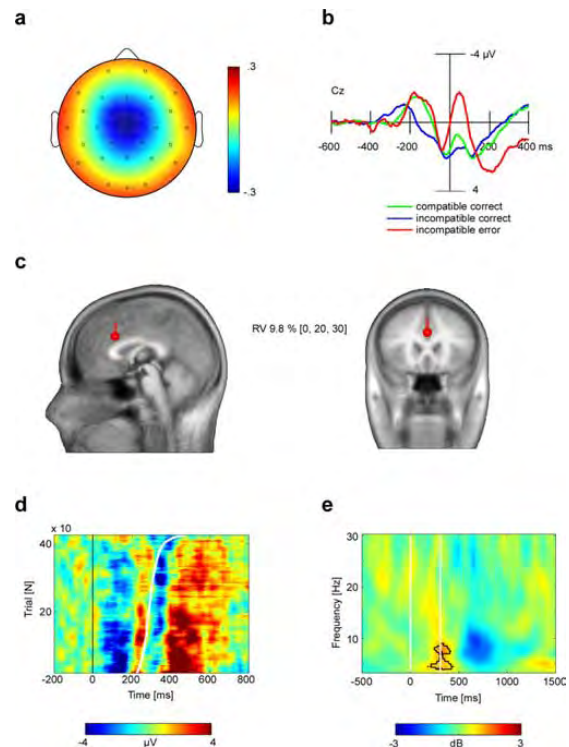


Figure 2. The selected ICs are equivalent to the scalp-recorded ERN. *a*, Identified components were characterized by a radial central topography. Depicted is the grand mean IC topography, after root-mean-square normalization (arbitrary units). *b*, Grand average ($n = 13$ subjects) IC activation ERPs for the vertex electrode (Cz), time-locked to response-onset times, revealed the ERN in the incompatible error condition. Negativity is plotted upwards. *c*, Informed dipole seeding of the grand mean IC topography shown in *a*, at Talairach coordinates (x, y, z) = 0, 20, 30. This location was derived from standard analysis of the concurrently recorded fMRI contrasting incompatible error and incompatible correct trials. The equivalent current dipole, which explained 90.2% of the variance, is plotted on a canonical magnetic resonance image template of the human head. RV, Residual variance. *d*, ERP-image plot of IC incompatible error trials at vertex electrode (Cz) aligned to stimulus onset (0). Sorting the trials by reaction time (sigmoid white line) and smoothing with a moving average across 30 trials visualizes the ERN–reaction time relationship. *e*, Time–frequency analysis of the total power difference (in decibels) between IC incompatible error and incompatible correct trials. Significantly more theta activity for the error condition is indicated by the black contour line. The white vertical lines denote the stimulus onset time (0 ms) and mean reaction time for erroneous responses, respectively.

EEG signal analysis and identification of independent component related to performance monitoring

After denoising the EEG from MR gradient and ballistocardiac artifacts, ERPs were computed (Fig. S1, available at www.jneurosci.org as supplemental material). As expected, a frontocentral ERN was clearly visible for incompatible error trials but strongly reduced, if not absent, for the correct response conditions (Fig. S2, available at www.jneurosci.org as supplemental material). To separate ERN-related EEG signals from other brain processes and artifacts, we performed ICA on each subject's MR-denoised raw EEG data (Bell and Sejnowski, 1995). ICA returns a set of spatial filters, which yield component activations that are maximally temporally independent from each other. In each subject, we identified one IC that met the following two criteria and therefore was the best candidate to account for the ERN. First, the IC

should have a near-radial central topography. Second, its backprojected ERP time course should yield a more negative deflection at the response interval in the incompatible error compared with the incompatible correct condition. The topographies of the selected ICs for each subject are shown in the supplemental material (Fig. S3, available at www.jneurosci.org). Independent components reflecting the parietal error positivity (Pe) or the N200 were not observed.

We performed several analyses to test whether the IC selected for each subject indeed reflects the spatial and temporal characteristics of the ERN. First, we performed fMRI-informed source modeling of the grand average IC map (Fig. 2*a,c*). A single equivalent current dipole was seeded into the RCZ, with the exact location taken from the conventional second-level fMRI analysis contrasting incompatible error and incompatible correct trials [Talairach coordinates (x, y, z) = 0, 20, 30] (Table 1) (see Fig. 5). This source dipole accounted for 90.2% of the variance (Fig. 2*c*). Seeding additional dipoles into other cortical areas identified by the same fMRI analysis (lateral prefrontal cortex, left anterior inferior insula) did not improve the model fit, suggesting that the identified ICs represent activity originating in the RCZ.

Second, grand mean ERPs of the back-projected IC activations revealed a clear ERN in the incompatible error condition (Fig. 2*b*). These IC ERPs strongly resembled those from the original scalp channel data, but their topography appeared now free of artifact contributions (Fig. S4, available at www.jneurosci.org as supplemental material). Typically, the ERPs showed a polarity reversal at outer electrodes (e.g., F7/8, P7/8) (see Fig. S4, available at www.jneurosci.org as supplemental material), which, taking into account the common average reference, supports the notion that the selected IC can be explained by a single equivalent dipole located in the RCZ.

Third, we explored the EEG signal on a single-trial level. ERPs are usually derived by averaging across trials, which prevents the study of trial-by-trial variations of the EEG signal. To overcome this limitation, so-called ERP images were computed showing the respective single-trial IC activations sorted by reaction time. These analyses demonstrate a good signal-to-noise ratio, because the negativity immediately after erroneous responses was evident in most trials (Fig. 2*d*).

Fourth, we performed a time–frequency analysis of the IC single-trial signals. ERPs and ERP images both suggest that the ERN was preceded and followed by a positive deflection, indicating an oscillation in the theta frequency range (Luu et al., 2004). Indeed, time–frequency analysis revealed a prominent theta power increase after stimulus onset lasting for ~600 ms. This theta power increase was significant in 11 of 13 subjects for the incompatible correct condition and in 10 of 13 subjects in the incompatible error condition (randomization test; $p < 0.01$). At the time of the erroneous response, the theta power increase was significantly stronger in incompatible error than in incompatible correct trials (Fig. 2*e*) (binomial; $p < 0.00001$). In summary, component map topography, fMRI-informed source modeling, ERP component morphology, and time–frequency results jointly led us to conclude that the IC identified in each subject is very likely equivalent to the ERN as usually obtained outside the MR environment.

Table 1. Results of fMRI analyses

| | Hemisphere | Coordinates | | | z value |
|--|------------|-------------|----|-----|---------|
| | | x | y | z | |
| Conventional analysis contrasting incompatible error versus incompatible correct | | | | | |
| Rostral cingulate zone (24) | Left | −2 | 20 | 30 | 4.02* |
| Inferior anterior insula | Left | −29 | 12 | −12 | 4.63 |
| Superior frontal gyrus (6/8) | Right | 12 | 11 | 57 | 3.76* |
| Sulcus frontalis inferior (9/46) | Left | −29 | 36 | 27 | 3.54* |
| EEG-informed analysis | | | | | |
| Rostral cingulate zone (32/6/8) | | 0 | 17 | 42 | −3.86* |

The table shows conventional random effects analysis modeling compatible correct, incompatible correct, and incompatible error trials with separate onset vectors. Contrast incompatible correct versus compatible correct is shown. Parametric analysis used single-trial amplitude quantification of error-related independent component of the EEG data set. Brodmann areas are in parentheses. * $p < 0.001$ and spatial extent criterion met.

Single-trial EEG amplitudes and the dynamics of performance monitoring

A key prediction that can be derived from performance monitoring models is that physiological signatures of error monitoring should predict behavioral adjustments at the single-trial level. To address this, ERN magnitude was obtained in every single trial by taking peak-to-peak measures of the 2–10 Hz bandpass-filtered IC signals (Fig. 3*a*). We examined the relationship of the resulting single-trial amplitudes for each subject (Fig. 3*b*) to behavior (Fig. 3*c*). For incompatible errors, the single-trial amplitude was significantly correlated with reaction time, such that short RTs were associated with high single-trial amplitudes ($b = 5.48$; $p = 0.002$; one-sided t test). Interestingly, the opposite relationship was found for incompatible correct trials. Here, short RTs were associated with small single-trial amplitudes ($b = -2.14$; $p = 0.046$), consistent with previous findings for the ERN in speeded tasks using a deadline procedure (Luu et al., 2000). However, these effects did not remain significant when RT and single-trial amplitude outliers (values > 3 SD) and trials followed by a late feedback were excluded from the analysis (incompatible errors, $b = 2.61$, $p = 0.103$; incompatible correct, $b = -2.01$, $p = 0.140$).

More importantly, we identified a clear relationship between ERN dynamics and subsequent behavioral adjustments. We found that higher single-trial amplitudes were associated with longer RTs on conflict trials after errors (Fig. 3*c,d*). Thus, activity variations of the performance monitoring system, as estimated by the single-trial EEG measure, significantly predicted posterror slowing ($b = -5.38$; $p = 0.043$). After exclusion of outliers and trials followed by the late feedback, this effect was even more pronounced ($b = -5.90$; $p = 0.032$). Moreover, this effect could not be explained by a correlation between RTs on errors and RTs on subsequent trials, which was absent (second level mean; $r = 0.06$; NS). The present analysis thus demonstrates that posterror slowing (Rabbitt, 1966) was driven by postresponse electrophysiological activity in the RCZ.

Trial-by-trial coupling of EEG and fMRI

A key question in the present context is whether hemodynamic signals related to error monitoring covary with the single-trial ERN (Nunez and Silberstein, 2000; Logothetis et al., 2001). If present, such a relationship should only be found in brain regions specifically involved in performance monitoring. To this end, we used the EEG single-trial amplitude to predict the fMRI BOLD signal. To take into account the slow time course of fMRI BOLD, the single-trial EEG amplitudes were convolved with the hemodynamic response function at button-press onset times. The following parametric random effects fMRI analysis identified a significant correlation of the single-trial amplitude with the BOLD response specifically in the RCZ (Fig. 4, Table 1). The direction of

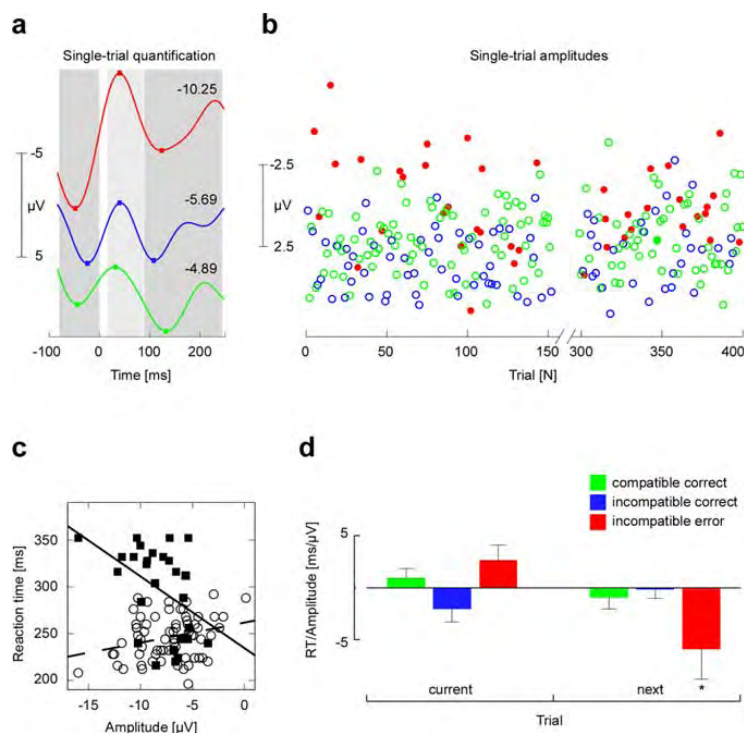


Figure 3. *a*, Quantification of IC single-trial amplitudes exemplified for three trials from the three different conditions. The color code is as in *d*. The mean of the ERN preceding (−80–0 ms) and after (85–240 ms) positive peaks was subtracted from the negative peak occurring after each button-press (15–85 ms), giving an amplitude for every single trial. The numbers state the corresponding single-trial amplitude. *b*, Resulting single-trial amplitudes for a representative subject over the course of ~250 trials (of 400 trials in total). For visualization, the single single-trial amplitude values are color-coded according to the stimulus–response condition. The color code is as in *d*. Note the considerable amount of variance within each experimental condition presumably reflecting the varying strength of performance monitoring. *c*, Single-subject example showing for the incompatible error condition the relationship between single-trial amplitude and reaction time, separately for the current trial (open circles; dashed regression curve) and for the reaction time of the following trial (filled squares; solid regression curve). *d*, Second-level result across all $n = 13$ subjects, showing the mean reaction time to single-trial amplitudes slope (\pm SEM) for all three conditions after removal of outlier (>3 SD) and late feedback trials, separately for the same trial and for the next trial. * $p < 0.05$.

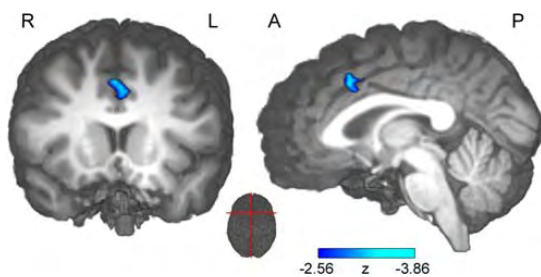


Figure 4. Result of the EEG-informed parametric fMRI analysis based on IC single-trial amplitudes, plotted on an individual brain. fMRI signals correlated with single-trial amplitudes solely in the RCZ along the banks of the cingulate sulcus [center of gravity at coordinates (x, y, z) = 0, 17, 42; $z = -3.86$]. The left part shows coronal view; the right part shows the sagittal view on the right hemisphere. The red lines on the middle top view inset indicate slice sections. R, Right; L, left; A, anterior; P, posterior.

the observed relationship confirmed that trials with greater absolute single-trial ERN amplitudes were associated with stronger BOLD responses in the RCZ. Although the EEG-informed approach as well as the conventional fMRI analysis identified the

RCZ, the conventional fMRI contrast revealed additional brain structures, such as insular and lateral prefrontal cortex (Fig. 5, Table 1). The conventional contrast extracted error-specific signal increases, whereas performance-monitoring-related activations present in both correct and incorrect trials cancelled out to a large degree. The EEG-informed fMRI analysis, on the other hand, was more specific to variations of the monitoring signal itself. These differences in process specificity might also account for the observation that the maxima of the RCZ foci were separated by ~12 mm in inferior–superior direction (Ullsperger and von Cramon, 2001). However, with the given the between-plane resolution, a functional interpretation of this finding remains speculative.

Discussion

The present study demonstrates an event-related trial-by-trial coupling of simultaneously recorded EEG, fMRI, and behavior in humans. The major advantage of simultaneous recordings is that these different measures are studied under identical sensory and motivational conditions, thereby allowing the investigation of trial-by-trial fluctuations. We found the single-trial ERN to be systematically related to ensuing behavioral adjustments. As predicted by performance-monitoring models, the ERN seems to signify the likelihood that the action outcome is worse than expected (Holroyd et al., 2004; Brown and Braver, 2005). On error trials, this likelihood estimate has been suggested to be driven primarily by postresponse conflict between executed and concurrently activated response tendencies (Yeung et al., 2004). Moreover, the single-trial ERN amplitude reflects activation of the RCZ neurons involved in controlling subsequent adjustments. This finding is paralleled by invasive recordings showing that performance adjustments are preceded by enhanced firing rates of RCZ neurons (Shima and Tanji, 1998; Williams et al., 2004). Our finding that posterror slowing was predicted by the single-trial ERN has not been reported in previous studies, in which this relationship was investigated by the study of the averaged ERN and correlations across subjects. At the group level, however, many other factors may contribute to averaged ERN amplitude variations (e.g., skull thickness, variations of the cingulate sulcus, and trait factors) (Pailing and Segalowitz, 2004). Therefore, a weak relationship between ERN and posterror slowing can be easily missed because of lack of statistical power, which might help to explain previously published mixed findings on the posterror slowing effect. In line with our results, however, is one study investigating this relationship at a within-subjects level and reporting that larger ERN amplitudes predicted increased posterror slowing (Gehring et al., 1993). We conclude that the single-trial measure of the ERN reflects trial-by-trial fluctuations in the activity of performance monitoring circuits that are responsible

for behavioral adjustments. The ability to measure the dynamics of the monitoring signal will significantly facilitate addressing its relationship to immediate and long-term control adjustments (Ridderinkhof et al., 2004).

The peak-to-peak measure used to quantify performance-monitoring-related EEG activity takes into account the ERN and the subsequent positive peak, which is also maximal at frontocentral sites. This frontocentral positive EEG deflection seems to result from activity in the RCZ as well, which is consistent with a previous source localization study (van Veen and Carter, 2002). Note that this positivity should not be confused with the parietal error positivity *Pe* (Falkenstein et al., 1990, 2000), which was not captured in the ICA decomposition. Furthermore, it has been hypothesized that ERN and preresponse N200 on correct trials may both reflect similar processes, namely response conflict monitoring (Yeung et al., 2004). We did not obtain a reliable N200 conflict effect in our data; in particular, we found no IC reflecting an N200 modulation. Usually, the N200 preresponse conflict effect is very small (up to $2\mu\text{V}$) (van Veen and Carter, 2002), and we therefore may have missed it as a result of the recording environment or the limited number of electrodes. The relationship between ERN and the N200 conflict effect remains an open question that should be optimally addressed by ICA decomposition of high-density EEG data acquired outside the MR environment.

For resting conditions, it has been shown previously that simultaneous EEG and fMRI BOLD can reveal systematic correlations (Goldman et al., 2002; Laufs et al., 2003). The event-related trial-by-trial correlation approach applied here presents a new strategy for integrating EEG and fMRI. Alternative approaches such as fMRI-informed ERP dipole seeding (Ullsperger and von Cramon, 2001; Thees et al., 2003) implicitly assume a tight link between the neural generators of ERPs and fMRI activation foci. However, as exemplified by the present study, conventional fMRI contrasts may well reveal cortical regions that do not comprise neuronal sources of the ERP and vice versa (Nunez and Silberstein, 2000). Because fMRI BOLD and ERP components can differ with regard to their sensitivity to experimental manipulations, fMRI-informed dipole seeding is not necessarily a valid solution of the inverse problem in EEG.

High magnetic fields provide adverse conditions for EEG recordings. Application of ICA offers a practical solution to minimize artifacts and to identify functionally meaningful EEG activity on a trial-by-trial basis (Debener et al., 2005; Makeig et al., 2002, 2004). The identified IC reflected all features of the ERN, including scalp topography, ERP morphology, and time–frequency characteristics. We also found that the fMRI-informed dipole seeding approach confirmed the RCZ as the major source of the selected ICA correlate of the ERN. This latter finding also validates the main assumption of ICA as applied to EEG data. Under favorable circumstances, a clean independent component should reflect the ongoing activity of a synchronous piece of cortex expressing a dipolar projection. More importantly, we conclude that the covariation of the single-trial ERN measure with

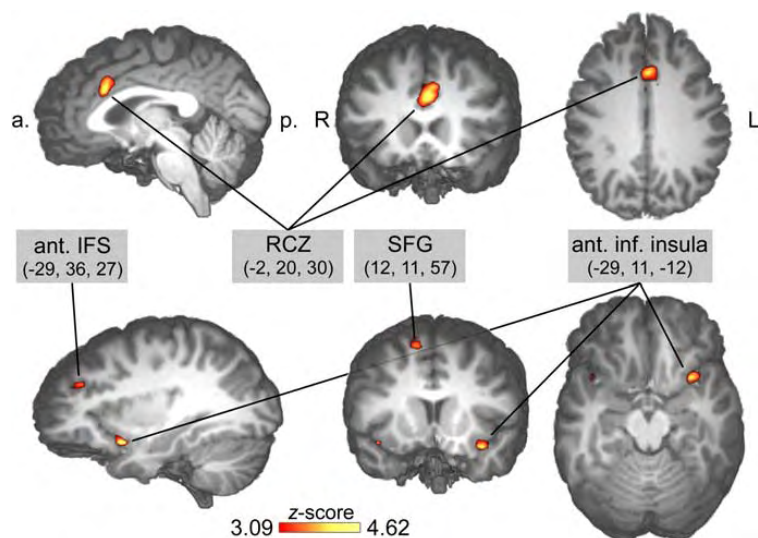


Figure 5. Significant error-related fMRI activations revealed by the conventional random effects analysis contrasting conditions incompatible error versus incompatible correct. a., Anterior; p., posterior; R, right; L, left; ant., anterior; inf., inferior; SFG, superior frontal gyrus; IFS, inferior frontal sulcus.

the fMRI BOLD response in the RCZ strongly supports the proposed RCZ source of the ERN (Holroyd et al., 2004; Ridderinkhof et al., 2004; Ullsperger and von Cramon, 2004). Thus, the fMRI signal and the ICA single-trial correlate of the ERN appear to reflect directly related neuronal and metabolic processes in the RCZ. Our data fit well with animal research on a coupling between BOLD and local field potentials (Logothetis et al., 2001; Logothetis, 2003), the latter being known to be the basis of the scalp-recorded EEG (Nunez and Silberstein, 2000).

The joint study of electrophysiological and hemodynamic signatures of regional event-related brain activity seems very promising because future studies may succeed in identifying multiple functionally relevant ICs. This would allow to relate several IC time courses to regional fMRI activation, thereby holding great potential to address two cardinal questions in the field of cognitive neuroscience. First, concurrent single-trial EEG/fMRI will facilitate addressing the dynamic interplay between ongoing and event-related brain activity (Arieli et al., 1996; Makeig et al., 2002). Second, adding electrophysiological information provides high temporal precision and thus helps to shape models on how cognitive processes are dynamically implemented in distinct cortical areas (Stephan et al., 2004). By successfully demonstrating a trial-by-trial coupling of noninvasive event-related EEG and fMRI, new avenues are opened for future experiments that address the dynamics of information processing within both anatomically and functionally defined neural networks.

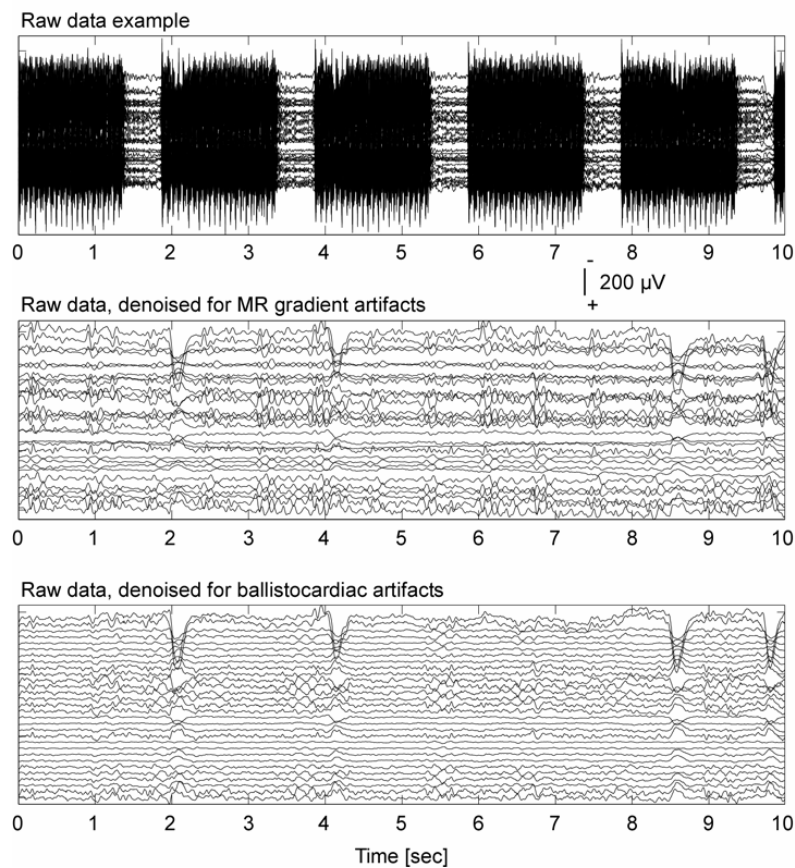
References

- Aguirre GK, Zarahn E, D'Esposito M (1997) Empirical analyses of BOLD fMRI statistics. II. Spatially smoothed data collected under null-hypothesis and experimental conditions. *NeuroImage* 5:199–212.
- Allen PJ, Polizzi G, Krakow K, Fish DR, Lemieux L (1998) Identification of EEG events in the MR scanner: the problem of pulse artifact and a method for its subtraction. *NeuroImage* 8:229–239.
- Allen PJ, Josephs O, Turner R (2000) A method for removing imaging artifact from continuous EEG recorded during functional MRI. *NeuroImage* 12:230–239.
- Arieli A, Sterkin A, Grinvald A, Aertsen A (1996) Dynamics of ongoing

- activity: explanation of the large variability in evoked cortical responses. *Science* 273:1868–1871.
- Bell AJ, Sejnowski TJ (1995) An information-maximization approach to blind separation and blind deconvolution. *Neural Comput* 7:1129–1159.
- Braver TS, Barch DM, Kelley WM, Buckner RL, Cohen NJ, Miezin FM, Snyder AZ, Ollinger JM, Akbudak E, Conturo TE, Petersen SE (2001) Direct comparison of prefrontal cortex regions engaged by working and long-term memory tasks. *NeuroImage* 14:48–59.
- Brown JW, Braver TS (2005) Learned predictions of error likelihood in the anterior cingulate cortex. *Science* 307:1118–1121.
- Büchel C, Wise RJS, Mummery CJ, Poline J-B, Friston KJ (1996) Nonlinear regression in parametric activation studies. *NeuroImage* 4:60–66.
- Büchel C, Holmes AP, Rees G, Friston KJ (1998) Characterizing stimulus-response functions using nonlinear regressors in parametric fMRI experiments. *NeuroImage* 8:140–148.
- Debener S, Makeig S, Delorme A, Engel AK (2005) What is novel in the novelty oddball paradigm? Functional significance of the novelty P3 event-related potential as revealed by independent component analysis. *Brain Res Cogn Brain Res* 22:309–321.
- Dehaene S, Posner MI, Tucker DM (1994) Localization of a neural system for error detection and compensation. *Psychol Sci* 5:303–305.
- Delorme A, Makeig S (2004) EEGLAB: an open source toolbox for analysis of single trial EEG dynamics including independent component analysis. *J Neurosci Methods* 134:9–21.
- Eriksen BA, Eriksen CW (1974) Effects of noise letters upon the identification of a target letter in a nonsearch task. *Percept Psychophys* 16:143–149.
- Falkenstein M, Hohnsbein J, Hoormann J, Blanke L (1990) Effects of errors in choice reaction tasks on the ERP under focused and divided attention. In: *Psychophysiological brain research* (Brunia CHM, Gaillard AWK, Kok A, eds), pp 192–195. Tilburg, The Netherlands: Tilburg UP.
- Falkenstein M, Hoormann J, Christ S, Hohnsbein J (2000) ERP components on reaction errors and their functional significance: a tutorial. *Biol Psychol* 51:87–107.
- Friston KJ, Holmes AP, Poline JB, Grasby PJ, Williams SC, Frackowiak RS, Turner R (1995) Analysis of fMRI time-series revisited. *NeuroImage* 2:45–53.
- Friston KJ, Fletcher P, Josephs O, Holmes A, Rugg MD, Turner R (1998) Event-related fMRI: characterizing differential responses. *NeuroImage* 7:30–40.
- Garavan H, Ross TJ, Murphy K, Roche RA, Stein EA (2002) Dissociable executive functions in the dynamic control of behavior: inhibition, error detection, and correction. *NeuroImage* 17:1820–1829.
- Gehring WJ, Goss B, Coles MG, Meyer DE, Donchin E (1993) A neural system for error detection and compensation. *Psychol Sci* 4:385–390.
- Goldman RI, Stern JM, Engel Jr J, Cohen MS (2002) Simultaneous EEG and fMRI of the alpha rhythm. *NeuroReport* 13:2487–2492.
- Holmes AP, Friston KJ (1998) Generalisability, random effects and population inference. *NeuroImage* 7:754.
- Holroyd CB, Nieuwenhuis S, Mars RB, Coles MGH (2004) Anterior cingulate cortex, selection for action, and error processing. In: *Cognitive neuroscience of attention* (Posner MI, ed), pp 219–231. New York: The Guilford Press.
- Josephs O, Turner R, Friston K (1997) Event-related fMRI. *Hum Brain Mapp* 5:243–248.
- Kerns JG, Cohen JD, MacDonald III AW, Cho RY, Stenger VA, Carter CS (2004) Anterior cingulate conflict monitoring and adjustments in control. *Science* 303:1023–1026.
- Laufs H, Krakow K, Sterzer P, Eger E, Beyerle A, Salek-Haddadi A, Kleinschmidt A (2003) Electroencephalographic signatures of attentional and cognitive default modes in spontaneous brain activity fluctuations at rest. *Proc Natl Acad Sci USA* 100:11053–11058.
- Lee TW, Girolami M, Sejnowski TJ (1999) Independent component analysis using an extended infomax algorithm for mixed subgaussian and supergaussian sources. *Neural Comput* 11:417–441.
- Logothetis NK (2003) The underpinnings of the BOLD functional magnetic resonance imaging signal. *J Neurosci* 23:3963–3971.
- Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A (2001) Neurophysiological investigation of the basis of the fMRI signal. *Nature* 412:150–157.
- Lohmann G, Müller K, Bosch V, Mentzel H, Hessler S, Chen L (2001) LIP-SIA—a new software system for the evaluation of functional magnetic resonance images of the human brain. *Comput Med Imaging Graph* 25:449–457.
- Luu P, Flaisch T, Tucker DM (2000) Medial frontal cortex in action monitoring. *J Neurosci* 20:464–469.
- Luu P, Tucker DM, Makeig S (2004) Frontal midline theta and the error-related negativity: neurophysiological mechanisms of action regulation. *Clin Neurophysiol* 115:1821–1835.
- Makeig S, Westerfield M, Jung TP, Enghoff S, Townsend J, Courchesne E, Sejnowski TJ (2002) Dynamic brain sources of visual evoked responses. *Science* 295:690–694.
- Makeig S, Debener S, Onton J, Delorme A (2004) Mining event-related brain dynamics. *Trends Cogn Sci* 8:204–210.
- Miezin FM, Maccotta L, Ollinger JM, Petersen SE, Buckner RL (2000) Characterizing the hemodynamic response: effects of presentation rate, sampling procedure, and the possibility of ordering brain activity based on relative timing. *NeuroImage* 11:735–759.
- Niazy RK, Beckmann CF, Iannetti GD, Brady JM, Smith SM (2005) Removal of fMRI environment artifacts from EEG data using optimal basis sets. *NeuroImage* 28:720–737.
- Nunez PL, Silberstein RB (2000) On the relationship of synaptic activity to macroscopic measurements: does co-registration of EEG with fMRI make sense? *Brain Topogr* 13:79–96.
- Pailing PE, Segalowitz SJ (2004) The error-related negativity as a state and trait measure: motivation, personality, and ERPs in response to errors. *Psychophysiology* 41:84–95.
- Rabbitt PM (1966) Errors and error correction in choice-response tasks. *J Exp Psychol* 71:264–272.
- Ridderinkhof KR, Ullsperger M, Crone EA, Nieuwenhuis S (2004) The role of the medial frontal cortex in cognitive control. *Science* 306:443–447.
- Shima K, Tanji J (1998) Role for cingulate motor area cells in voluntary movement selection based on reward. *Science* 282:1335–1338.
- Stephan KE, Harrison LM, Penny WD, Friston KJ (2004) Biophysical models of fMRI responses. *Curr Opin Neurobiol* 14:629–635.
- Talairach P, Tournoux J (1988) A stereotactic coplanar atlas of the human brain. Stuttgart, Germany: Thieme.
- Thees S, Blankenburg F, Taskin B, Curio G, Villringer A (2003) Dipole source localization and fMRI of simultaneously recorded data applied to somatosensory categorization. *NeuroImage* 18:707–719.
- Ullsperger M, von Cramon DY (2001) Subprocesses of performance monitoring: a dissociation of error processing and response competition revealed by event-related fMRI and ERPs. *NeuroImage* 14:1387–1401.
- Ullsperger M, von Cramon DY (2004) Neuroimaging of performance monitoring: error detection and beyond. *Cortex* 40:593–604.
- van Veen V, Carter CS (2002) The timing of action-monitoring processes in the anterior cingulate cortex. *J Cogn Neurosci* 14:593–602.
- Williams ZM, Bush G, Rauch SL, Cosgrove GR, Eskandar EN (2004) Human anterior cingulate neurons and the integration of monetary reward with motor responses. *Nat Neurosci* 7:1370–1375.
- Worsley KJ, Friston KJ (1995) Analysis of fMRI time-series revisited—again. *NeuroImage* 2:173–181.
- Yeung N, Cohen JD, Botvinick MM (2004) The neural basis of error detection: conflict monitoring and the error-related negativity. *Psychol Rev* 111:931–959.
- Zarahn E, Aguirre GK, D'Esposito M (1997) Empirical analyses of BOLD fMRI statistics. I. Spatially unsmoothed data collected under null-hypothesis conditions. *NeuroImage* 5:179–197.

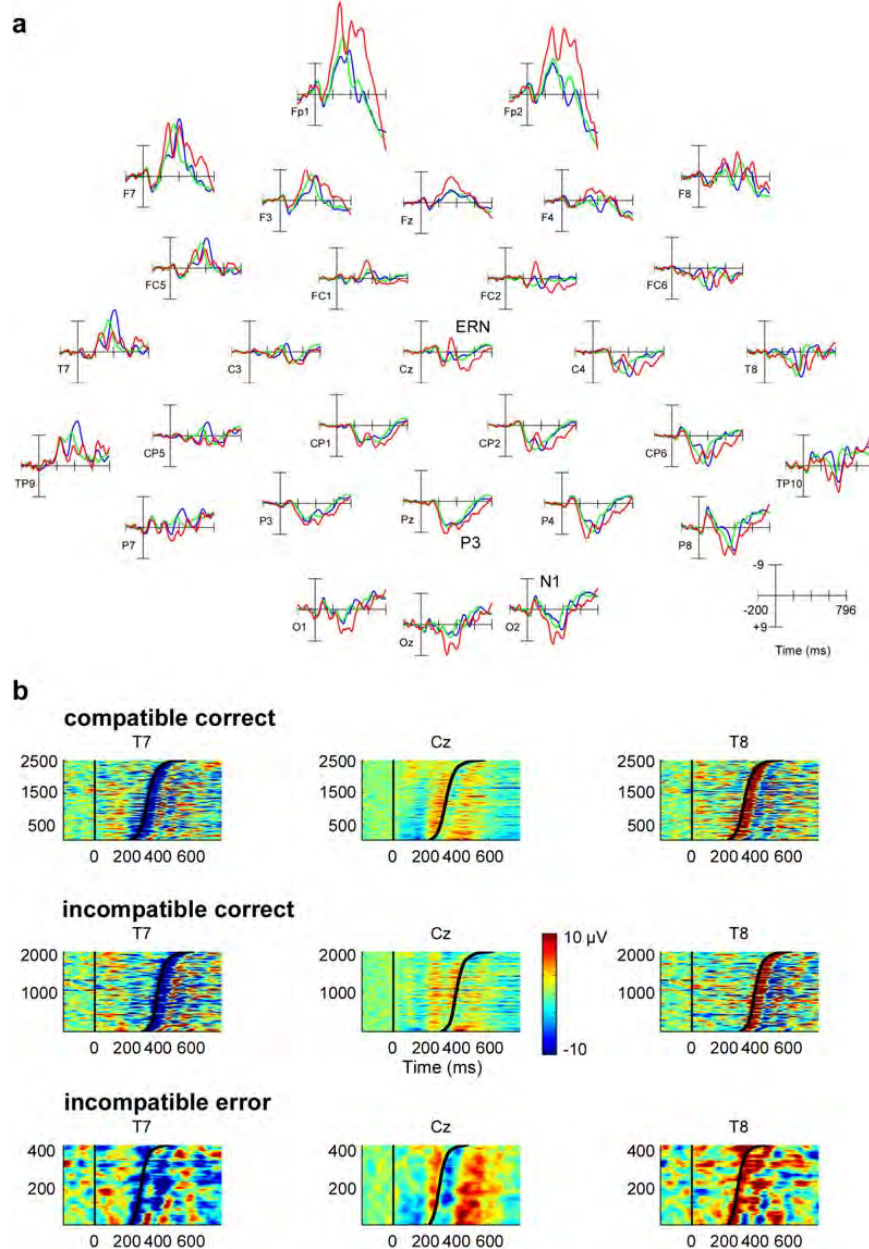
Supplemental Material***Trial-by-trial coupling of concurrent EEG and fMRI identifies the dynamics of performance monitoring***

By Stefan Debener, Markus Ullsperger, Markus Siegel, Katja Fiehler, D. Yves von Cramon, and Andreas K. Engel

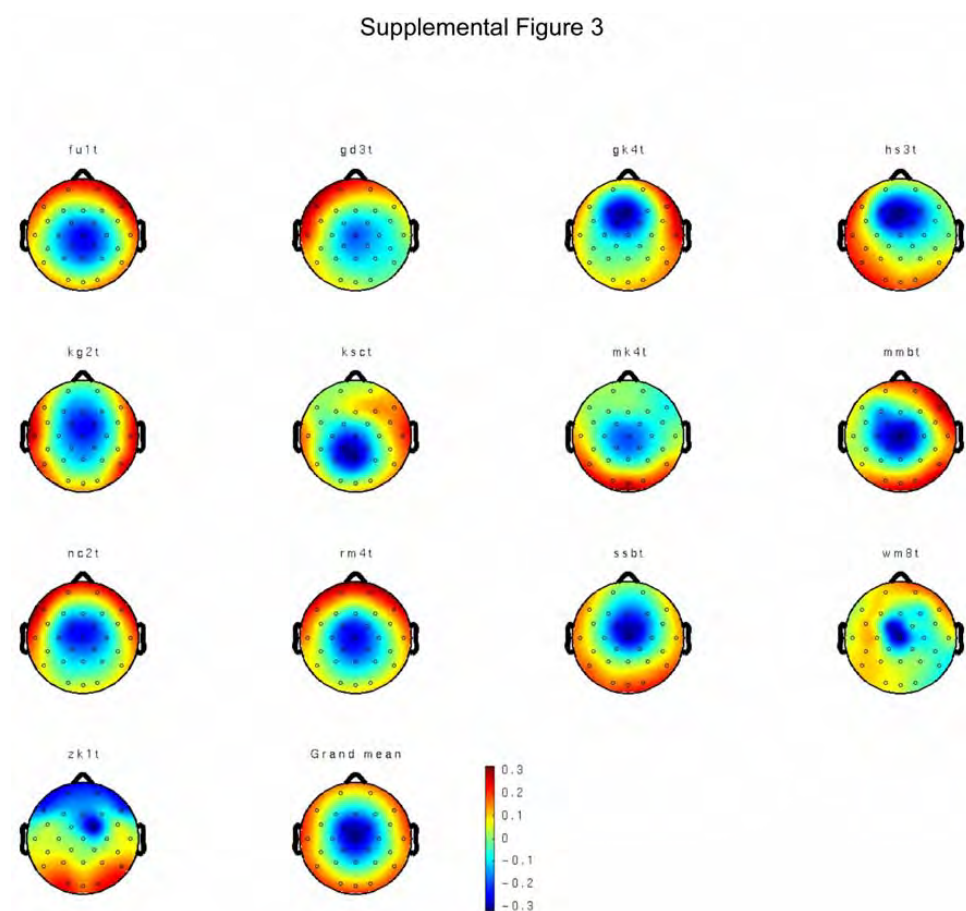
Supplemental Figure 1

Supplemental Figure 1. Exemplary time series of EEG data after recording (upper row), after correction for MR gradient artifacts (middle row), and after correction for ballistocardiac artifacts (lower row).

Supplemental Figure 2

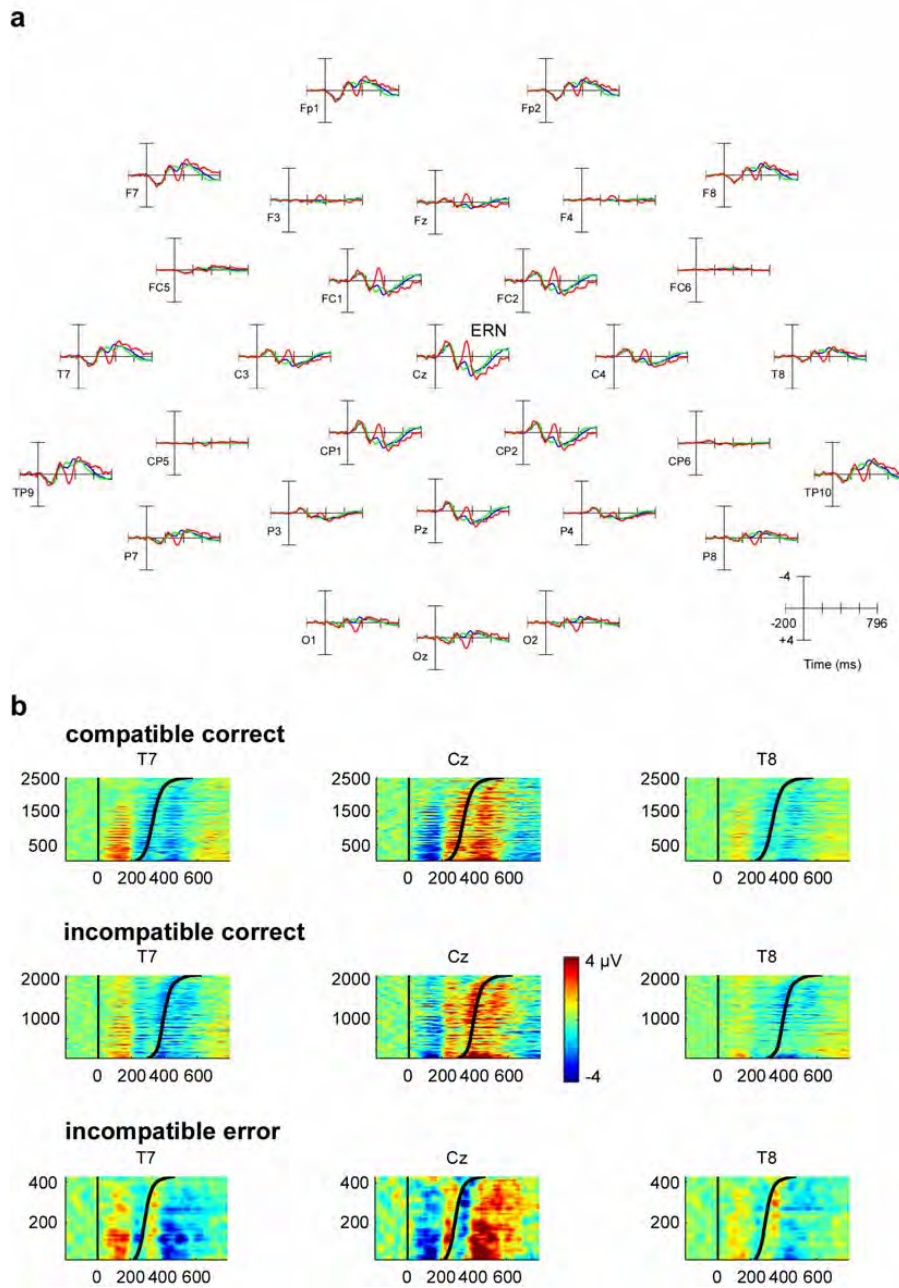


Supplemental Figure 2. Stimulus-locked grand mean average waveforms of scalp-recorded ERP data for the three stimulus-response conditions (green = compatible correct, blue = incompatible correct, red = incompatible error). The lower part depicts the ERP images for the three stimulus-response conditions. Trials are sorted by ascending reaction time, as indicated by the black sigmoid curve.



Supplemental Figure 3. Scalp topography maps of the independent component accounting for performance-monitoring-related EEG activity shown for each individual subject and for the grand mean average across subjects (root mean square normalized).

Supplemental Figure 4



Supplemental Figure 4. Stimulus-locked grand mean average waveforms of the EEG time course resulting from backprojection of the independent component related to performance monitoring, shown for the three stimulus-response conditions (color code as in Supplemental Fig. 2). The lower part depicts the ERP images for the three stimulus-response conditions. Trials are sorted by ascending reaction time, as indicated by the black sigmoid curve.

Chapter 6

The role of the medial frontal cortex in cognitive control

Concluding Part II, Chapter 6 provides a comprehensive metaanalysis of the fMRI findings on performance monitoring published between 1997 and March, 2004. It relates the neuroimaging findings to EEG studies in humans and invasive recordings in non-human primates. The major result is a unified view of the pFMC's role in performance monitoring and cognitive control. It is engaged whenever the state of an individual or the outcome of an individual's action is worse than intended. It is also active when the outcome of an action is at risk, e.g., during response conflict and decision uncertainty. In line with this view the pFMC has been proposed to be involved in estimating error likelihood (Brown and Braver, 2005). The pFMC appears to signal the need for adjustments to optimize the individual's state and the outcome of his/her actions (Ullsperger and von Cramon, 2004).

An alternative view suggesting that the pFMC, particularly the RCZ, is involved in the control of autonomic responses and arousal (Critchley et al., 2003, 2005), does not necessarily contradict our hypothesis. As pointed out by Paus (2001), the anatomical location of the RCZ is well-suited to form an interface between cognitive, motor, emotional and autonomic functions.

The idea that the pFMC underlies higher order social cognition (Eisenberger and Lieberman, 2004) may be somewhat too specific, however. Social exclusion, as investigated in the studies by Eisenberger and Lieberman, is also an outcome that does not match the individual's goals and that requires compensation and adjustments. We believe that even very complex behavioral phenomena can be reconciled with basic cognitive principles of reward processing and adaptive behavior. Therefore, we favor the view that the *pFMC monitors for potential and real divergence from the intended and expected state of the individual, and signals the need for adjustments to prevent harm and to optimize goal achievement. This signal seems to be conveyed to regions involved in cognitive and motor control, autonomic and affective regulation, rendering it an essential prerequisite of flexible, adaptive human behavior. It needs to function on all levels of information processing, starting with primary reinforcers (reward, pain), including increasingly abstract cognitive operations (monitoring for errors, response conflicts and uncertainty), and extending even to the social level* (Ullsperger et al., 2004).

Studies published after completion of the metaanalysis further supported its results (e.g., Hester et al., 2004; Rushworth et al., 2004; Brown and Braver, 2005). As a study investigating how the brain makes use of feedback in a modified task switching paradigm indicated, it is more the potential utility of information for adjustments rather than the negative outcome itself that drives the activity in the pFMC (Walton et al., 2004). Currently the adjustments themselves are being moved into the focus of research. *How does the pFMC signal the need, and which brain areas it communicates with in this attempt?* Interactions with the lateral prefrontal cortex have been found (Garavan et al., 2002; Kerns et al., 2004). A recent study showed response-conflict-induced changes in

perceptual association cortices, likely to reflect adjustments of stimulus perceptions to the current task demands (Egner and Hirsch, 2005). A challenge for future research is to demonstrate the way how information about the necessary adjustments is conveyed to the brain regions involved in perceptual processing.

Note that in the following paper the term pMFC (posterior medial frontal cortex) has been used for editorial reasons. It is synonymous to pFMC.

merical reference may play a role in the emergence of a fully formed conception of number. The challenge now is to delineate that role.

References and Notes

1. L. Gleitman, A. Papafragou, in *Handbook of Thinking and Reasoning*, K. J. Holyoak, R. Morrison, Eds. (Cambridge Univ. Press, New York, in press).
2. D. Gentner, S. Golden-Meadow, Eds., *Language and Mind: Advances in the Study of Language and Thought* (MIT Press, Cambridge, MA, 2003).
3. S. C. Levinson, in *Language and Space*, P. Bloom, M. Peterson, L. Nadel, M. Garrett, Eds. (MIT Press, Cambridge, MA, 1996), Chap. 4.
4. R. Gelman, S. A. Cordes, in *Language, Brain, and Cognitive Development: Essays in Honor of Jacques Mehler*, E. Dupoux, Ed. (MIT Press, Cambridge, MA, 2001), pp. 279–301.
5. B. Butterworth, *The Mathematical Brain* (McMillan, London, 1999).
6. C. R. Gallistel, *The Organization of Learning* (Bradford Books/MIT Press, Cambridge, MA, 1990).
7. J. A. Fodor, *The Language of Thought* (T. Y. Crowell, New York, 1975).
8. P. Gordon, *Science* **306**, 496 (2004).
9. P. Pica, C. Lemer, V. Izard, S. Dehaene, *Science* **306**, 499 (2004).
10. D. L. Everett, (2004) <http://lings.in.man.ac.uk/info/staff/DE/cultgram.pdf> (cited by permission).
11. C. R. Gallistel, R. Gelman, in *Handbook of Thinking and Reasoning*, K. J. Holyoak, R. Morrison, Eds. (Cambridge University Press, New York, in press).
12. E. M. Brannon, H. S. Terrace, in *The Cognitive Animal: Empirical and Theoretical Perspectives on Animal Cognition*, M. Bekoff, C. Allen, Eds. (MIT Press, Cambridge, MA, 2002), pp. 197–204.
13. S. Dehaene, *The Number Sense* (Oxford University Press, Oxford, 1997).
14. R. Gelman, B. Butterworth, *Trends Cognit. Sci.*, in press.
15. L. Gleitman, J. Trueswell, K. Cassidy, R. Nappa, A. Papafragou, *Lang. Learn. Dev.*, in press.
16. S. Carey, *Daedalus* **133**, 59 (2004).
17. E. von Glaserfeld, in *The Development of Numerical Competence: Animal and Human Models*, S. T. Boysen, E. J. Capaldi (Lawrence Erlbaum Associates, Hillsdale, NJ, 1993), pp. 225–244.
18. H. Davis, R. Pélus, *Behav. Brain Sci.* **11**, 561 (1988).
19. P. B. Buckley, C. B. Gillman, *J. Exp. Psychol.* **103**, 1131 (1974).

REVIEW

The Role of the Medial Frontal Cortex in Cognitive Control

K. Richard Ridderinkhof,^{1,2*} Markus Ullsperger,³ Eveline A. Crone,⁴ Sander Nieuwenhuis⁵

Adaptive goal-directed behavior involves monitoring of ongoing actions and performance outcomes, and subsequent adjustments of behavior and learning. We evaluate new findings in cognitive neuroscience concerning cortical interactions that subserve the recruitment and implementation of such cognitive control. A review of primate and human studies, along with a meta-analysis of the human functional neuroimaging literature, suggest that the detection of unfavorable outcomes, response errors, response conflict, and decision uncertainty elicits largely overlapping clusters of activation foci in an extensive part of the posterior medial frontal cortex (pmFC). A direct link is delineated between activity in this area and subsequent adjustments in performance. Emerging evidence points to functional interactions between the pmFC and the lateral prefrontal cortex (LPFC), so that monitoring-related pmFC activity serves as a signal that engages regulatory processes in the LPFC to implement performance adjustments.

Flexible goal-directed behavior requires an adaptive cognitive control system for selecting contextually relevant information and for organizing and optimizing information processing. Such adaptive control is effortful, and therefore it may not be efficient to maintain high levels of control at all times. Here we review recent studies in cognitive neuroscience that have advanced our understanding of how the brain determines and communicates the need to recruit cognitive control. Convergent evidence suggests that the posterior medial frontal cortex (pmFC) and lateral prefrontal cortex (LPFC) are im-

portant contributors to cognitive control. Our focus is on the role of the pmFC in performance monitoring, especially in situations in which pmFC activity is followed by performance adjustments. Evaluating the adequacy and success of performance is instrumental in determining and implementing appropriate behavioral adjustments. For instance, detection of a performance error may be used to shift performance strategy to a more conservative speed/accuracy balance. Based on the evidence reviewed below, we develop the tentative hypothesis that one unified function of the pmFC is performance monitoring in relation to anticipated rewards. The monitored signals may index the failure (errors or negative feedback) or reduced probability (conflicts or decision uncertainty) of obtaining such rewards, and as such signal the need for increased control.

Performance Monitoring

Flexible adjustments of behavior and reward-based association learning require the continuous assessment of ongoing actions and the outcomes of these actions. The abil-

ity to monitor and compare actual performance with internal goals and standards is critical for optimizing behavior. We first review evidence from primate, electrophysiological, and functional neuroimaging studies that points toward the importance of pmFC areas (Fig. 1A) in monitoring unfavorable performance outcomes, response errors, and response conflicts, respectively. These conditions have in common that they signal that goals may not be achieved or rewards may not be obtained unless the level of cognitive control is subsequently increased.

Although the pmFC can also be activated by positive events (such as rewards) (1, 2), we focus here on negative events and their consequences. Because errors and conflicts are intrinsically negative, and because unfavorable outcomes are typically more consequential for the regulation of cognitive control than are favorable outcomes, our review focuses on the role of the pmFC in monitoring negative events.

Monitoring unfavorable outcomes. Electrophysiological recordings in nonhuman primates implicate the pmFC in monitoring performance outcomes. Distinct neuron populations in the pmFC, particularly in the supplementary eye fields and the rostral cingulate motor area (CMAr), are sensitive to reward expectancy and reward delivery (1, 3, 4). In addition, CMAr neurons exhibit sensitivity to unexpected reductions in reward (5). Likewise, specific groups of neurons in the depth of the cingulate sulcus (area 24c) react to response errors and to unexpected omissions of rewards (5). These findings are consistent with a role for these neuronal populations in comparing expected and actual outcomes.

¹Department of Psychology, University of Amsterdam, Roetersstraat 15, 1018 WB Amsterdam, Netherlands. ²Department of Psychology, Leiden University, Wassenaarseweg 52, 2333 AK Leiden, Netherlands. ³Max Planck Institute for Human Cognitive and Brain Sciences, Stephanstrasse 1A, 04103 Leipzig, Germany. ⁴Center for Mind and Brain, University of California Davis, 202 Cousteau Place, Suite 201, Davis, CA 95616, USA. ⁵Department of Cognitive Psychology, Vrije Universiteit, Van der Boechorststraat 1, 1081 BT Amsterdam, Netherlands.

*To whom correspondence should be addressed. E-mail: K.R.Ridderinkhof@uva.nl

COGNITION AND BEHAVIOR

Human neuroimaging studies implicate the pMFC, including the dorsal anterior cingulate cortex (ACC), along with other brain structures, in differential processing of unfavorable outcomes (Fig. 1B). These include studies using monetary rewards and punishments (6) and studies using abstract performance feedback (7). Similar parts of the pMFC are activated by primary re-

inforcers such as pain affect and pleasant tastes, suggesting that the pMFC plays a general role in coding the motivational value of external events.

Electrophysiological recordings in humans have identified the purported event-related brain potential correlate of the pMFC response to unfavorable outcomes: the feedback-related error-related negativity (or "feedback ERN"). This negative-polarity voltage deflection peaks approximately 250 to 300 ms after a stimulus indicating the outcome, and is greater in amplitude for negative performance feedback and outcomes indicating monetary losses than for positive feedback and monetary gains (8). The timing of this brain potential suggests that the pMFC computes or has access to a rapid evaluation of the outcome stimulus. Furthermore, initial studies report that the amplitude of the feedback ERN shows a graded sensitivity to the value of outcome stimuli that is normalized with respect to the subjectively expected outcome value (mean) and experienced range of outcome values (variance) (9).

Monitoring response errors. Primate studies show that, in addition to feedback-sensitive cells, the CMAR also contains error-sensitive cells (4, 10). Corroborating these results, subsequent human functional neuroimaging studies have reported increased pMFC activation in response to errors as compared to correct responses in various two-alternative forced-choice tasks (11). The reported error-related activations cover a wide range along the anterior-posterior extent of the pMFC, with particular clustering in the rostral cingulate zone (RCZ) (12), the human homolog of the monkey's CMAR (Fig. 1B).

Consistent with these single-cell recordings and brain imaging studies, electrophysiological scalp recordings have found an error-sensitive event-related brain potential localized to the pMFC, which is attenuated in patients with damage to the dorsal ACC (13). This response-related ERN (or "response ERN") develops at the time of the first incorrect muscle activity and peaks about 100 ms later, indicating that the underlying generator has access to an efference copy of the initiated incorrect response (14). The response ERN is triggered by errors elicited under speeded response conditions, independent of the response effector (such as hands, feet, eyes, or voice), and increases in amplitude with the size or degree of error (15). Errors in these tasks result predominantly from premature responding, but continued stimulus processing after the response can provide sufficient information for outcome assessment. The morphology, polarity, and scalp distribution of the response ERN are similar to those of the feedback ERN, suggesting that the two ERN potentials may index a generic error-processing system in the pMFC.

A recent theory has extended the notion that the role of the dorsal ACC in coding outcome- and error-related information may be understood in terms of a common functional and neurobiological mechanism (8). The theory is predicated on prior research indicating that errors in reward prediction are coded by phasic changes in the activity of the midbrain dopamine system: a phasic increase when ongoing events are suddenly better than expected, and a phasic decrease when ongoing events are suddenly worse than expected (16). The theory builds on this research by proposing that these phasic dopamine signals are conveyed to the RCZ, where the signals are used to improve task performance in accordance with the principles of reinforcement learning. Furthermore, it proposes that the phasic dopamine signals modulate the activity of motor neurons in the RCZ, which is measurable at the scalp as changes in ERN amplitude. Phasic decreases in dopamine activity (indicating a negative reward prediction error) are associated with large ERNs and phasic increases (indicating a positive reward prediction error) with small ERNs.

A strong prediction of this theory is that the same region of the dorsal ACC should be activated by response errors and unexpected negative feedback. Also, during reward-based action learning, neural activity in this area should gradually propagate back from the feedback to the action that comes to predict the value of the feedback. These predictions have been confirmed using neuroimaging, ERN measurements, and computational modeling (8, 17).

Monitoring response conflict. An alternative theory is that the pMFC, and in

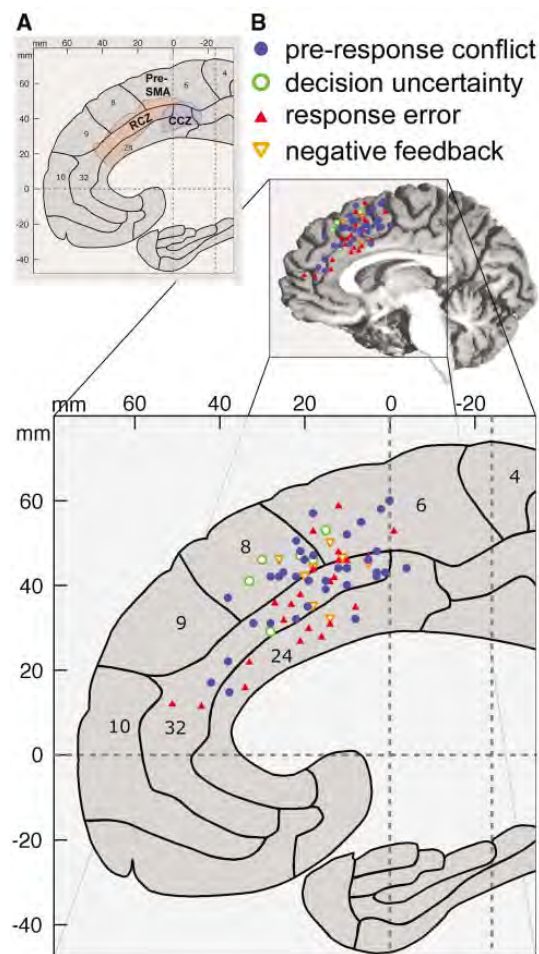


Fig. 1. Areas in the medial frontal cortex involved in performance monitoring. (A) Anatomical map of the medial frontal cortex. This is a schematic map of anatomical areas in the human pMFC, based on the atlas by Talairach and Tournoux (see supporting online material). The numbers indicate Brodmann areas. The area shaded in red encompasses the RCZ, and the area shaded in blue indicates the caudal cingulate zone (CCZ), as suggested by Picard and Strick (17). (B) Outcome of a meta-analysis of midline foci of activation reported in 38 fMRI studies published between 1997 and 2004 investigating brain activity associated with pre-response conflict, decision uncertainty, response errors, and negative feedback (20). In the upper part of the figure, the activation foci are superimposed on a sagittal slice of an anatomical MRI scan at $x = 4$. In the lower part, the activation foci are superimposed on the enlarged schematic area map. The majority of activations cluster in the posterodorsal medial frontal cortex, in the region where areas 8, 6, 32, and 24 border each other.

particular the dorsal ACC, is involved in the monitoring of response conflict (18). Response conflict occurs when a task concurrently activates more than one response tendency; for example, when the stimulus primes a prepotent but incorrect response or when the correct response is underdetermined. Often, incorrect response tendencies are overridden in time by the overt correct response, resulting in high response conflict before the correct response (pre-response conflict). In contrast, occasional errors resulting from premature responding are characterized by response conflict after the response: The correct response tendency resulting from continued stimulus processing conflicts with the already executed incorrect response. In underdetermined responding (that is, under conditions requiring choosing from a set of responses, none of which is more compelling than the others), decision uncertainty occurs. Thus, decision uncertainty involves conflict similar to response conflict observed in tasks in which a prepotent response is overridden (18).

The conflict-monitoring theory is consistent with the neuroimaging evidence for pMFC activation in response to errors, reviewed above, and with the timing of the response ERN, indicating post-response conflict. In addition, the theory predicts that the pMFC should be active in correct trials characterized by high pre-response conflict, a prediction that has been confirmed by a large number of studies (Fig. 1B). Moreover, the predicted timing of such conflict-related activity is consistent with the occurrence of an ERN-like component, the N2, just before the response (19). Finally, the detection of high post-response conflict may be used as a reliable basis for internal error detection, thereby obviating the need for an explicit error detection mechanism (19).

The theory further holds that, upon the detection of response conflict, the pMFC signals other brain structures that the level of cognitive control needs to be increased.

Convergence and divergence in performance monitoring. The findings reviewed above suggest that the detection of unfavorable outcomes, response errors, response conflict, and decision uncertainty elicits largely overlapping clusters of activation foci in the pMFC. This assumption is consistent with a meta-analysis of the human neuroimaging literature (table S1), focusing on pMFC activations in response to these types of events (Fig. 1B) (20). The high degree of overlap should not be taken, however, as direct evidence for a generic role of neurons (or neuronal populations) in this brain area in monitoring various aspects of performance. First, although there is considerable overlap, there are some apparent differences as well, with foci associated

with pre-response conflict clustering slightly more dorsally than foci activated during error and feedback monitoring (21, 22). Second, single-cell recordings in monkeys suggest that different (neighboring) neurons within specific pMFC regions can be involved in different aspects of performance monitoring (4). Thus, the overlap between the activation foci identified in human neuroimaging studies does not necessarily imply identical functions for all neurons or neuronal ensembles within the pMFC.

A potential link between the outlined theories of pMFC functions is that pre-response conflict and decision uncertainty signal a reduced probability of obtaining reward, whereas errors and unexpected negative feedback signal the loss of anticipated reward. The pMFC, particularly the RCZ, is engaged when the need for adjustments to achieve action goals becomes evident. Interestingly, the monitoring processes examined here cluster primarily in the transition zone between the cingulate and paracingulate (areas 24 and 32), association (area 8), and premotor cortices (area 6), an area that has extensive connections with brain areas involved in the control of cognitive and motor processes and has been implicated in the regulation of autonomic arousal (23, 24). This presumably places the pMFC in a strategically located position for signaling the need for performance adjustments and for interacting with brain areas involved in motor and cognitive, as well as autonomic and motivational, functions.

Performance Adjustments

Although the pMFC is consistently implicated in action monitoring, the mechanisms underlying the implementation of subsequent performance adjustments are less well understood. Two important questions are: (i) Is there a link between pMFC activation associated with performance monitoring and subsequent performance adjustments? (ii) What brain structures may be involved in the implementation of such control adjustments? In neuroimaging and neuropsychological studies, the LPFC has been broadly implicated in the coordination of adaptive goal-directed behavior (25–29). We review studies that address the first question, and we briefly evaluate the scant literature on functional interactions between the pMFC and LPFC in the service of adaptive control.

pMFC activity and immediate control adjustments. When stimuli elicit conflicting response tendencies or overt response errors, appropriate performance adjustments may be aimed not only at immediate correction of these tendencies but also at preventing errors on subsequent trials. A distinction can be made between two types of trial-to-trial performance adjustments: (i) shifts in the

tradeoff between speed and accuracy of responding that place the cognitive system in a more cautious (as opposed to impulsive) response mode, and (ii) increases in control that improve the efficiency of information processing. Speed/accuracy tradeoffs may be expressed in “post-error slowing,” the observation that reaction times typically slow down after errors and correct, high-conflict trials (18). Changes in control, induced by such trials, can become evident in improved performance due to reduced interference from distracting information. For example, the increase in reaction times normally observed for incongruent stimuli (where target and distractor stimuli call for opposing responses) as compared to congruent stimuli (when distractors elicit the same action as the target stimulus) is typically reduced on trials after errors (30).

Several observations are consistent with a close link between modulations of pMFC activity and subsequent changes in performance. One study categorized trials in terms of their ERN amplitudes and found that the reaction time on the subsequent trial slowed progressively with increasing ERN amplitude on the current trial (14). In a similar vein, response errors on a two-alternative forced-choice task are foreshadowed by modulation of this pMFC activity during the immediately preceding (correct) response. Error-preceding trials were characterized by increased positivity in the time window typically associated with the ERN (31). This “error-preceding positivity” may reflect a transient disengagement of the monitoring system, resulting in occasional failures to implement appropriate control adjustments and hence in errors. Experimental factors that affect ERN amplitude may also affect subsequent performance adjustments. For example, alcohol consumption led to a reduction in the ERN amplitude and eliminated the post-error reduction of interference observed in a control condition (30). The relation between these findings and the associated neural circuitry was captured more directly in recent neuroimaging studies of Stroop task and response-inhibition performance (32, 33): Post-hoc reaction time analyses revealed that greater ACC activity during error trials was associated with greater post-error slowing.

The latter studies also addressed the role of the LPFC in implementing control adjustments and its interaction with the pMFC. Trials exhibiting the greatest behavioral adjustments after errors and correct, high-conflict trials were associated with increased activity in the LPFC. Further, the degree of pMFC activity on conflict and error trials accurately predicted activity in the LPFC on the next trial. These and other findings are consistent with the idea that the pMFC, as a

COGNITION AND BEHAVIOR

monitor, and the LPFC, as a controller, interact in the regulation of goal-directed behavior (18).

pMFC activity and reward-based association learning. In addition to the link between pMFC activity and immediate adjustments in performance, there also seems to be a close relation between pMFC activity and reward-based association learning. A study of reward-based reversal learning in monkeys identified cells in the CMAr that fired only when two conditions were met: (i) reward was less than anticipated, and (ii) the reduction in reward was followed by changes in the monkeys' action selection (5). This finding has been corroborated by two recent functional magnetic resonance imaging (fMRI) studies of reversal learning, showing that ACC activity was observed under the same conjunctive condition (34, 35). Reversal learning studies typically also show activation of the LPFC and other structures in association with changes in choice behavior (36). Whether these behavioral adjustments are implemented by or pMFC or whether the pMFC merely signals the LPFC or other structures to implement the adjustments remains to be explored.

Finally, there is evidence for an intimate relation between ERN amplitude and associative learning. In scalp electrophysiological activity, recorded from human participants who were required to learn stimulus-response contingencies on the basis of trial-to-trial positive or negative feedback, the feedback ERN to negative feedback decreased as participants were learning the contingencies, which is consistent with the theory discussed above that the ERN reflects a reward prediction error signal (8). Also, as participants learned the response associated with each stimulus, the response ERN associated with choice errors (provoked through the use of a stringent reaction time deadline) increased. In a temporal difference-learning model, not only did the ERN correlate with a reward prediction error but the brain activity underlying the ERN could also serve as a reinforcement learning signal for associative learning and hence optimizing task performance (8).

Conclusions and Future Directions

We have provided an overview of the evidence suggesting a critical role for the pMFC in performance monitoring and the implementation of associated adjustments in cognitive control. Our meta-analysis indicates that an extensive part of the pMFC—including areas 6, 8, 24, and 32, largely falling into a region referred to as the RCZ in humans—is consistently activated after the detection of response conflict, errors, and unfavorable outcomes. The similarities between two brain potentials generated by this

area, the ERN and feedback ERN, are consistent with the view that the pMFC accommodates a unified functional and neurobiological performance-monitoring mechanism (8). This mechanism allows the pMFC to signal the likelihood of obtaining an anticipated reward (either definitive, as observed in studies of error detection and feedback processing, or probabilistic, as observed in studies of decision uncertainty and pre-response conflict).

Three conclusions from the meta-analysis should be emphasized. First, performance monitoring is associated with pMFC activations in a functionally integrated region (the RCZ) that cuts across various Brodmann areas beyond the "traditionally" reported ACC. Second, the most pronounced cluster of activations is in area 32 for all types of monitored events, suggesting the importance of this area for a unified performance monitoring function. Thus, the conclusion that error monitoring and conflict monitoring are performed by different areas, as derived from initial studies that were designed to identify differential involvement, is not ubiquitously confirmed by the meta-analysis. Third, activations related to pre-response conflict and uncertainty occur more often in area 8 and less often in area 24 than do activations associated with errors and negative feedback. Thus, although there is considerable overlap, there are some apparent differences as well, with activation foci associated with reduced probabilities of obtaining reward clustering slightly more dorsally than foci associated with errors and failures to obtain anticipated reward.

This generic monitoring function endows the pMFC with the capacity to signal the need for performance adjustment. Indeed, further evidence indicates a tight link between activity in this area and subsequent adjustments in performance, suggesting that the pMFC signals other brain regions that changes in cognitive control are needed. Although direct evidence is sparse, a likely candidate structure for effecting these control adjustments is the LPFC. Thus, monitoring-related pMFC activity may serve as a signal that engages control processes in the LPFC that are needed to regulate task performance in an adaptive fashion.

This conclusion notwithstanding, several questions remain. First, most studies of the pMFC and performance monitoring have tried to relate pMFC activity to control adjustments on the subsequent trial. An unresolved issue is whether the monitoring signal from the pMFC can also be used to resolve response conflicts on a within-trial basis (34). There is in principle no reason why such adjustments could not be implemented already within the same trial (to resolve conflict and correct the activation of

inappropriate responses before they eventuate in an overt error). It is hard to tackle this question empirically using neuroimaging studies, because it requires disentangling the monitoring signal (indicating the need for control) and the answer to this signal (control implementation), which may be partly overlapping in time.

Another unresolved issue concerns the nature of the connection between the pMFC and LPFC. Anatomical studies in monkeys show dense reciprocal connections of the pMFC and LPFC (37, 38). In humans, evidence for such connections is more indirect. Neuroimaging studies show concomitant activations in the LPFC and pMFC (39), suggesting close functional connectivity between these two areas. Little is known, however, about differential or selective reciprocal projections between various portions of the pMFC on the one hand and various subdivisions of the LPFC on the other. Possibly, this functional interplay is in part mediated by subcortical structures such as the basal ganglia and mesencephalic nuclei (7, 8) or by the supplementary motor area (SMA) or pre-SMA (29, 40).

Electrophysiological studies of patients with LPFC lesions have reported abnormal pMFC activity in response to errors (41). Such studies argue against the possibility of unidirectional information flow between the pMFC and LPFC, and instead suggest that performance monitoring and the regulation of cognitive control may be realized through intricate reciprocal projections between these two structures. It is a challenge for future research to further identify and characterize these interactions.

Although our review of the literature capitalizes on the role of the pMFC in performance monitoring, leading to performance adjustments on subsequent trials, other studies have suggested a more executive role for the pMFC in implementing control directly (42). Studies in nonhuman primates have shown that cells in the pMFC (especially in the monkey homolog of the RCZ) are well situated for this role, because this area has direct and indirect projections to primary and supplementary motor areas (43, 44). It has been argued that some of these cells are involved in "goal-based action selection" (that is, selecting between competing actions in view of the anticipated reward associated with each of these actions) (43, 44). The relation between these complementary functions remains to be further explored.

References and Notes

1. M. Shidara, B. Richmond, *Science* **296**, 1709 (2002).
2. B. Knutson, G. W. Fong, C. M. Adams, J. L. Varner, D. Hommer, *Neuroreport* **12**, 3683 (2001).
3. V. Stuphorn, T. L. Taylor, J. D. Schall, *Nature* **408**, 857 (2000).

COGNITION AND BEHAVIOR

SPECIAL SECTION

4. S. Ito, V. Stuphorn, J. W. Brown, J. D. Schall, *Science* **302**, 120 (2003).
5. K. Shima, J. Tanji, *Science* **282**, 1335 (1998).
6. J. O'Doherty, M. L. Kringelbach, E. T. Rolls, J. Hornak, C. Andrews, *Nature Neurosci.* **4**, 95 (2001).
7. M. Ullsperger, D. Y. von Cramon, *J. Neurosci.* **23**, 4308 (2003).
8. C. B. Holroyd, M. G. H. Coles, *Psychol. Rev.* **109**, 679 (2002).
9. C. B. Holroyd, J. T. Larsen, J. D. Cohen, *Psychophysiology* **41**, 245 (2004).
10. H. Gemba, K. Sasaki, V. B. Brooks, *Neurosci. Lett.* **70**, 223 (1986).
11. M. Ullsperger, D. Y. Von Cramon, *Cortex*, in press.
12. N. Picard, P. L. Strick, *Cereb. Cortex* **6**, 342 (1996).
13. C. B. Holroyd, S. Nieuwenhuis, R. B. Mars, M. G. H. Coles, in *Cognitive Neuroscience of Attention*, M. I. Posner, Ed. (Guilford, New York, in press).
14. W. J. Gehring, B. Goss, M. G. H. Coles, D. E. Meyer, E. Donchin, *Psychol. Sci.* **4**, 385 (1993).
15. M. Falkenstein, J. Hoormann, S. Christ, J. Hohnsbein, *Biol. Psychol.* **51**, 87 (2000).
16. W. Schultz, *Neuron* **36**, 241 (2002).
17. C. B. Holroyd et al., *Nature Neurosci.* **7**, 497 (2004).
18. M. M. Botvinick, T. S. Braver, D. M. Barch, C. S. Carter, J. D. Cohen, *Psychol. Rev.* **108**, 624 (2001).
19. N. Yeung, M. M. Botvinick, J. D. Cohen, *Psychol. Rev.*, in press.
20. Materials and methods are available as supporting material on Science Online.
21. R. Hester, C. Fassbender, H. Garavan, *Cereb. Cortex* **14**, 986 (2004).
22. The majority of activations fall into the border zone between areas 8, 6, and 32, with some extension into area 24. Recent research in nonhuman primates seems to suggest a functional-anatomical dissociation of regions subserving pre-response conflict monitoring from structures sensitive to errors and omission of reward (1, 4). Although in humans this view is still under debate (11, 13, 21), the present meta-analysis does not provide unequivocal evidence for or against such a dissociation. Activations related to pre-response conflict and uncertainty occur more often in area 8 and less often in area 24 than do signal increases associated with errors and negative feedback (area 8, 32.5% versus 9.7%; area 24, 7.5% versus 25.8%), supporting the dissociation view. However, both groups of activations cluster primarily in area 32 (pre-response, 42.5%; error, 41.9%), suggesting that pre- as well as post-response monitoring processes share at least one underlying structure. It seems that the currently available spatial resolution in fMRI, in conjunction with anatomical variability and differences in scanning and preprocessing methods between studies, limit the ability to resolve this debate about a possible dissociation in the range of 10 mm or less.
23. T. Paus, *Nature Rev. Neurosci.* **2**, 417 (2001).
24. H. D. Critchley et al., *Brain* **126**, 2139 (2003).
25. E. K. Miller, J. D. Cohen, *Annu. Rev. Neurosci.* **24**, 167 (2001).
26. A. R. Aron, T. W. Robbins, R. A. Poldrack, *Trends Cogn. Sci.* **8**, 170 (2004).
27. D. Badre, A. D. Wagner, *Neuron* **41**, 473 (2004).
28. S. A. Bunge, K. N. Ochsner, J. E. Desmond, G. H. Glover, J. D. E. Gabrieli, *Brain* **124**, 2074 (2001).
29. M. Brass, D. Y. von Cramon, *J. Cogn. Neurosci.* **16**, 609 (2004).
30. K. R. Ridderinkhof et al., *Science* **298**, 2209 (2002).
31. K. R. Ridderinkhof, S. Nieuwenhuis, T. R. Bashore, *Neurosci. Lett.* **348**, 1 (2003).
32. J. G. Kerns et al., *Science* **303**, 1023 (2004).
33. H. Garavan, T. J. Ross, K. Murphy, R. A. Roche, E. A. Stein, *Neuroimage* **17**, 1820 (2002).
34. G. Bush et al., *Proc. Natl. Acad. Sci. U.S.A.* **99**, 523 (2002).
35. J. O'Doherty, H. Critchley, R. Deichmann, R. J. Dolan, *J. Neurosci.* **23**, 7931 (2003).
36. R. Cools, L. Clark, A. M. Owen, T. W. Robbins, *J. Neurosci.* **22**, 4563 (2002).
37. J. F. Bates, P. S. Goldman-Rakic, *J. Comp. Neurol.* **336**, 211 (1993).
38. M. Petrides, D. N. Pandya, *Eur. J. Neurosci.* **11**, 1011 (1999).
39. L. Koski, T. Paus, *Exp. Brain Res.* **133**, 55 (2000).
40. K. Fiehler, M. Ullsperger, D. Y. von Cramon, *Eur. J. Neurosci.* **19**, 3081 (2004).
41. W. J. Gehring, R. T. Knight, *Nature Neurosci.* **3**, 516 (2000).
42. M. I. Posner, G. J. DiGirolamo, in *The Attentive Brain*, R. Parasuraman, Ed. (MIT Press, Cambridge, MA, 1998), pp. 401–423.
43. K. Matsumoto, K. Tanaka, *Science* **303**, 969 (2004).
44. K. Matsumoto, K. Tanaka, *Curr. Opin. Neurobiol.* **14**, 178 (2004).
45. This research was supported by a TALENT grant (E.A.C.) and a VENI grant (S.N.) of the Netherlands Organization for Scientific Research and by the Priority Program Executive Functions of the German Research Foundation (M.U.). Helpful comments by S. Bunge are gratefully acknowledged.

Supporting Online Material
www.sciencemag.org/cgi/content/full/306/5695/443/DC1
 Materials and Methods
 Table S1
 References

REVIEW

Neuroeconomics: The Consilience of Brain and Decision

Paul W. Glimcher^{1*} and Aldo Rustichini²

Economics, psychology, and neuroscience are converging today into a single, unified discipline with the ultimate aim of providing a single, general theory of human behavior. This is the emerging field of neuroeconomics in which consilience, the accordance of two or more inductions drawn from different groups of phenomena, seems to be operating. Economists and psychologists are providing rich conceptual tools for understanding and modeling behavior, while neurobiologists provide tools for the study of mechanism. The goal of this discipline is thus to understand the processes that connect sensation and action by revealing the neurobiological mechanisms by which decisions are made. This review describes recent developments in neuroeconomics from both behavioral and biological perspectives.

The full understanding of utility will come from biology and psychology by reduction to the elements of human behavior followed by a bottom-up synthesis, not from the social sciences by top-down inference and guesswork based on intuitive knowledge. It is in biology and psychology that economists and social scientists will find the

premises needed to fashion more predictive models, just as it was in physics and chemistry that researchers found the premises that upgraded biology. (p. 206) (1)

Consider the famous St. Petersburg paradox (2). Which of the following would you prefer, \$40 or a lottery ticket that pays according to the outcomes of one or more fair coin tosses: heads you get \$2 and the game ends, tails you get another toss and the game repeats, but now if the second toss lands heads up you get \$4, and so on. If the *n*th toss is the first to land heads up, you get

2^{*n*} dollars. The game continues, however long it takes, until the coin lands heads up. We can assess the average objective, or expected, value of this lottery by multiplying the probability of a win on each flip by the amount of that win:

$$\begin{aligned}\text{Expected value} &= (0.5 \times 2) + (0.25 \times 4) + \\ &\quad (0.125 \times 8) \dots \\ &= 1 + 1 + 1 + \dots\end{aligned}$$

This simple calculation reveals that the expected value of the lottery is infinite even though the average person is willing to pay less than \$40 to play it. How could this be?

For an economist, any useful explanation must begin with a set of assumptions that renders behavior formally tractable to coherent theoretical and mathematical analysis. Economists therefore explain this behavior by assuming that the desirability of money does not increase linearly, but rather grows more and more slowly as the total amount at stake increases. For example, the desirability of a given amount might be a power function

¹Center for Neural Science, New York University, New York, NY 10003, USA. ²Department of Economics, University of Minnesota, Minneapolis, MN 55455, USA.

*To whom correspondence should be addressed. E-mail: glimcher@cns.nyu.edu

Supplementary Online Material

Materials and Methods

The meta-analysis shown in Fig. 1B focuses on hemodynamic signal increases in the medial frontal cortex (MFC) associated with pre-response conflict (PRC), decision uncertainty (DU), response errors (RE), and negative feedback (NF). A literature search revealed 58 papers (published between 1997 and April, 2004) reporting activations for at least one of the conditions of interest. Papers that did not report coordinates were excluded, as were studies in which the statistical contrasts did not unequivocally pertain to the conditions of interest. Additionally, papers with methodological problems such as insufficient trial numbers to enable reliable statistical analyses were also excluded. The resulting set of studies that were included in the meta-analysis comprises 38 fMRI studies, listed in Table S1. If more than one coordinate per condition was reported, the three most significant activation coordinates were included in the meta-analysis. This was done to account for extended activations. Restricting the analysis to one coordinate per study might have occluded overlapping foci of activation. As a result, a total of 71 coordinates were included (PRC, 34; DU, 6; RE, 23; NF 8). For studies in which coordinates referred to the Montréal Neurological Institute (MNI) standard brains, a conversion of the coordinates to Talairach space (*1*) was performed according to the method developed by M. Brett (<http://www/mrc-cbu.cam.ac.uk/Imaging/mnispace.html>). The mean x coordinate for the entire sample of contrasts was 0.99 (SEM = .72; not significantly different from 0, $p > .17$), suggesting that the activations did not tend to be lateralized to either hemisphere. This was also tested for each condition separately, revealing no lateralization for PRC (mean $x = -0.22$, SEM = 1.30; $p > .87$) and NF (mean $x = 1.87$, SEM = 1.57; $p > .27$) and a tendency for a lateralization to the right for RE (mean $x = 1.73$, SEM = .89; $T(21) = 1.94$, $p = .065$). In the DU condition, all six coordinates were on the right hemisphere (mean $x = 4.00$, SEM = .93; $T(5) = 4.30$, $p < .01$).

In Fig. 1B the y and z coordinates were visualized on one sagittal midline slice. For each activation focus, a symbol corresponding to the condition of interest was mapped onto a schematic sagittal slice taken from the atlas by Talairach and Tournoux (*S1*), showing the borders of the Brodmann areas (BA). The same schematic has been used in previous meta-analyses (*S2*). It is important to note that the borders between BAs can only serve as an approximation.

Table S1. Studies and coordinates included in meta-analysis.

| Reference | Coordinates (x/y/z) |
|---|--|
| Badre D, Wagner AD, <i>Neuron</i> 41 , 473 (2004). | PRC, 8.91/19.23/34.96 |
| Barch DM, Braver TS, Sabb FW, Noll DC, <i>J Cogn Neurosci</i> 12 , 298 (2000). | PRC, 4.5/15/39, 10.50/3/42.00, -4.5/21/48 |
| Barch DM <i>et al.</i> , <i>Cereb Cortex</i> 11 , 837 (2001). | DU, 3/28/29 |
| Botvinick MM, Nystrom LE, Fissell K, Carter CS, Cohen JD, <i>Nature</i> 402 , 179 (1999). | PRC, -2/28/31 |
| Braver TS, Barch DM, Gray JR, Molfese DL, Snyder A, <i>Cereb Cortex</i> 11 , 825 (2001). | PRC, 2/3/48; RE, -1/21/27 |
| Carter CS <i>et al.</i> , <i>Science</i> 280 , 747 (1998). | PRC, 4/25/43 |
| Carter CS <i>et al.</i> , <i>Proc Natl Acad Sci U S A</i> 97 , 1944 (2000). | PRC, 0/15/41 |
| Carter CS, MacDonald AW, Ross LL, Stenger VA, <i>Am J Psychiatry</i> 158 , 1423 (2001). | RE, 0/27/36 |
| Casey BJ <i>et al.</i> , <i>Proc Natl Acad Sci U S A</i> 97 , 8728 (2000). | PRC, -8/22/32, -5/18/57 |
| Dassonville P <i>et al.</i> , <i>Neuroimage</i> 13 , 1 (2001). | PRC, -6/5/46, -6/12/44 |
| Durston S <i>et al.</i> , <i>Neuroimage</i> 20 , 2135 (2003). | PRC, 3/42/17, 19/38/37 |
| Erickson KI <i>et al.</i> , <i>Human Brain Mapping</i> 21 , 98 (2004). | PRC, 2/22/42 |
| Fan J, Flombaum JI, McCandliss BD, Thomas KM, Posner MI, <i>Neuroimage</i> 18 , 42 (2003). | PRC, -5.94/37.64/14.70* |
| Fiehler K, Ullsperger M, von Cramon DY, <i>Eur J Neurosci</i> , 19 , 3081 (2004). | RE, 1/21/38 |
| Garavan H, Ross TJ, Murphy K, Roche RA, Stein EA, <i>Neuroimage</i> 17 , 1820 (2002). | RE, 5/10/46 |
| Garavan H, Ross TJ, Kaufman J, Roche RA, Stein EA, <i>Neuroimage</i> 20 , 1298 (2003). | RE, 2/12/48, -3/33/22, 9/16/28 |
| Holroyd CB <i>et al.</i> , <i>Nature Neuroscience</i> in press (2004). | RE, 1/18/44; NF, 4/18/44 |
| Hazeltine E, Poldrack R, Gabrieli JD, <i>J Cogn Neurosci</i> 12 Suppl 2 , 118 (2000). | PRC, -18/0/60 |
| Kerns JG <i>et al.</i> , <i>Science</i> 303 , 1023 (2004). | PRC, 1/10/40; RE, 3/14/41 |
| Kiehl KA, Liddle PF, Hopfinger JB, <i>Psychophysiol.</i> 37 , 216 (2000). | RE, 3.96/23.15/35.69, -7.92/44.29/11.60* |

| | |
|---|--|
| Kaufman JN, Ross TJ, Stein EA, Garavan H, <i>J Neurosci</i> 23 , 7839 (2003). | RE, 4/14/31, 4/12/46 |
| Knutson B, Westdorp A, Kaiser E, Hommer D, <i>Neuroimage</i> 12 , 20 (2000). | NF 4/14/32, -1/5/45 |
| Laurens KR, Ngan ET, Bates AT, Kiehl KA, Liddle PF, <i>Brain</i> 126 , 610 (2003). | RE, -7.92/51.11/12.18, 0/24.91/31.92* |
| MacDonald AW, Cohen JD, Stenger VA, Carter CS, <i>Science</i> 288 , 1835 (2000). | PRC, 4/1/43 |
| Milham MP, Banich MT, Barad V, <i>Brain Res Cogn Brain Res</i> 17 , 212 (2003). | PRC, 4/38/22, 8/8/32, -22/-4/44 |
| Milham MP, Banich MT, Claus ED, Cohen NJ, <i>Neuroimage</i> 18 , 483 (2003). | PRC, 0/20/46, 0/10/52, -2/2/58,00 |
| Milham MP <i>et al.</i> , <i>Brain Res Cogn Brain Res</i> 12 , 467 (2001). | PRC, 0/10/44 |
| Monchi O <i>et al.</i> , <i>J Neurosci</i> 24 , 702 (2004). | NF, -8/20/42, 3/26/46, 4/14/50 |
| O'Doherty JP, Dayan P, Friston K, Critchley H, Dolan RJ, <i>Neuron</i> 38 , 329 (2003). | NF, 2.97/11.07/46.43* |
| Rubia K, Smith AB, Brammer MJ, Taylor E, <i>Neuroimage</i> 20 , 351 (2003). | RE, 3/34/16 |
| Ruff CC, Woodward TS, Laurens KR, Liddle PF, <i>Neuroimage</i> 14 , 1150 (2001). | PRC, -3.96/21.95/50.49, -3.96/6.64/54.94, 7.92/17.89/47.01* |
| Ullsperger M, von Cramon DY, <i>Neuroimage</i> 14 , 1387 (2001). | PRC, 4/28/42, 4/19/41, -5/34/3; RE, 7/19/30, 2/13/42, -2/5/47 |
| Ullsperger M, von Cramon DY, <i>J Neurosci</i> 23 , 4308 (2003). | NF, 6/18/35; DU, 4/15/53 |
| Ullsperger M, von Cramon DY, <i>Cortex in press</i> (2004). | RE, 4/8/35, 4/18/53, 4/-1/53 |
| van Veen V, Cohen JD, Botvinick MM, Stenger VA, Carter CS, <i>Neuroimage</i> 14 , 1302 (2001). | PRC, -3/32/31 |
| Volz KG, Schubotz RI, von Cramon DY, <i>Neuroimage</i> , 19 , 271 (2003). | DU, 8/18/46, 4/30/46 |
| Volz KG, Schubotz RI, von Cramon DY. <i>Neuroimage</i> , 21 , 848 (2004). | DU, 4/21/47, 1/33/41 |
| Zysset S, Muller K, Lohmann G, von Cramon DY, <i>Neuroimage</i> 13 , 29 (2001). | PRC, 1/26/42 |

Note: PRC = pre-response conflict, DU = decision uncertainty, RE = response error, NF = negative feedback; * coordinates transferred from MNI to Talairach space according to method by Brett.

References

- S1. Talairach PT, Tournoux JA. *Stereotactic Coplanar Atlas of the Human Brain* Stuttgart: Thieme, 1988.
- S2. Picard N, Strick PL, *Cereb Cortex* **6**, 342 (1996).

Part III

The Performance Monitoring Network and its Dysfunction after Localized Brain Lesions

Chapter 7

Interactions of focal cortical lesions with error processing: evidence from event-related potentials

While the previous Part was dedicated to the role of the pFMC, and the RCZ in particular, in performance monitoring, Part III addresses the issue which brain regions interact with these frontomedian cortices. The pFMC signals the need for adjustments, but where does it receive the necessary information from, and which brain structures regulate the pFMC function? Functional neuroimaging has provided some hints that the lateral (pre)frontal cortex is involved in performance monitoring by providing information about the task at hand and by increasing or decreasing the amount of top-down influences on perceptual areas in response to the performance monitoring signals. However, for a number of reasons neuroimaging and EEG alone cannot equivocally solve the question which brain regions are involved and necessary in performance monitoring and which not. First, both methods can provide information only from some of the structures in the brain (be it the majority in the case of fMRI). For example, deep brain structures in which neurons form a 'closed-field' configuration (Rugg and Coles, 1995), such as the basal ganglia, are unlikely to directly contribute to the scalp-recorded EEG. Also fMRI is not equally sensitive in all brain areas. The signals from orbitofrontal cortex are often distorted or even lost due to susceptibility artifacts caused by nearby air-filled sinuses. Similarly, the pallidum often contains a higher concentration of metallic ions (e.g., iron) which cause local field inhomogeneities rendering fMRI signal changed less likely than in the cortex. Second, EEG and fMRI are correlative methods which *per se* cannot prove the necessity of a brain region for a certain process.

To circumvent these difficulties patient studies can be very helpful. Careful selection of patients with well-described focal lesions in the brain region of interest is essential. This and the following Chapters reports data from a series of ERP studies performed in patients suffering from circumscribed brain lesions in the lateral frontal cortex, the orbitofrontal and frontopolar cortex, the temporal cortex, and the basal ganglia. When considering data from patient studies a number of factors have to be taken into account for the interpretation. First, the time since lesion is important, as plasticity and regeneration can have led to a functional recovery. It may be that certain measures are more sensitive than others; e.g., behavioral measures can already normalize while the electrophysiological correlates may remain changed. Second, it needs to be paid attention to the homologue structures in the contralateral hemisphere. Is the lesion unilateral or bilateral? Third, the specificity of findings needs to be tested by investigating a clinical control group. It must be ruled out that the findings are a general result of being ill. In the present studies, patients with temporal cortex lesions form such a control group. The finding that in these patients and in patients with bilateral frontopolar/orbitofrontal lesions the ERN is normal demonstrates the specificity of the findings in the lateral frontal cortex and the basal ganglia groups.

Part III demonstrates the feasibility and the importance of ERP studies addressing performance monitoring deficits in patients. The ERN is a robust measure having great

potential to serve as a routine marker for pathological changes in the performance monitoring network. Chapter 9 provides a comprehensive overview about studies of performance monitoring in neurological and psychiatric patients. In moreover suggests guidelines for clinical studies of performance monitoring deficits.

Interactions of Focal Cortical Lesions With Error Processing: Evidence From Event-Related Brain Potentials

Markus Ullsperger and D. Yves von Cramon
Max Planck Institute of Cognitive Neuroscience
and University of Leipzig

Notger G. Müller
Humboldt University

Electrophysiological and hemodynamic studies have suggested that structures in the vicinity of the anterior cingulate cortex are involved in performance monitoring, particularly in detection of errors. Bidirectional interactions between the frontomedian system involved in performance monitoring and the lateral prefrontal cortex as well as the orbitofrontal cortex have been proposed, but few studies have directly addressed this issue. The authors used a speeded flankers task to investigate error-related event-related potentials in 3 patient groups with different focal cortical lesions. Whereas bilateral frontopolar lesions involving the orbitofrontal cortex as well as temporal lesions did not alter the error-related negativity (ERN), lesions of the lateral frontal cortex resulted in an abolition of the ERN and in a reduction of the error positivity.

For complex, goal-directed behavior, it is important to detect when actions are erroneous and to apply appropriate remedial mechanisms. These performance-monitoring functions have become a major focus of research over the past decade. Cumulative evidence, particularly from event-related potential (ERP) studies, gave rise to the error-detection model proposing an error-processing system made up of (a) a monitoring system that detects errors and (b) a remedial action system (cf. Coles, Scheffers, & Holroyd, 1998; 2001; Falkenstein, Hoormann, Christ, & Hohnsbein, 2000). The error-detection system has been suggested to compare the representations of the correct (appropriate and intended) and the actually performed response (Coles et al., 2001; Falkenstein et al., 2000; Falkenstein, Hohnsbein, Hoormann, & Blanke 1990; Holroyd, 2001). When the system detects a mismatch between these representations, a negative-going ERP with a frontocentral maximum is elicited within about 80 ms after the response: the error negativity (Ne; Falkenstein et al., 1990) or error-related negativity (ERN; Gehring, Goss, Coles, Meyer, & Donchin, 1993). The representation of the actual response appears to be derived from an efference copy that is sent to the monitoring system when the motor command is issued (Gehring et al., 1993). The correct (appropriate) response representation results from full evaluation of the stimuli and the application of the

task-relevant stimulus–response mappings and decision criteria. In most studies investigating performance monitoring, the majority of errors were due to premature responses given before completion of stimulus evaluation (Coles et al., 2001). Thus, the representation of the correct response can still be derived from ongoing stimulus evaluation while the erroneous response is initiated. Holroyd and colleagues (Holroyd, 2001; Holroyd, Reichler, & Coles, 1999) argued that the comparison process may involve the basal ganglia, a view supported by a recent study of error processing in Parkinson's disease (Falkenstein et al., 2001).

In addition to the ERN, a centroparietal positivity occurring about 300 ms after incorrect responses has repeatedly been described and named the error positivity (Pe; Falkenstein et al., 1990, 2000). Recent studies have suggested that the Pe may reflect the awareness of an error followed by the implementation of remedial actions (Davies, Segalowitz, Dywan, & Pailing, 2001; Nieuwenhuis, Ridderinkhof, Blom, Band, & Kok, 2001). On the basis of the finding that (in contrast to an unchanged ERN) the amplitude of the Pe was larger when error rates were high as compared with low, Falkenstein et al. (2000) argued that the Pe may also reflect a "subjective/emotional error assessment process, which is modulated by the individual significance of an error" (p. 104).

Evidence from electrophysiological as well as hemodynamic measures suggests that structures of the frontomedian wall, such as the anterior cingulate cortex (ACC) are active during error detection (e.g., Carter et al., 1998; Dehaene, Posner, & Tucker, 1994; Holroyd, Dien, & Coles, 1998; Kiehl, Liddle, & Hopfinger, 2000). Recently, the functional anatomy of error processing was refined by the suggestion that the human homologue of the cingulate motor area (CMA) located in the ventral bank of the anterior cingulate sulcus generates the ERN (Holroyd, 2001). This view was supported by a combined functional magnetic resonance imaging (fMRI) and ERP study investigating the neural correlates of performance monitoring (Ullsperger & von

Markus Ullsperger and D. Yves von Cramon, Max Planck Institute of Cognitive Neuroscience, Leipzig, Germany, and Day Clinic for Cognitive Neurology, University of Leipzig, Leipzig, Germany; Notger G. Müller, Department of Neurology, Charité, Humboldt University, Berlin, Germany.

We thank M. Brass for helpful comments on an earlier version of the article.

Correspondence concerning this article should be addressed to Markus Ullsperger, Max Planck Institute of Cognitive Neuroscience, P.O. Box 500 355, D-04303, Leipzig, Germany. E-mail: ullsperg@cns.mpg.de

Cramon, 2001). It was shown that the homologue of the CMA was most engaged during error processing.

The conflict-monitoring theory (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Carter et al., 2000) differs to some extent from the error-detection model as described above. It suggests that the frontomedian cortices in the vicinity of the ACC “provide an on-line conflict signal, indicating the need to engage brain regions such as dorso-lateral prefrontal cortex and inferior parietal cortex to implement strategic process” (Carter et al., 2000, p. 1947). However, concerning the generation of the ERN, the conflict-monitoring model provides assumptions similar to those of the error-detection model: It proposes that the CMA generates the ERN when “post-response conflict” arises, that is, when the representation of the actually performed response is in conflict with the appropriate response required by the task (Carter, 2001).

Although considerable knowledge about the error processing system has been gathered, its integration with other aspects of complex behavior and higher cognitive functions is still insufficient. The interplay of the frontomedian structures involved in error and performance monitoring with other cortices known to play important roles in complex cognitive functions is still poorly understood. Reciprocal influences among performance monitoring, affective and motivational processes, and control functions for resolving task requirements (task-set management) must be assumed to explain complex human behavior.

Interactions With the Lateral Prefrontal Cortex

Several lines of evidence have shown the significance of the lateral prefrontal cortex in working memory functions such as maintenance and manipulation of information (D’Esposito, Postle, & Rypma, 2000; Goldman-Rakic, 1996; Gruber & von Cramon, 2001; Müller, Machado, & Knight, *in press*; Petrides, 1996). In addition, functional neuroimaging studies have suggested an important role of the lateral prefrontal cortex in dealing with conflicts and interference (e.g., Carter et al., 2000; Hazeltine, Poldrack, & Gabrieli, 2000; MacDonald, Cohen, Stenger, & Carter, 2000; Zysset, Müller, Lohmann, & von Cramon, 2001). Furthermore, the functional connectivity of the prefrontal cortex with the ACC has been demonstrated in anatomical studies in primates (e.g., Barbas & Pandya, 1989; Bates & Goldman-Rakic, 1993) and in a study combining repetitive transcranial magnetic stimulation and positron emission tomography (PET; Paus, Castro-Alamancos, & Petrides, 2000; see also Paus, 2001).

Therefore, it is conceivable that the lateral prefrontal cortex interacts with performance monitoring in several ways. First, the lateral prefrontal cortex seems to be involved in the maintenance and manipulation of the mapping of sensory attributes on a set of responses by decision criteria (i.e., the task set; cf. Rogers & Monsell, 1995). In other words, it participates in task-set management processes (Zysset et al., 2001). These processes are required when response conflict must be resolved or remedial actions are necessary after errors; thus, they are closely linked to

performance monitoring (Carter et al., 2000; Ullsperger & von Cramon, 2001). Second, the representation of the correct response, which is formed by ongoing stimulus evaluation on the basis of the task set, must be held in working memory for the comparison process proposed by the error-detection model. Therefore, it can be hypothesized that dysfunctions of the lateral prefrontal cortex lead to (a) problems with remedial actions during response conflict or after errors and (b) problems with the representation of the correct (appropriate) response, which may reduce the ability to detect errors. In fact, a recent study by Gehring and Knight (2000) demonstrated that lesions of the lateral prefrontal cortex interact with the electrophysiological correlates of error processing. In these patients, electrical brain activity—particularly the frontocentral negativity—was the same after errors as after correct responses.

Interactions With Orbitofrontal Cortices

Recent studies (e.g., Luu, Collins, & Tucker, 2000; Luu & Tucker, 2001) have suggested an interaction of error detection (involving the caudal ACC) with limbic and paralimbic structures such as the orbitofrontal cortex and the rostral division of the ACC. The ERN amplitude was larger in participants who experienced high levels of subjective distress during errors than in participants with low negative affect (Luu, Collins, & Tucker, 2000). Furthermore, Tucker, Hartry-Speiser, McDougal, Luu, and deGrandpre (1999) provided evidence that potentials similar to the ERN are also generated in tasks that involve affective judgments. Recently, a close relationship between error processing and reward-related brain activity, particularly reinforcement learning, has been put forward (e.g., Holroyd, 2001; Holroyd et al., 1999; Schultz & Dickinson, 2000). Clinical studies have shown that patients with bilateral lesions of the orbitofrontal cortex have problems with performance monitoring: They are unable to deal with positive and negative consequences of actions (reward and punishment) and uncertainty (Bechara, Damasio, Tranel, & Damasio, 1997; Bechara, Tranel, Damasio, & Damasio, 1996). A further study provided evidence that lesions of the anterior orbitofrontal cortex were sufficient to produce a hypersensitivity to rewards and an insensitivity to punishments in a gambling task, whereas working memory functions were unaffected (Bechara, Damasio, Tranel, & Anderson, 1998).

An interesting question is which subprocesses of performance monitoring, particularly of error processing, are impinged on by orbitofrontal lesions. It seems conceivable that the detection of errors may induce an emotional response similar to that evoked by punishment. Therefore, it could be hypothesized that patients with orbitofrontal lesions develop an emotional insensitivity to their errors, although error detection itself may be intact. If the Pe reflects an emotional assessment of the error as proposed by Falkenstein et al. (2000), it may be reduced when the orbitofrontal cortex is damaged. The ERN as a correlate of error detection, however, may remain unaffected.

In contrast, two studies by Gehring and colleagues would suggest that the ERN also may be influenced by the sub-

jective significance of an error. It was shown that the ERN amplitude for accuracy instructions was significantly bigger than under speed conditions (Gehring et al., 1993). In addition, the ERN amplitude was larger in individuals with obsessive-compulsive disorders than in matched controls and correlated with symptom severity (Gehring, Himle, & Nisenson, 2000). It could be speculated that if errors lose their emotional significance after damage of the orbitofrontal cortex, the ERN might also be smaller.

The aim of the present study was to investigate the impact of lateral frontal, frontopolar-orbitofrontal, and temporal cortical lesions on the electrophysiological correlates of error processing, the ERN and the Pe, and thus to draw inferences on the functional role of the lesioned cortices in performance monitoring.

In patients with unilateral prefrontal cortex lesions, a replication of the findings reported by Gehring and Knight (2000) was expected—that is, similar waveforms of the response-locked ERPs in the time range of 0–100 ms after the response (i.e., the time range of the ERN) for correct and error trials. In addition, the present study aimed at extending these results by investigating the Pe, which had not been examined in this patient group before. If the ability to distinguish between correct and incorrect responses is compromised because of the lesion of the lateral frontal cortex, this might be reflected by a reduction or abolition of the Pe, because compromised error detection may also lead to problems with awareness and assessment of errors.

As pointed out above, in patients whose orbitofrontal and frontopolar cortex were damaged bilaterally, several hypotheses are plausible. If the Pe reflects an emotional assessment of errors, it should be reduced in amplitude in these patients. On the other hand, findings by Falkenstein et al. (2000) would predict the ERN should be unaffected, and on the basis of the study of Gehring et al. (1993), an amplitude reduction of the ERN could be anticipated.

To our knowledge, no evidence for an involvement of temporal cortices in performance monitoring has been reported to date. Therefore, no specific hypotheses can be formulated for these patients who served as clinical controls.

Method

Participants

Three patient groups with different localized lesions took part in the study: (a) a group with unilateral lesions centered in the lateral frontal cortex ($n = 7$, mean age 50.7 years, $SD = 11.3$), (b) a group with bilateral frontopolar lesions involving the orbitofrontal cortex ($n = 6$, mean age 38.8 years, $SD = 9.5$), and (c) a group with unilateral temporal lesions ($n = 6$, mean age 38.4 years, $SD = 11.7$). Demographic data, lesion side, description, and etiology are shown in Table 1. For illustration, T2 weighted magnetic resonance images of the lesions are depicted in Figure 1. Two healthy control groups, a younger ($n = 9$, mean age 38.4 years, $SD = 8.9$) and an older ($n = 9$, mean age 51.1 years, $SD = 8.5$), participated in the study. The younger control group was age matched with the bifrontopolar and the temporal lesion groups, whereas the older control group was age matched with the patients with lateral frontal cortex lesions.

Informed consent was obtained from each participant before testing. The experiments complied with German legal requirements. Patients and control persons were paid for their participation.

Task

A speeded modified flankers task known to produce response conflict and to yield high error rates was used (cf. Kopp, Rist, & Mattler, 1996). Participants had to respond as fast and as accurately as possible to a target arrow briefly presented in the center of the screen. When the target pointed to the right, the right button was to be pressed, and when the target pointed to the left, response with the left button was required. The target arrow was preceded by irrelevant flankers (arrows or neutral signs) displayed above and below the screen center. Thus, first the flankers appeared on the screen for 100 ms; then the target arrow was added to the picture. After another 30 ms, a blank screen was presented. The arrows were 0.46° tall and 1.08° wide, and the four flankers were presented 0.52° and 1.04° above and below the screen center. Flankers could point in the same direction as the target arrow (compatible trials, 30% of trials), in the opposite direction as the target arrow (incompatible trials, 30% of trials), or could have no direction information (neutral trials, 30% of trials). Compatible, incompatible, and neutral trials appeared in randomized order. When participants did not respond within 700 ms, a feedback ("respond faster") appeared on the screen for 710 ms; otherwise, the screen remained blank. The trial duration amounted to 1,540 ms. A total of 720 trials were presented, with five short breaks after each 120 trials.

ERP Data Collection

Participants were seated in a dimly lit, electrically shielded chamber. The electroencephalograph (EEG) activity was recorded with Ag/AgCl electrodes mounted in an elastic cap (Electrocap International, Eaton, OH) from 29 scalp sites of the 10–20 system. Electrode labeling was based on the standard nomenclature described in Sharbrough et al. (1990). The ground electrode was positioned 10% of the distance between the two preocular points right to Cz. The vertical electrooculogram (EOG) was recorded from electrodes located above and below the right eye. The horizontal EOG was collected from electrodes positioned at the outer canthus of each eye. Electrode impedance was kept below 5 k Ω . The right mastoid was recorded as an additional channel. All scalp electrodes were referenced to the left mastoid and were re-referenced off line to linked mastoids. The EEG and EOG were recorded continuously with a band pass from DC to 30 Hz and were A–D converted with 16-bit resolution at a sampling rate of 250 Hz and stored on hard disc and CD-ROM for off-line analysis.

ERP Data Analysis

In a first step, the EEG epochs were scanned for muscular and large EOG artifacts. Whenever the standard deviation in a 200-ms interval exceeded 50 μ V, the epoch was rejected. In a second step, small horizontal and vertical EOG artifacts that were still present in the EEG signal were corrected by an eye movement correction procedure (Pfeifer, 1993) based on a linear regression method described by Gratton, Coles, and Donchin (1983). Finally, ERPs were separately averaged for correct and erroneous responses on incompatible trials and for correct responses on compatible trials (there were too few errors on compatible trials to obtain reliable ERPs from these trials). Late responses followed by the feedback "respond faster" were excluded from the average. The epochs were response locked and lasted from 100 ms before to 500 ms after the

CORTICAL LESIONS AND ERROR PROCESSING

551

Table 1
Demographic and Lesion Data of the Three Patient Groups

| Patient ID | Sex | Age at test (years) | Side of lesion | Etiology | Description of lesion |
|-----------------------------------|-----|---------------------|----------------|----------|--|
| Lateral frontal group | | | | | |
| 102 | M | 50 | L | MCAI | Frontolateral, anterior insula |
| 120 | M | 51 | R | MCAI | Frontolateral, insula, anterior temporolateral |
| 237 | M | 60 | L | MCAI | Frontolateral, anterior insula |
| 325 | M | 39 | L | AVM | Frontolateral, anterior insula |
| 369 | F | 47 | L | MCAI | Frontolateral, anterior insula |
| 370 | M | 38 | R | TBI | Frontolateral, anterior temporolateral |
| 403 | M | 70 | L | MCAI | Frontolateral |
| Bifrontopolar-orbitofrontal group | | | | | |
| 150 | M | 26 | B | TBI | Frontopolar, orbitofrontal |
| 203 | F | 49 | B | TU | Frontopolar, orbitofrontal ^a |
| 291 | M | 38 | B | TBI | Frontopolar, orbitofrontal |
| 300 | M | 39 | B | TBI | Frontopolar, orbitofrontal |
| 330 | M | 50 | B | TBI | Frontopolar, orbitofrontal |
| 342 | M | 31 | B | TBI | Frontopolar, orbitofrontal |
| Temporal group | | | | | |
| 148 | F | 46 | R | AN | Anterior temporolateral ^b |
| 252 | M | 45 | L | TU | Anterior temporolateral ^c |
| 315 | F | 38 | L | HSE | Anterior temporolateral, insula |
| 317 | F | 55 | L | TBI | Anterior temporolateral |
| 328 | M | 38 | R | MCAI | Posterior temporolateral, insula, occipitotemporal, parietal operculum |
| 372 | M | 25 | L | VI | Anterior temporolateral ^d |

Note. ID = identification number; M = male; F = female; L = left; R = right; B = bilateral; MCAI = middle cerebral artery infarction; AVM = arteriovenous malformation; TBI = traumatic brain injury; TU = tumor; AN = aneurysm; HSE = herpes simplex encephalitis; VI = venous infarction.

^a After resection of meningioma in the olfactory groove. ^b Ruptured aneurysm of right middle cerebral artery, spasm of M2. ^c After resection of astrocytoma up to 6 cm posterior from temporal pole. ^d VI following TBI.

response button press. The average voltages in the 100 ms preceding the response onset served as a baseline. Mean amplitude measures in given time windows (centered around the peaks of the ERN and the Pe) at the electrodes that spanned the region where the ERN and Pe are largest (F3, Fz, F4, FC3, FCz, FC4, C3, Cz, C4, P3, Pz, P4) were used for statistical analysis. Lateral electrodes for individuals from the temporal and the lateral frontal groups with lesions on the right side were switched so that F3, FC3, C3, and P3 corresponded to the side ipsilateral to the lesion (e.g., cf. Gehring & Knight, 2000). Because most errors were made on incompatible trials, the analysis of error processing was restricted to the comparison of correct and error trials within the incompatible condition. By subjecting the data to mixed-type analyses of variance (ANOVAs) with the between-subjects factor Group (two levels) and the within-subjects factors Response Type (two levels), Anterior-Posterior Dimension (four levels), and Lateral Dimension (three levels), data were tested as to whether or not the ERP amplitudes differed between correct and erroneous trials. Further, to test whether the ERPs were topographically different, the same ANOVA was conducted after rescaling such that amplitude differences between the two contrasted conditions were removed (McCarthy & Wood, 1985). All effects with more than one degree of freedom in the numerator were adjusted for violations of sphericity according to the formula of Huynh and Feldt (1970). To avoid reporting large amounts of statistical results not relevant for the issues under investigation, only main effects or interactions,

including the Response Type factor, are reported here. Topographic scalp potential maps were generated using a two-dimensional spherical spline interpolation (Perrin, Pernier, Bertrand, & Echallier, 1989) and a radial projection from Cz, which respects the length of the median arcs.

In studies investigating the ERN, prestimulus and preresponse baselines were shown to differ between correct and incorrect responses (Hohnsbein, Falkenstein, & Hoormann, 1998; Morgan, Wenzl, Lang, Lindinger, & Deeke, 1992); therefore, a second analysis was conducted in which the baseline problem was avoided by measuring the amplitudes as the difference between the preceding positive peak and the peak of the ERN or the negativity following correct responses, respectively (cf. Falkenstein et al., 2000; Kopp et al., 1996). These amplitude measures at FCz were subjected to ANOVAs with the between-subjects factor Group (two levels) and the within-subjects factor Response Type (two levels). We also obtained peak latencies of the ERN at FCz with respect to the response.

Results

Behavioral Data

Lateral Frontal Group

Error rates did not differ significantly between the patient group with lateral frontal lesions ($M = 11.62\%$, $SEM =$

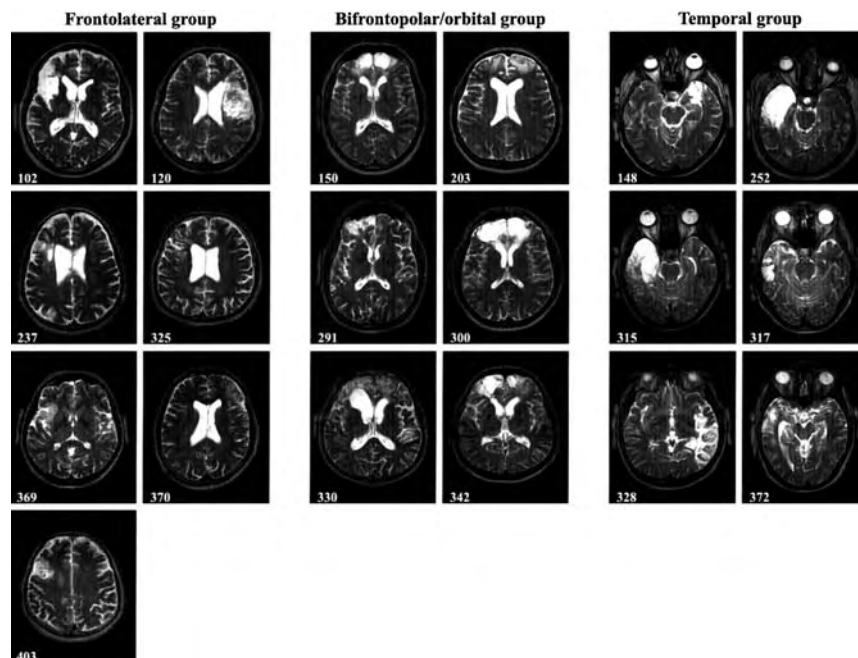


Figure 1. Axial slices of T2 weighted magnetic resonance images of each patient. The left hemisphere is oriented to the left on each image.

4.05) and the older control group ($M = 7.99\%$, $SEM = 3.04$); $t(14) = .73$, $p > .47$. The reaction times (RTs) on correct and incorrect responses were longer in the patient group (for correct, $M = 457.8$ ms, $SEM = 12.8$; for incorrect, $M = 359.8$ ms, $SEM = 18.8$) than in controls (for correct, $M = 405.3$ ms, $SEM = 13.1$; for incorrect, $M = 306.8$ ms, $SEM = 8.1$). This impression was confirmed by an ANOVA with the between-subjects factor Group (two levels) and the within-subjects factor Response Type (two levels), which revealed a main effect of group, $F(1, 14) = 9.84$, $p < .01$, and a main effect of response type, $F(1, 14) = 140.87$, $p < .01$, but no interaction of these factors ($p > .90$). The rate of late responses was significantly higher in the patient group ($M = 12.1\%$, $SEM = 4.8$) than in the controls ($M = 0.8\%$, $SEM = 0.2$, $p < .05$).

Bifrontopolar Group

Error rates were comparable across the two respective patient groups (for bifrontopolar, $M = 7.85\%$, $SEM = 1.63$; for temporal, $M = 4.88\%$, $SEM = 1.10$) and the young control group ($M = 5.93\%$, $SEM = 0.99$). t tests revealed no significant difference in error rates between the bifrontopolar patients and controls ($p > .30$) or between the temporal group and the controls ($p > .50$). The RTs of the patients with bifrontopolar lesions (for correct, $M = 406.5$ ms, $SEM = 16.7$; for incorrect, $M = 313.8$, $SEM = 12.4$) were

not significantly different from those of the control persons (for correct, $M = 383.4$ ms, $SEM = 6.1$; for incorrect, $M = 295.4$ ms, $SEM = 8.9$) as revealed by an ANOVA with the factors Group (2 levels, between subjects) \times Response Type (2 levels, within subjects): No main effect of Group ($p > .14$) and no interaction with the Group factor ($p > .70$) were obtained. A main effect for Response Type was revealed, $F(1, 13) = 160.42$, $p < .01$, reflecting that in both groups the correct responses were slower than errors. The late response rate was $M = 9.8\%$ ($SEM = 7.4$) in the bifrontopolar patient group and $M = 0.8\%$ ($SEM = 0.3$) in the controls. However, the variance across the patients was very high in this regard; thus, the difference in late responses between the groups was not significant ($p = .26$).

Temporal Group

Patients with temporal lobe lesions showed a tendency to respond slower than the age-matched controls (RT correct, $M = 411.7$ ms, $SEM = 16.0$; RT incorrect, $M = 320.7$, $SEM = 15.1$). The ANOVA gave rise to an almost significant main effect of group, $F(1, 13) = 3.42$, $p = .09$, and a significant main effect of response type, $F(1, 13) = 235.89$, $p < .01$. The temporal lobe patients showed a trend of producing more late responses ($M = 3.2\%$, $SEM = 1.1$) than the controls ($p = .07$).

Compatibility Effects

To validate whether the different groups performed the task normally, the flanker compatibility effect was investigated. The distribution of error rates as well as the RTs for correct trials across the compatibility conditions are shown in Table 2. All patient groups showed the same compatibility effects as the control groups: Error rates and RTs were higher for incompatible than for compatible trials, and neutral trials were in between. We tested these findings using repeated-measure ANOVAs with the within-subjects factor Compatibility (three levels) and the between-subjects factor Group. The ANOVA for the frontolateral lesion patients and their controls gave rise to a main effect of Compatibility, $F(2, 28) = 17.2$, $p < .01$, and no significant Compatibility \times Group interaction ($p = .73$). The same findings were revealed by the ANOVAs for the bifrontopolar lesion group and their controls, main effect of Compatibility, $F(2, 26) = 43.77$, $p < .01$ and of Compatibility \times Group, $p = .93$, as well as for the temporal lesion patients and the corresponding controls, main effect of compatibility, $F(2, 26) = 42.17$, $p < .01$, and of Compatibility \times Group, $p = .32$.

No significant effect of previous errors on accuracy or RTs in following trials was found in any of the patient or control groups. This was probably due to insufficient statistical power and the specific task.

ERP Results

The grand mean waveforms of the ERPs for compatible correct, incompatible correct, and incompatible erroneous

trials are depicted in Figure 2 for each group; the scalp topographies in the time window of the ERN are shown in Figure 3.

Frontolateral Group

For the patient group with lateral prefrontal lesions, there was a negative peak—the ERN—on incompatible errors as well as a negative peak of similar size on compatible correct responses. The negativity on correct incompatible trials was larger than the ERN (Figure 2, left panel). In contrast, in the corresponding age-matched control group, the ERN had a larger amplitude than the negative deflection on correct (incompatible and compatible) trials. In both groups, in a later time range, from about 300 ms to 450 ms after the response, a positive deflection—the Pe—was found on error trials, however strongly reduced in the patient group. The mean peak latency of the ERN was 78.2 ms ($SEM = 6.3$) in the frontolateral group and 78.7 ms ($SEM = 5.6$) in the controls. A t test revealed no significant latency differences between the groups ($p > .90$). To investigate differences in error processing, the amplitude data from the incompatible trials during an early and a late time window (capturing the ERN and the Pe time ranges) were subjected to mixed ANOVAs with the between-subjects factor Group and the within-subjects factor Response Type (correct, incorrect) and the topographical factors Anterior–Posterior Dimension and Lateral Dimension. The significant results are reported in Table 3 (upper panel).

The ERN. In the early time window, a significant interaction of Response Type \times Group was obtained. Inspection of the ERPs suggests that this interaction reflects a reduction of the ERN amplitude in frontolateral patients, whereas the negativity on correct incompatible trials is unchanged with respect to the control group. To test this notion, separate ANOVAs were calculated comparing the ERPs for each response type between the two groups. Although no significant group effect was found for incompatible correct trials, a trend for a main effect of group was observed for erroneous trials, $F(1, 14) = 3.12$, $p < .10$. Furthermore, separate ANOVAs contrasting correct and erroneous incompatible trials were performed for each group. Although no response type effect was present in the frontolateral lesion group, the age-matched controls showed a trend for an ERP amplitude difference between correct and incorrect responses in the early time window, $F(1, 8) = 4.45$, $p < .10$.

To investigate the effect of flanker compatibility (reflecting response conflict and uncertainty) on response monitoring, we subjected the ERP data from correct compatible and correct incompatible trials to an ANOVA with the factors Group, Compatibility, Anterior–Posterior Dimension, and Lateral Dimension. A significant interaction of Compatibility and Anterior–Posterior Dimension was revealed, $F(3, 42) = 6.44$, $p < .01$; furthermore, there was a trend for a main effect of compatibility, $F(1, 14) = 3.14$, $p < .05$, reflecting a larger amplitude of the negativity on incompatible corrects as compared with compatible ones. Post hoc tests revealed the largest difference at frontocentral electrodes, $F(1, 28) = 5.06$, $p < .05$. To test whether the

Table 2
Error Rates and Reaction Times (RTs) on Correct Trials for Compatible, Neutral, and Incompatible Trials

| Group | Error rate (%) | | RT (ms) | |
|---------------------|----------------|------------|----------|------------|
| | <i>M</i> | <i>SEM</i> | <i>M</i> | <i>SEM</i> |
| Compatible trials | | | | |
| Frontolateral | 3.13 | 1.13 | 424.0 | 15.3 |
| Older controls | 0.94 | 0.69 | 360.7 | 11.6 |
| Bifrontopolar | 2.71 | 1.13 | 373.5 | 15.6 |
| Temporal | 0.54 | 0.21 | 363.5 | 14.9 |
| Younger controls | 1.15 | 0.41 | 339.1 | 4.8 |
| Incompatible trials | | | | |
| Frontolateral | 22.77 | 8.06 | 492.5 | 19.2 |
| Older controls | 19.90 | 6.57 | 459.0 | 12.4 |
| Bifrontopolar | 16.67 | 3.21 | 445.5 | 17.8 |
| Temporal | 11.22 | 1.80 | 462.3 | 18.0 |
| Younger controls | 14.61 | 2.66 | 432.9 | 9.1 |
| Neutral trials | | | | |
| Frontolateral | 8.97 | 3.45 | 459.9 | 13.3 |
| Older controls | 3.13 | 2.05 | 408.4 | 13.1 |
| Bifrontopolar | 4.17 | 1.39 | 408.3 | 17.5 |
| Temporal | 2.90 | 1.44 | 414.9 | 17.4 |
| Younger controls | 2.05 | 0.54 | 385.9 | 6.0 |

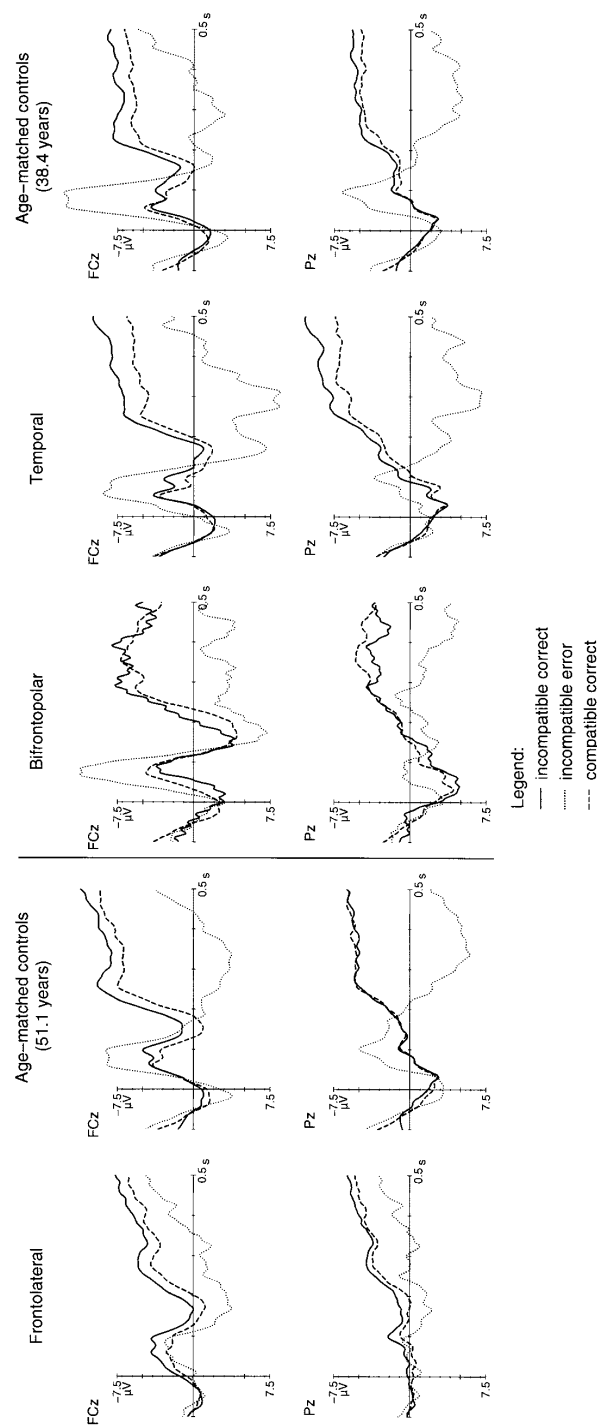


Figure 2. Grand mean ERP waveforms for each group at FCz and Pz from erroneous trials (dotted lines) and correct trials (solid lines). Left panel: Lateral frontal and the corresponding older control group. Right panel: Bifrontopolar, temporal, and the corresponding young control group.

CORTICAL LESIONS AND ERROR PROCESSING

555

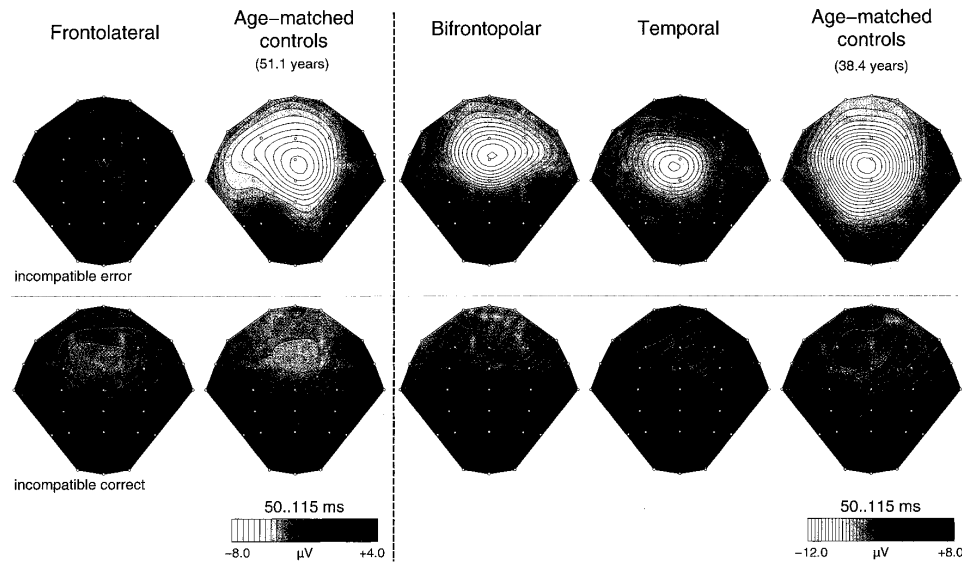


Figure 3. Topographical scalp potential distribution from each group in a time range from 50 ms to 115 ms after errors (upper row) and correct responses (lower row). Left panel: Lateral frontal and the corresponding older control group. Right panel: Bifrontopolar, temporal, and the corresponding young control group. Anterior direction: Top.

interaction with Anterior–Posterior Dimension reflected a topographical difference, the same ANOVA was performed on the amplitude-normalized data (McCarthy & Wood, 1985), revealing a significant interaction of Compatibility \times Anterior–Posterior Dimension, $F(3, 42) = 18.48$, $p < .01$.

Peak amplitudes at FCz. The amplitudes of the negativity following the response at FCz measured relative to the preceding positive peak are depicted on Figure 4. As pointed out in the Method section, this measurement of the ERN peak amplitude avoids the baseline problem (Falkenstein et al., 2000; Kopp et al., 1996). To contrast the ERN on erroneous and the negativity on correct incompatible trials, an ANOVA was performed with the factors Group and Response Type. It gave rise to a significant main effect of Response Type, $F(1, 14) = 10.83$, $p < .01$, and a Response Type \times Group interaction, $F(1, 14) = 7.24$, $p < .05$. This interaction was examined using the Tukey honestly significant difference test performed on an alpha level of .05. Although the amplitude of the negativity on correct incompatible trials did not differ significantly between groups (frontolateral patients, $M = 6.12 \mu V$; controls, $M = 7.24 \mu V$; minimum significant difference = 5.13), the ERN was significantly larger in the control group than in the frontolateral patients (frontolateral patients, $M = 6.86 \mu V$; controls, $M = 14.62 \mu V$; minimum significant difference = 7.67). Moreover, separate follow-up ANOVAs for each group revealed a significant main effect of Response Type in the control group, $F(1, 8) = 18.44$, $p < .01$, but no such effect in the frontolateral patient group ($p > .68$). These results suggest that when the lateral prefrontal cortex

was damaged, the ERN was reduced to the amplitude of the negativity following correct responses. In separate ANOVAs, we also tested the influence of Compatibility on the amplitude of the negativity following correct responses. There was a main effect of Compatibility found for the patient group, $F(1, 6) = 7.96$, $p < .03$, suggesting that the amplitude on incompatible trials was larger than on compatible ones. This effect was absent for the controls ($p > .20$).

The Pe. The ANOVA contrasting the ERPs for correct and erroneous incompatible trials in the late time window revealed a main effect of Response Type, reflecting that in both groups a Pe was present on erroneous trials (cf. Table 3, upper panel). This fact was supported by ANOVAs performed separately for both groups revealing significant main effects of Response Type: frontolateral group, $F(1, 8) = 16.42$, $p < .01$; controls, $F(1, 8) = 41.24$, $p < .01$. Moreover, the Response Type \times Group interaction and a trend for the Response Type \times Lateral Dimension interaction were found. The follow-up ANOVA for correct incompatible trials revealed neither a main effect of nor an interaction with the factor Group, suggesting that the late ERPs on correct trials did not differ significantly between frontolateral patients and their controls. In contrast, the ANOVA for erroneous trials gave rise to a main effect of group, $F(1, 14) = 4.80$, $p < .05$, reflecting that the Pe was present in both groups but lower in amplitude for the patients. Post hoc contrasts were performed to examine the interaction with Lateral Dimension and revealed that in both groups, the ERPs in the late time window differed most at midline

Table 3
Results of the Mixed Analysis of Variance Performed
for the Mean Amplitude Measures

| Factor | 50–115 ms | | 300–450 ms | |
|---|-----------|----------|------------|----------|
| | df | F | df | F |
| Frontolateral group versus older controls | | | | |
| Group | — | — | — | — |
| Response | — | — | 1, 14 | 50.36*** |
| Response × Group | 1, 14 | 4.74** | 1, 14 | 8.83** |
| Response × Lateral | — | — | 2, 28 | 3.66* |
| Bifrontopolar group versus young controls | | | | |
| Group | — | — | — | — |
| Response | 1, 13 | 12.98*** | 1, 13 | 33.23** |
| Response × Group | — | — | — | — |
| Response × Ant/Post | 3, 39 | 5.50** | — | — |
| Response × Ant/Post × Group | — | — | 3, 39 | 4.00** |
| Response × Lateral | 2, 26 | 17.29*** | — | — |
| Response × Ant/Post × Lateral | 6, 78 | 6.55*** | — | — |
| Temporal group versus young controls | | | | |
| Group | — | — | — | — |
| Response | 1, 13 | 5.56** | 1, 13 | 30.57*** |
| Response × Group | — | — | — | — |
| Response × Ant/Post | 3, 39 | 4.90** | 3, 39 | 10.45*** |
| Response × Lateral | 2, 26 | 9.45*** | 2, 26 | 6.04*** |
| Response × Ant/Post × Lateral | 6, 78 | 5.25*** | — | — |

Note. Dashes represent nonsignificant results. Ant/Post = anterior-posterior dimension.

* $p < .10$. ** $p < .05$. *** $p < .01$.

electrodes, $F(1, 14) = 48.03$, $p < .01$. The Response Type × Lateral Dimension interaction was also present when the data were subjected to the same ANOVA after amplitude normalization, $F(2, 28) = 6.76$, $p < .01$, suggesting a topographical difference between the late ERPs on correct and erroneous trials.

Bifrontopolar Group

As can be seen in Figure 2, patients with bifrontopolar and orbitofrontal lesions as well as the corresponding age-matched control group showed an ERN after incorrect responses. A smaller negative wave of similar latency was also elicited on correct trials (incompatible as well as compatible) in both groups. In the late time range, the error positivity (Pe) is visible for erroneous but not for correct responses in the patients as well as the controls. The peak latencies of the ERN at FCz did not differ significantly between the patient ($M = 80.0$ ms, $SEM = 6.3$) and the control ($M = 79.1$ ms, $SEM = 6.0$) groups ($p > .91$).

The ERN. The results of the ANOVA examining the effect of Response Type in the bifrontopolar and control groups can be found in Table 3 (middle panel). No significant main effect of Group nor a Group × Response Type interaction were observed, suggesting that the early electrophysiological correlates of response monitoring did not differ between the groups. Several significant interactions of Response Type and topographical factors were investigated by post hoc comparisons, revealing that the ERP difference between erroneous and correct incompatible trials was largest at the midline electrodes FCz, $F(1, 13) = 16.25$, $p < .01$, and Cz, $F(1, 13) = 24.95$, $p < .01$. The same ANOVA performed on amplitude-normalized data gave rise to the interactions Response Type × Anterior-Posterior Dimen-

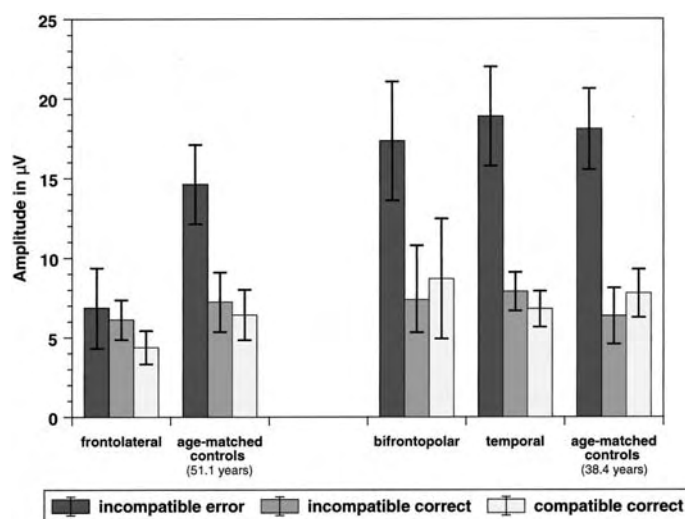


Figure 4. Peak amplitudes of the negativity following incompatible erroneous (the error-related negativity) and correct responses at FCz for all groups.

sion, $F(3, 39) = 6.22, p < .01$, Response Type \times Lateral Dimension, $F(2, 26) = 13.50, p < .01$, and Response Type \times Anterior–Posterior \times Lateral Dimension, $F(6, 78) = 8.49, p < .01$, suggesting a topographical difference in ERP scalp distribution between correct and incorrect responses. The ANOVA examining the influence of compatibility on the ERPs following correct responses revealed neither amplitude nor topography differences and no Group effects.

Peak amplitudes at FCz. The ANOVA contrasting the peak amplitudes (cf. Figure 4) of the negativity on correct and incorrect incompatible trials revealed a main effect of Response Type, $F(2, 26) = 18.42; p < .01$. There was no main effect of and no interaction with the Group factor. In a further ANOVA contrasting correct incompatible and compatible trials, no main effects or interactions of the factors Group and Compatibility were obtained. This supports the above-mentioned findings that the early electrophysiological correlates of response monitoring did not differ between these groups.

The Pe. In the late time window, in addition to the main effect of Response Type, a Response Type \times Anterior–Posterior Dimension \times Group was obtained. To test whether this interaction reflected a group difference in the Pe, separate follow-up ANOVAs for correct and erroneous trials were performed. There was a trend for a Group \times Anterior–Posterior Dimension interaction only for erroneous trials, $F(3, 39) = 3.77, p < .06$; no such interaction was obtained for correct trials ($p > .86$). The same interaction was significant when amplitude-normalized data from error trials were subjected to the same ANOVA, $F(3, 39) = 4.36, p < .05$, suggesting a topographical difference in scalp distribution of the Pe between the groups. As can be seen in Figure 5, depicting the mean amplitude in the late time window at midline electrodes, the Pe was focused more anteriorly in the bifrontopolar patients than in the controls.

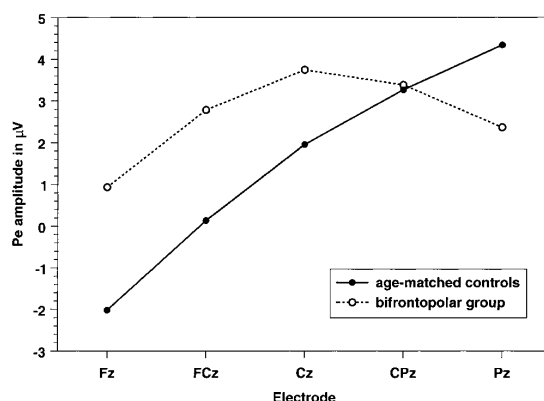


Figure 5. Mean amplitudes of the error positivity Pe at midline electrodes in the bifrontopolar and the age-matched control group.

Temporal Group

In patients with temporal lobe lesions, errors also elicited an ERN as well as a Pe (Figure 2). The latency of the ERN at FCz amounted to $M = 70.7$ ms ($SEM = 8.5$) and did not differ significantly from the peak latency in the corresponding control group ($p > .58$). As in the controls, at FCz a smaller negative deflection similar to the ERN was observed for correct trials.

The ERN. The mixed ANOVA testing the effects of Response Type in the temporal and the control groups gave rise to a main effect of Response Type and interactions of Response Type with both topographical factors (cf. Table 3, lower panel). No Response Type \times Group interaction was found, suggesting that the groups did not differ with respect to the ERPs for correct and incorrect responses. Follow-up comparisons were performed to further investigate the interactions with the topographical factors. They revealed that the amplitude difference between the ERPs on correct incompatible trials and the ERN was largest at FCz, $F(1, 13) = 8.14, p < .05$, and Fz, $F(1, 13) = 11.78, p < .01$. When the ANOVA was performed on the data after amplitude normalization, the same topographical interactions were found, reflecting differences in scalp distribution of the ERPs for correct and incorrect incompatible trials: Response \times Anterior–Posterior Dimension, $F(3, 39) = 5.92, p < .01$; Response \times Lateral Dimension, $F(2, 26) = 8.45, p < .01$; Response \times Anterior–Posterior Dimension \times Lateral Dimension, $F(6, 78) = 4.51, p < .01$. The ANOVA contrasting incompatible and compatible correct trials did not reveal any significant main effects of Group or Response Type and no interactions with these factors, such that no effect can be claimed of Compatibility on response monitoring of correct responses.

Peak amplitudes at FCz. The peak amplitude data at FCz for temporal patients and their controls, measured as the difference of the preceding positive deflection and the negative deflection after the response, are visible in Figure 4. No significant group differences were found when contrasting correct and erroneous incompatible responses. As expected, there was a main effect of Response Type, $F(1, 13) = 27.04, p < .01$, reflecting that the ERN is also significantly larger in temporal lesions than the negativity following the correct responses. The ANOVA contrasting compatible and incompatible correct trials did not reveal significant effects or interactions of Group or Compatibility ($p > .80$).

The Pe. As shown in Table 3 (lower panel), in the late time window the ANOVA examining correct and erroneous incompatible trials revealed no main effect of and no interactions with the factor Group. The main effect of Response Type suggests that temporal lesion patients also had a Pe. The interactions of Response type with Lateral Dimension and Anterior–Posterior Dimension factors were investigated in follow-up comparisons, revealing that the largest difference between correct and incorrect trials was at parietal electrodes, with the maximum at Pz, $F(1, 13) = 51.31, p < .01$. The interactions of Response Type and topographical factors were also obtained for amplitude-normalized data:

Response \times Anterior–Posterior, $F(3, 39) = 9.25, p < .015$;
 Response \times Lateral Dimension, $F(2, 26) = 6.35, p < .01$;
 Response \times Anterior–Posterior \times Lateral Dimension, $F(6, 78) = 2.42, p < .05$.

Discussion

The results in the lateral frontal cortex group replicated and extended the findings by Gehring and Knight (2000): In the time window of the ERN, the ERPs on correct and incorrect trials did not differ. In addition, our results show a smaller Pe amplitude in the patient group than in matched controls. In contrast to Gehring and Knight (2000), who reported an amplitude increase for the negativity following correct responses and an unaffected ERN, our results suggest that the ERN amplitude was reduced, whereas the amplitude of the negativity on correct trials was comparable to the one in controls. When interpreting these findings, one first has to find whether the negativities in response-locked ERPs to correct and incorrect responses reflect similar processes or not (cf. Coles et al., 2001). If yes, the amplitude difference between both conditions is the most critical aspect of the results across groups. If, however, the scalp topographies of the ERPs differ between correct and incorrect responses, at least partly different underlying neural processes must be assumed. Then, only the absolute amplitude of the ERN can be compared between groups; that is, it would be very difficult—if not impossible—to interpret lesion effects on the amplitude difference between correct and error trials. In our data set, we found topographical differences between the two response types in all groups except for the frontolateral lesion patients and the older control group. Thus, one cannot claim that neural processes immediately after the response differ qualitatively with respect to the response type in these two groups. What process could be reflected in an ERN-like wave that is also present after correct responses? One could speculate that this process is an ongoing conflict about whether the response was correct or not. This view was indirectly supported by a study demonstrating an increase of the ERN amplitude in late responses, in which higher conflict about the correct response can be assumed (Luu, Flaisch, & Tucker, 2000). Within the error-detection framework, this would be the case when the comparison process is disturbed (see below). In the nomenclature of the response conflict model, the response conflict would continue even after the response and would change to “post-response conflict” (Carter, 2001). One may speculate further that the time needed to resolve (pre-) response conflicts depends on the type of task. It seems conceivable that the task used by Gehring and Knight (2000; a cue determining the target had to be held in memory and the correct task set had to be selected for the correct response) involved a larger working memory load and more task-set management processes than the flanker task as used in the present study. This could explain why (postresponse) conflict and its putative ERP correlate—the negativity on correct responses—were higher in the Gehring and Knight study. This view could also explain why, in the frontolateral patients, the negativity on correct incompatible

trials was larger than in correct compatible ones (which do not involve high response conflict). An explanation derived from the conflict-monitoring theory for this latter finding in the patient group could be suggested: It might be due to a reduced attentional contrast between the central target arrow and the flankers, resulting in increased response conflict. In other words, the frontolateral patients might have been less able to focus on the target stimulus such that the response priming from flanker signals would be enhanced. On incompatible trials, the response priming from the flankers would compete with the correct response, whereas on compatible trials, the flanker signal would facilitate the correct response and reduce conflict. Alternatively, one might also speculate that in patients with lateral frontal lesions the response conflict persisted longer than in younger patients and controls rather than increasing because of problems with attentional contrast. This could also explain why we did not find any amplitude differences of the negativity on correct compatible and correct incompatible trials in the younger groups: In these participants, the conflict might have been completely resolved before the response was issued.

It seems that unilateral lesions of the lateral frontal cortex render the generators of the ERN unable to distinguish between correct and erroneous responses. Interestingly, the ERN scalp distribution did not differ between patients and controls; specifically, it was not changed at lateral frontal electrodes (covering the lesion site). This supports the notion that the lateral frontal cortex is not directly involved in the electrical generation of the ERN but has rather an indirect, modulating effect on error detection. How can detection of errors be disrupted? As pointed out by Coles et al. (2001), either the representation of the correct response or the representation of the actually performed response may be disturbed. The representation of the correct response arises from an ongoing evaluation of the stimuli and application of the rules from the currently relevant task set. It is conceivable that the lateral prefrontal cortex might be involved in several ways: The relevant task set must be maintained and the stimulus representations must be manipulated according to the mapping rules. Furthermore, the resulting representation of the correct response must be maintained for comparison with the actually performed response. The lateral prefrontal cortex has been shown to be engaged in maintenance and manipulation of information (D’Esposito et al., 2000; Goldman-Rakic, 1996; Gruber & von Cramon, 2001; Müller et al., in press) and in task-set related management functions (MacDonald et al., 2000; Ullsperger & von Cramon, 2001; Zysset et al., 2001), which may be disturbed when the lateral prefrontal cortex is damaged. The prolongation of the RTs as well as the increase in late responses in the frontolateral group could reflect difficulties in applying the stimulus–response mapping rules (i.e., the task set) and in establishing the correct response representation. An incomplete representation of the correct response would make error detection difficult, which is reflected in a lower amplitude of the ERN, and may also be accompanied by an ERN-like wave on correct trials (Coles et al., 2001; Scheffers & Coles, 2000).

If errors cannot be properly detected, the alerting error signal is less reliable, and resulting processes such as awareness and assessment of the error must also be affected. This could explain why the Pe amplitude is reduced in the frontolateral group. Consistent with these considerations, Gehring and Knight (2000) reported that remedial actions after errors were partly disturbed in patients with lateral prefrontal lesions. However, the mere presence of the Pe indicates that errors must have been detected to some extent—though less reliably than in healthy controls. One explanation might be the unilaterality of the lateral prefrontal lesions, such that the error-detection system received input from at least one healthy frontal lobe and could function on a suboptimal level. It would be interesting to follow the question of whether bilateral frontal lesions have even larger effects (i.e., abolition of the Pe). We did not find significant differences in performance according to whether the erroneous response was ipsi- or contralateral to the lesion. It might be interesting to investigate in future studies whether the ERN results vary with the laterality of stimuli and responses.

Our data suggest that lesions in frontopolar and anterior orbitofrontal cortices as well as in temporal cortices do not significantly interfere with performance monitoring. It seems that the frontomedian generator of the ERN was not influenced by these lesions. Only the maximum of the Pe was localized more anteriorly in the bifrontopolar group as compared with controls. Also, behavioral performance did not differ between the young patient groups and their healthy controls. This finding was expected for the temporal group and supports the idea that the temporal lobes are not largely involved in performance monitoring.¹

However, the findings for the patients with bifrontopolar-orbitofrontal lesions were not entirely in accordance with the hypotheses. As pointed out at the beginning of this article, previous research has suggested a role of the orbitofrontal cortex regarding the affective and motivational input to performance monitoring (e.g., Bechara et al., 1997, 1998; Luu & Tucker, 2001; Tucker et al., 1999). However, generation of the ERN was not affected, and the maximum of the Pe was only shifted anteriorly but not significantly reduced (Figure 5). Although a topographical difference suggests at least partly different underlying neuronal processes, it can only be speculated that different scalp distribution of the Pe could reflect a change in the emotional assessment of the committed errors. The presence of an unaffected ERN suggests that the generation of this component is not strongly dependent on input from the anterior orbitofrontal cortex. It is interesting to note that Swick et al. (2001) reported an abolition of the ERN in three patients with lesions of the orbitofrontal cortex, which is not consistent with our findings. However, it seemed that in their patients, lesions extended into the pregenual ACC and subcallosal area (BA 24a, 24b, 25). In contrast, the entire anterior cingulate as well as subcallosal cortex was spared in all patients who participated in the present study. Lesions of the rostral, particularly pregenual ACC and subcallosal cortex, have been shown to reduce or abolish the ERN (Segalowitz, Davies, Pailing, & Stemmer, 2000; Swick et

al., 2001; Swick & Turken, 2000). Thus, anatomical and functional integrity of the emotional subdivision of the ACC itself (cf. Bush, Luu, & Posner, 2000) seems to play an important role for the generation of the ERN. According to primate studies, limbic input to the caudal ACC, including the CMA, is indirect through the pregenual ACC and subcallosal area (BA 24a, 24b, 25; Morecraft & van Hoesen, 1998; Paus, 2001). Our results suggest that the rostral ACC rather than the orbitofrontal cortex may be the most relevant structure for emotional input to the error-detection system. Future studies should address whether the influence of the orbitofrontal cortex on the awareness and assessment of errors and the consequences on motivation, affect, and possibly long-term strategic adjustments is larger when accuracy is directly coupled to reward and punishment (Bechara et al., 1998; Dikman & Allen, 2000; Gehring et al., 1993).

Finally, in the young patients as well as in their controls we did not find ERP differences between compatible and incompatible correct responses. Performance data suggest that the task was slightly easier for the young groups than for the older participants, particularly for the frontolateral patients. In other words, they might have had enough time to resolve response conflict before the correct response was issued. Therefore, response conflict or uncertainty probably did not continue over the response and did not influence response-locked ERPs.

Conclusion

The present study provides further support for the strong functional interconnection of the lateral prefrontal cortex and the cingulate motor area in monitoring behavior. In addition, a third system involved in the generation of the Pe must be assumed.

Furthermore, it was demonstrated that frontopolar and anterior orbitofrontal as well as temporal cortices have little influence on error detection and on its early electrophysiological correlate, the ERN. A hint for a role of the orbitofrontal cortex in emotional assessment of errors was provided by topographic changes of the Pe.

However, it remains unclear why the performance of patients whose electrophysiological correlates of error processing are disturbed shows only minor or no changes, as was the case in this and other patient studies investigating performance monitoring (Gehring et al., 2000; Gehring & Knight, 2000; Segalowitz et al., 2000; Swick et al., 2001). The investigation of error awareness, its behavioral reflection, and its relationship to the Pe will be important topics to study for a better understanding of how people make and correct errors. In sum, the results suggest that performance

¹ Note that the temporal lesions did not affect the temporoparietal junction area, which was shown to be important for the generation of the P3b (e.g., Knight & Scabini, 1998). Therefore, it seems plausible that the Pe—a component with similarities to the P3b (Davies et al., 2001; Falkenstein et al., 2000)—was unaffected in these patients.

monitoring is a very complex set of processes, involving a widespread network of brain structures.

References

- Barbas, H., & Pandya, D. N. (1989). Architecture and intrinsic connections of the prefrontal cortex in the rhesus monkey. *Journal of Comparative Neurology*, 289, 353–375.
- Bates, J. F., & Goldman-Rakic, P. S. (1993). Prefrontal connections of medial motor areas in the rhesus monkey. *Journal of Comparative Neurology*, 336, 211–228.
- Bechara, A., Damasio, H., Tranel, D., & Anderson, S. W. (1998). Dissociation of working memory from decision making within the human prefrontal cortex. *The Journal of Neuroscience*, 18, 428–437.
- Bechara, A., Damasio, H., Tranel, D., & Damasio, A. R. (1997, February 28). Deciding advantageously before knowing the advantageous strategy. *Science*, 275, 1293–1295.
- Bechara, A., Tranel, D., Damasio, H., & Damasio, A. R. (1996). Failure to respond autonomically to anticipated future outcomes following damage to prefrontal cortex. *Cerebral Cortex*, 6, 215–225.
- Botvinick, M. M., Braver, T. S., Barch, D. M., Carter, C. S., & Cohen, J. D. (2001). Conflict monitoring and cognitive control. *Psychological Review*, 108, 624–652.
- Bush, G., Luu, P., & Posner, M. I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends in Cognitive Sciences*, 4, 215–222.
- Carter, C. S. (2001, June). *Modular functional contributions of medial and lateral frontal cortex to executive control: Evidence from event-related fMRI and ERP*. Paper presented at TENNET XII, Montreal, Quebec, Canada.
- Carter, C. S., Braver, T. S., Barch, D. M., Botvinick, M. M., Noll, D., & Cohen, J. D. (1998, May 1). Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science*, 280, 747–749.
- Carter, C. S., MacDonald, A. M., III, Botvinick, M., Ross, L. L., Stenger, V. A., Noll, D., & Cohen, J. D. (2000). Parsing executive processes: Strategic vs. evaluative functions of the anterior cingulate cortex. *Proceedings of the National Academy of Sciences*, 97, 1944–1948.
- Coles, M. G. H., Scheffers, M. K., & Holroyd, C. (1998). Berger's dream? The error-related negativity and modern cognitive psychophysiology. In H. Witte, U. Zwiener, B. Schack, & A. Döring (Eds.), *Quantitative and topological EEG and MEG analysis* (pp. 96–102). Jena-Erlangen, Germany: Druckhaus Mayer Verlag.
- Coles, M. G. H., Scheffers, M. K., & Holroyd, C. B. (2001). Why is there an ERN or Ne on correct trials? Response representations, stimulus-related components, and the theory of error-processing. *Biological Psychology*, 56, 173–189.
- Davies, P. L., Segalowitz, S. J., Dywan, J., & Pailing, P. E. (2001). Error-negativity and positivity as they relate to other ERP indices of attentional control and stimulus processing. *Biological Psychology*, 56, 191–206.
- Dehaene, S., Posner, M. I., & Tucker, D. M. (1994). Localization of a neural system for error detection and compensation. *Psychological Science*, 5, 303–305.
- D'Esposito, M., Postle, B. R., & Rypma, B. (2000). Prefrontal cortical contributions to working memory: Evidence from event-related fMRI studies [Electronic version]. *Experimental Brain Research*, 133, 3–11.
- Dikman, Z. V., & Allen, J. J. B. (2000). Error monitoring during reward and avoidance learning in high- and low-socialized individuals. *Psychophysiology*, 37, 43–45.
- Falkenstein, M., Hielscher, H., Dziobek, I., Schwarzenau, P., Hoormann, J., Sundermann, B., & Hohnsbein, J. (2001). Action monitoring, error detection, and the basal ganglia: An ERP study. *NeuroReport*, 12, 157–161.
- Falkenstein, M., Hohnsbein, J., Hoormann, J., & Blanke, L. (1990). Effects of errors in choice reaction tasks on the ERP under focused and divided attention. In C. H. M. Brunia, A. W. K. Gaillard, & A. Kok (Eds.), *Psychophysiological brain research* (pp. 192–195). Tilburg, the Netherlands: Tilburg University Press.
- Falkenstein, M., Hoormann, J., Christ, S., & Hohnsbein, J. (2000). ERP components on reaction errors and their functional significance: A tutorial. *Biological Psychology*, 51, 87–107.
- Gehring, W. J., Goss, B., Coles, M. G. H., Meyer, D. E., & Donchin, E. (1993). A neural system for error detection and compensation. *Psychological Science*, 4, 385–390.
- Gehring, W. J., Himle, J., & Nisenson, L. G. (2000). Action-monitoring dysfunction in obsessive-compulsive disorder. *Psychological Science*, 11, 1–6.
- Gehring, W. J., & Knight, R. T. (2000). Prefrontal-cingulate interactions in performance monitoring. *Nature Neuroscience*, 3, 516–520.
- Goldman-Rakic, P. S. (1996). Regional and cellular fractionation of working memory. *Proceedings of the National Academy of Sciences*, 93, 13473–13480.
- Gratton, G., Coles, M. G. H., & Donchin, E. (1983). A new method for off-line removal of ocular artifact. *Electroencephalography and Clinical Neurophysiology*, 55, 468–484.
- Gruber, O., & von Cramon, D. Y. (2001). Domain-specific distribution of working memory processes along human prefrontal and parietal cortices: A functional magnetic resonance imaging study. *Neuroscience Letters*, 297, 29–32.
- Hazeltine, E., Poldrack, R., & Gabrieli, J. D. E. (2000). Neural activation during response competition. *Journal of Cognitive Neuroscience*, 12(Suppl. 2), 118–129.
- Hohnsbein, J., Falkenstein, M., & Hoormann, J. (1998). Performance differences in reaction tasks are reflected in event-related brain potentials (ERPs). *Ergonomics*, 41, 622–633.
- Holroyd, C. B. (2001). *Reinforcement learning and the error-related negativity: A computational and neurophysiological investigation*. Unpublished doctoral dissertation, University of Illinois at Urbana-Champaign.
- Holroyd, C. B., Dien, J., & Coles, M. G. H. (1998). Error-related scalp potentials elicited by hand and foot movements: Evidence for an output-independent error-processing system in humans. *Neuroscience Letters*, 242, 65–68.
- Holroyd, C. B., Reichler, J., & Coles, M. G. H. (1999). Is the error-related negativity generated by a dopaminergic error signal for reinforcement learning? Hypothesis and model. *Journal of Cognitive Neuroscience*, 11, 45.
- Huynh, H., & Feldt, L. S. (1970). Conditions under which mean square ratio repeated measurements designs have exact *F* distributions. *Journal of the American Statistical Association*, 65, 1582–1589.
- Kiehl, K. A., Liddle, P. F., & Hopfinger, J. B. (2000). Error processing and the rostral anterior cingulate: An event-related fMRI study. *Psychophysiology*, 37, 216–223.
- Knight, R. T., & Scabini, D. (1998). Anatomic bases of event-related potentials and their relationship to novelty detection in humans. *Journal of Clinical Neurophysiology*, 15, 3–13.
- Kopp, B., Rist, F., & Mattler, U. (1996). N200 in the flanker task as a neurobehavioral tool for investigating executive control. *Psychophysiology*, 33, 282–294.

CORTICAL LESIONS AND ERROR PROCESSING

561

- Luu, P., Collins, P., & Tucker, D. M. (2000). Mood, personality, and self-monitoring: Negative affect and emotionality in relation to frontal lobe mechanisms of error monitoring. *Journal of Experimental Psychology: General*, 129, 43–60.
- Luu, P., Flaisch, T., & Tucker, D. M. (2000). Medial frontal cortex in action monitoring. *Journal of Neuroscience*, 20, 464–469.
- Luu, P., & Tucker, D. M. (2001). Regulating action: Alternating activation of midline frontal and motor cortical networks. *Clinical Neurophysiology* 112, 1295–1306.
- MacDonald, A. W., III, Cohen, J. D., Stenger, V. A., & Carter, C. S. (2000, June 9). Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science*, 288, 1835–1838.
- McCarthy, G., & Wood, C. C. (1985). Scalp distributions of event-related potentials: An ambiguity associated with analysis of variance models. *Electroencephalography and Clinical Neurophysiology*, 62, 203–208.
- Morecraft, R. J., & van Hoesen, G. W. (1998). Convergence of limbic input to the cingulate motor cortex in the rhesus monkey. *Brain Research Bulletin*, 45, 209–232.
- Morgan, J. M., Wenzl, M., Lang, W., Lindinger, G., & Deeke, L. (1992). Frontocentral DC-potential shifts predicting behavior with or without a motor task. *Electroencephalography and Clinical Neurophysiology*, 83, 378–388.
- Müller, N. G., Machado, L., & Knight, R. T. (in press) Contributions of subregions of the prefrontal cortex to working memory: Evidence from brain lesions in humans. *Journal of Cognitive Neuroscience*.
- Nieuwenhuis, S., Ridderinkhof, K. R., Blom, J., Band, G. P. H., & Kok, A. (2001). Error-related brain potentials are differentially related to awareness of response errors: Evidence from an antisaccade task. *Psychophysiology*, 38, 752–760.
- Paus, T. (2001) Primate anterior cingulate cortex: Where motor control, drive and cognition interface. *Nature Reviews Neuroscience*, 2, 417–424.
- Paus, T., Castro-Alamancos, M., & Petrides, M. (2000). Cortico-cortical connectivity of the human mid-dorsolateral frontal cortex and its modulation by repetitive transcranial magnetic stimulation: A combined TMS/PET study. *NeuroImage*, 11(Suppl.), S765.
- Perrin, F., Pernier, J., Bertrand, O., & Echallier, J. F. (1989). Spherical splines for scalp potential and current density mapping. *Electroencephalography and Clinical Neurophysiology*, 72, 184–187.
- Petrides, M. (1996, October 29). Specialized systems for the processing of mnemonic information within the primate frontal cortex. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, 351, 1455–1462.
- Pfeifer, E. (1993). IPCM—Iterative PCA correction method. A new method for the correction of ocular artifacts in ERP-data. *Psychophysiology*, 30, 51.
- Rogers, R. D., & Monsell, S. (1995). Costs of a predictable switch between simple cognitive tasks. *Journal of Experimental Psychology: General*, 124, 207–231.
- Scheffers, M. K., & Coles, M. G. H. (2000). Performance monitoring in a confusing world: Error-related brain activity, judgments of response accuracy, and types of errors. *Journal of Experimental Psychology: Human Perception and Performance*, 26, 141–151.
- Schultz, W., & Dickinson, A. (2000). Neuronal coding of prediction errors. *Annual Review of Neuroscience*, 23, 473–500.
- Segalowitz, S. J., Davies, P. L., Pailing, P. E., & Stemmer, B. (2000). Error-related ERP responses: Error detection or beyond? *Psychophysiology*, 37(Suppl. 1), S10.
- Sharbrough, F., Chatrian, G., Lesser, R. P., Lüders, H., Nuwer, M., & Picton, T. W. (1990). *Guidelines for standard electrode position nomenclature*. Bloomfield, IN: American EEG Society.
- Swick, D., & Turken, A. U. (2000). Neuropsychological perspective on error monitoring and response selection in the anterior cingulate cortex. In W. Mitner & M. G. H. Coles (Eds.), *Executive control, errors, and the brain 2000* (p. 25). Jena, Germany: Friedrich-Schiller-Universität Jena.
- Swick, D., Turken, A. U., Larsen, J., Roxby, C., Kopelovich, J. C. S., Jovanovich, J., & Miller, K. M. (2001). Anterior cingulate cortex: Error monitoring or conflict monitoring? *Journal of Cognitive Neuroscience*, 13(Suppl. 1), S72.
- Tucker, D. M., Hartry-Speiser, A., McDougal, L., Luu, P., & deGrandpre, D. (1999). Mood and spatial memory: Emotion and right hemisphere contribution to spatial cognition. *Biological Psychology*, 50, 103–125.
- Ullsperger, M., & von Cramon, D. Y. (2001). Subprocesses of performance monitoring: A dissociation of error processing and response competition revealed by event-related fMRI and ERPs. *NeuroImage*, 14, 1387–1401.
- Zysset, S., Müller, K., Lohmann, G., & von Cramon, D. Y. (2001). Color-word matching Stroop task: Separating interference and response conflict. *NeuroImage*, 13, 29–36.

Received August 27, 2001

Revision received February 11, 2002

Accepted April 11, 2002 ■

Chapter 8

The role of intact frontostriatal circuits in error processing

This Chapter reports a direct follow-up study on the findings in patients with lateral frontal lesions. It addresses the role of the frontostriatal circuits in performance monitoring by investigating two patient groups with lateral frontal and basal ganglia lesions. Based on the findings from this study it can be hypothesized that lesions of the (anterior ventrolateral) thalamus should also interfere with performance monitoring. The according study is currently in progress.

The Role of Intact Frontostriatal Circuits in Error Processing

Markus Ullsperger and D. Yves von Cramon

Abstract

■ The basal ganglia have been suggested to play a key role in performance monitoring and resulting behavioral adjustments. It is assumed that the integration of prefrontal and motor cortico-striato-thalamo-cortical circuits provides contextual information to the motor anterior cingulate cortex regions to enable their function in performance monitoring. So far, direct evidence is missing, however. We addressed the involvement of frontostriatal circuits in performance monitoring by collecting event-related brain potentials (ERPs) and behavioral data in nine patients with focal basal ganglia lesions and seven patients with lateral prefrontal cortex lesions while they performed a flanker task. In both patient groups, the amplitude of the error-related

negativity was reduced, diminishing the difference to the ERPs on correct responses. Despite these electrophysiological abnormalities, most of the patients were able to correct errors. Only in lateral prefrontal cortex patients whose lesions extended into the frontal white matter, disrupting the connections to the motor anterior cingulate cortex and the striatum, were error corrections severely impaired. In sum, the fronto-striato-thalamo-cortical circuits seem necessary for the generation of error-related negativity, even when brain plasticity has resulted in behavioral compensation of the damage. Thus, error-related ERPs in patients provide a sensitive measure of the integrity of the performance monitoring network. ■

INTRODUCTION

In a changing environment, continuous performance monitoring and subsequent behavioral adjustments are indispensable for adaptive, goal-directed behavior. For more than 10 years, researchers have focused on an event-related potential (ERP) associated with response errors, the error-related negativity (ERN) or error negativity (Ne) (Gehring, Goss, Coles, Meyer, & Donchin, 1993; Falkenstein, Hohnsbein, Hoormann, & Blanke, 1990). It is elicited by execution of prepotent but incorrect responses in choice reaction time tasks, peaks about 50 to 100 msec after the erroneous response, and has a frontocentral scalp distribution. A second error-related ERP, the error positivity (Pe), has a centroparietal distribution and occurs about 300 to 500 msec after the erroneous response (Falkenstein, Hoormann, Christ, & Hohnsbein, 2000). Its functional significance is still unclear (Falkenstein, 2004); it may be related to the conscious awareness of errors (Nieuwenhuis, Ridderinkhof, Blom, Band, & Kok, 2001).

According to current theories, the ERN reflects post-response conflict or mismatch between the erroneous response and the competing correct response tendency (Yeung, Cohen, & Botvinick, 2004; Coles, Scheffers, & Holroyd, 2001). It is assumed to be generated in the anterior cingulate cortex (ACC), specifically in the rostral

cingulate zone (RCZ; Swick & Turken, 2002; Ullsperger & von Cramon, 2001; Dehaene, Posner, & Tucker, 1994), the human homologue of the monkey's rostral cingulate motor area. Neuroimaging and single-unit recordings showed that this cortical area is part of a larger network signaling the need for behavioral change to optimize action outcome (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004; Ullsperger, Volz, & von Cramon, 2004; Williams, Bush, Rauch, Cosgrove, & Eskandar, 2004). Evidence from nonhuman primates suggests that it receives inputs from the adjacent pre-SMA and dorsal premotor cortex as well as the thalamic ventroanterior nucleus (pars caudalis) and the oral part of the ventrolateral nucleus (Hatanaka et al., 2003). These thalamic nuclei, in turn, are sites of termination of pallidal efferents (Dum & Strick, 1993). The RCZ projects to premotor and caudal motor areas as well as the striatum, particularly in the putamen and the striatal cell bridges (Haber, 2003; Takada et al., 2001). Furthermore, reciprocal connections of the ACC and lateral prefrontal cortex (LPFC) have been described (Petrides & Pandya, 1999; Bates & Goldman-Rakic, 1993). In humans, the RCZ and pre-SMA are functionally connected with the LPFC (Derrfuss, Brass, & von Cramon, 2004; Paus, Castro-Alamancos, & Petrides, 2001; Koski & Paus, 2000). The LPFC itself also projects to the BG, specifically to the rostral striatum. Whereas original models suggested segregated parallel information processing cortico-striato-thalamocortical circuits (Alexander, Crutcher, & DeLong, 1990), more recent

Max Planck Institute for Human Cognitive and Brain Sciences,
Leipzig, Germany

views advocate an additional integrative function of the BG (Bar-Gad, Morris, & Bergman, 2003; Haber, 2003). In particular, the structure of the BG–thalamus–cortex connections appears to “mediate information flow from higher cortical “association” areas of the prefrontal cortex to rostral motor areas” (Haber, 2003, p. 325).

These mutual connections suggest that, in addition to the RCZ, the basal ganglia (BG) and the LPFC play an important role in performance monitoring. The BG have been suggested to be involved in motor control, in encoding and predicting the serial order of events, and in learning—functions that are highly relevant for performance monitoring in the service of response adjustments. Several computational models have addressed how the BG mediate these functions (Bar-Gad et al., 2003; Gillies & Arbuthnott, 2000). Relevant to learning and adaptive behavior are actor–critic models integrating knowledge about BG anatomy and physiology (Barto, 1995; Houk, Adams, & Barto, 1995). It is assumed that the striatal patch compartments and the mesencephalic dopamine neurons form the basis of the adaptive critic (striatal patch neurons project to the mesencephalic dopamine system (Graybiel, Aosaki, Flaherty, & Kimura, 1994; Gerfen, 1992)). According to the models, the critic learns to predict rewards from the ongoing actions and information from the environment. Any unexpected discrepancy from outcome prediction results in phasic teaching signals of the dopamine system used by the actor module to optimize behavior and by the critic to optimize prediction. The actor module has been associated with the striatal matrix compartments (Barto, 1995; Houk et al., 1995) and with the RCZ (Holroyd & Coles, 2002). A recent functional magnetic resonance imaging study suggested partly dissociable contributions of the ventral and dorsal striatum to an actor–critic architecture, with the former corresponding to the critic and the latter to the actor (O’Doherty et al., 2004). Studies in monkeys demonstrated phasic changes in activity of the mesencephalic dopamine system signaling errors in reward prediction to the striatum as well as to the cortex (Schultz, 2002). It has been suggested that the ERN is generated when the dopaminergic teaching signal is conveyed from the midbrain to the ACC (Holroyd & Coles, 2002). Specifically, it has been proposed that the phasic dopamine signals modulate the activity of motor neurons in the RCZ, which is measurable at the scalp as changes in ERN amplitude. Phasic decreases in dopamine activity (indicating a negative reward prediction error) are associated with large ERNs and phasic increases (indicating a positive reward prediction error) with small ERNs.

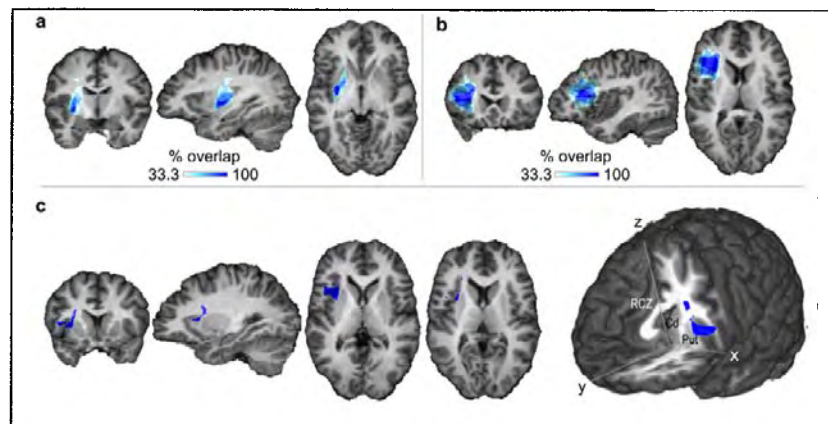
The LPFC has been shown to be involved in processes related to maintenance and updating of task representations in task preparation (Brass & von Cramon, 2004; Derrfuss et al., 2004; MacDonald, Cohen, Stenger, & Carter, 2000). Thus, it may be assumed that it provides

contextual information about the goals and the task at hand that is needed to predict and evaluate the events associated with an action.

In sum, the anatomical connectivity and computational models suggest that the RCZ receives inputs from the LPFC and from the BG circuits providing information on task context, ongoing events, and competing motor responses, and that these inputs are modulated by the dopamine activity in the midbrain. These considerations lead to the prediction that lesions to any of these structures—the motor striato–thalamo–cortical circuit, LPFC, and the RCZ itself—should impair performance monitoring and resulting behavioral adjustments. In fact, unilateral lesions of the LPFC were shown to impair the generation of electrophysiological correlates of error processing (Ullsperger, von Cramon, & Müller, 2002; Gehring & Knight, 2000). Both studies revealed a diminished difference between ERPs on correct and incorrect trials. In the former study, this was due to increase in ERN-like responses on correct trials, whereas the latter study reported a decrement of the ERN on error trials. Moreover, results on immediate error correction in these patients were not conclusive. Studies on the role of the BG in error processing by investigating patients with mild to moderate Parkinson’s disease did not reveal unequivocal findings. Although one study, decreased ERN amplitudes were found (Falkenstein et al., 2001), another group did not find impairments of the ERN in patients with unilateral symptoms (Holroyd, Praamstra, Plat, & Coles, 2002). As the decrease in dopamine release may have affected the BG and the mesocortical pathway to the RCZ, interpretation is difficult.

Here we report an ERP study of error processing in nine patients with unilateral lesions of the BG and seven patients with unilateral lesions of the LPFC (Figure 1A and B; Table 1) while they committed errors in a speeded flanker task. The BG lesions focused to the putamen and the pallidum, the latter being the output relay of the BG. Thus, the information flow in the cortico–striato–thalamo–cortical circuits could be expected to be impaired. We additionally investigated immediate corrective behavior in these patient groups by instructing them to immediately correct encountered errors by a second key press. Intentional error corrections are associated with activity in the RCZ and pre-SMA (Fiehler, Ullsperger, & von Cramon, 2004), and lesions of the RCZ result in decrease in error correction abilities (Swick & Turken, 2002). Moreover, corrective responses are associated with an additional negative deflection, the correction-related negativity (CoRN; Fiehler, Ullsperger, & Von Cramon, 2005). Incidental (i.e., spontaneous, noninstructed) error corrections have been suggested to be delayed correct responses (Rabbitt, 2002). However, the instruction to correct errors leads to an increase in slow error corrections, which are likely to result from performance monitoring,

Figure 1. Lesion overlay plots. Lesions of each individual were segmented manually and overlaid on a healthy brain template after normalization to stereotactic space. (A) Lesion overlap of all basal ganglia patients. The lesion segment of Patient 329 was flipped to the left hemisphere. Coronal ($y = -9$), sagittal ($x = -30$), and axial slice ($z = 0$). (B) Lesion overlap of all lateral prefrontal cortex (LPFC) patients. The lesion segment of Patient 370 was flipped to the left hemisphere. Coronal ($y = 18$), sagittal ($x = -38$), and axial slice ($z = 13$). (C) Lesion part unique to the three LPFC patients with impaired error correction. Left: coronal ($y = 10$), sagittal ($x = -27$), and axial ($z = 6, 11$) slices. Right: oblique topographical view from above and front. RCZ = rostral cingulate zone; Cd = caudate nucleus; Put = putamen.



as ERP and functional imaging studies suggest (Fiehler et al., 2004, 2005).

Given the theoretical considerations about the importance of the LPFC and BG in performance monitoring, we expected impairments of the ERP correlates of error processing and of error correction.

METHODS

Participants

Two groups of patients and two control groups of healthy participants who were matched to the corresponding patient groups with respect to age and socioeconomic status participated in the study. Demographic data and lesion descriptions are shown in Table 1.

One group of nine patients (one woman) suffered from chronic unilateral lesions of the basal ganglia (BG group; mean age 49.1 years, range 29–66; mean years of education 11.3, range 10–13; mean time since lesion 3.6 years, range 1.5–5.5 years). A lesion overlay plot is shown in Figure 1A; representative anatomical MR slices for each patient can be found in Figure 2. The corresponding control group ($n = 9$, one woman) had a mean age of 49.8 years (range 29–67) and, on average, 11.6 years of education (range 10–13).

The second group of patients consisted of seven patients (two women) with unilateral lesions of the lateral prefrontal cortex (LPFC group; mean age 54.6 years, range 41–73; mean years of education 10.9, range 8–16; mean time since lesion 5.2 years, range 2.5–7.5 years). A lesion overlay plot is shown in Figure 1B; representa-

tive anatomical MR slices for each patient can be found in Figure 2 (bottom). The corresponding control group ($n = 7$, two women) had a mean age of 54.7 years (range 40–73) and, on average, 11.0 years of education (range 10–13).

Patients as well as healthy volunteers gave written informed consent prior to participating in the study. The experiments were conducted in accordance with the Declaration of Helsinki and were approved by the ethical committee of the University of Leipzig.

Procedure

A speeded modified flanker task known to elicit the ERN and to be suitable for patient studies was used in the study (Ullsperger et al., 2002). In the task, participants were presented with a fixation mark for about 500 msec at the center of a screen, after which four flanker arrows occurred for 110 msec. The arrows were 0.46° tall and 1.08° wide, and appeared 0.52° and 1.04° above and below the screen center. The target arrow was presented for 30 msec in the center of the flanker arrows; its onset was delayed by 80 msec from the flanker's onset. In 50% of trials (total trial number 480) the flankers pointed in the same direction as the target (compatible trial), and in the other half in the opposite direction (incompatible trial). Compatible and incompatible trials appeared in pseudorandomized order. Participants were instructed to respond with maximal speed and accuracy to the target arrow with the hand indicated by its direction. Additionally, participants were instructed to

Table 1. Demographic Data of Patients

| Patient ID | Sex | Age at Test (years) | Time Since Lesion (years) | Side of Lesion | Etiology | Lesion Description |
|--|-----|---------------------|---------------------------|----------------|----------|--|
| <i>Basal ganglia group</i> | | | | | | |
| P157 | m | 60 | 5.5 | L | MCAI | Ant. GPe, ant. IC |
| P214 | m | 51 | 5 | L | ICH | Post. put., GPe, post. EC, IC, lat. thal. |
| P329 | m | 42 | 4.5 | R | ICH | Post. put. post. EC |
| P353 | m | 46 | 4 | L | ICH | Put., GPe, EC, ant. IC, reduced volume of caud. |
| P364 | m | 29 | 3.5 | L | MCAI | Post. put., caud. (body), middle ins., parietal operculum |
| P438 | m | 52 | 3 | L | LI | GPe, polar thal., IC (knee) |
| P536 | m | 66 | 2.5 | L | MCAI | Caud. (ant. body), ant. put., GPe, EC, ant. IC, ant. ins., preinsular WM |
| P723 | f | 38 | 1.5 | L | MCAI | Caud. (body), put., GPe, ant. IC, EC, parietal operculum, post. ins. |
| P621 | m | 58 | 3 | L | MCAI | Caud. (body), put., GPe, IC, EC |
| <i>Lateral prefrontal cortex group</i> | | | | | | |
| P009 | f | 60 | 7.5 | L | MCAI | LPFC, ant. ins., preinsular WM, ant. put. |
| P102 | m | 53 | 7 | L | MCAI | LPFC, ant. ins., preinsular WM, ant. put. |
| P237 | m | 63 | 5 | L | MCAI | LPFC, ant. ins., preinsular WM |
| P325 | m | 42 | 5 | L | AVM | LPFC, ant. ins. |
| P369 | f | 50 | 4 | L | MCAI | LPFC, ant. Ins. |
| P370 | m | 41 | 5.5 | R | TBI | LPFC, ant. lat. temporal |
| P403 | m | 73 | 2.5 | L | MCAI | LPFC |

m = male; f = female; L = left; R = right; MCAI = middle cerebral artery infarct (involving striolenticular arteries); ICH = intracerebral hemorrhage; LI = lacunar infarcts; AVM = arteriovenous malformation; TBI = traumatic brain injury; ant. = anterior; post. = posterior; caud. = caudate nucleus; EC = external capsule system; IC = internal capsule; ins. = insula; GPe = globus pallidus externus; GPi = globus pallidus internus; LPFC = lateral prefrontal cortex; put. = putamen; thal. = thalamus; WM = white matter.

correct errors whenever they noticed one. At 1400 msec after target onset, each response was followed by a symbolic feedback (600 msec) informing participants whether their answer was fast enough or should be speeded up. After the feedback, a fixation cross was presented for 500 msec, such that the intertrial interval amounted to 2580 msec.

We introduced an adaptive algorithm, which dynamically adjusted the response time pressure based on the participant's performance (Fiehler et al., 2005). The algorithm aimed at an optimization of error rate (goal: 20% incompatible errors) and a minimization of late response rates. This procedure helped to reduce dropouts for a low number of error trials.

Electrophysiological Recordings

The participants were seated comfortably in a dimly lit, electrically shielded chamber. The electroencephalo-

gram (EEG) was recorded with Ag/AgCl electrodes from 28 electrode sites (FP1, FP2, F7, F3, Fz, F4, F8, FT7, FCz, FT8, T7, C3, Cz, C4, T8, CP5, CP6, P7, P3, Pz, P4, P8, O1, O2, A2,) referenced to the left mastoid and off-line re-referenced to linked mastoids. Electrode impedance was kept below 5 k Ω . The vertical electrooculogram (EOG) was recorded from electrodes placed above and below the right eye. To monitor horizontal eye movements, the EOG was collected from electrodes placed on the outer canthus of the left and right eye. EEG and EOG were recorded continuously with a low-pass filter of 70 Hz and AD converted with 22-bit resolution at a sampling rate of 250 Hz. First, the EEG epochs were scanned for muscular and large EOG artifacts. Whenever the standard deviation in a 200-msec interval exceeded 50 μ V, the epoch was rejected. Next, small horizontal and vertical EOG artifacts that were still present in the EEG signal were corrected by an eye movement correction procedure based on a linear

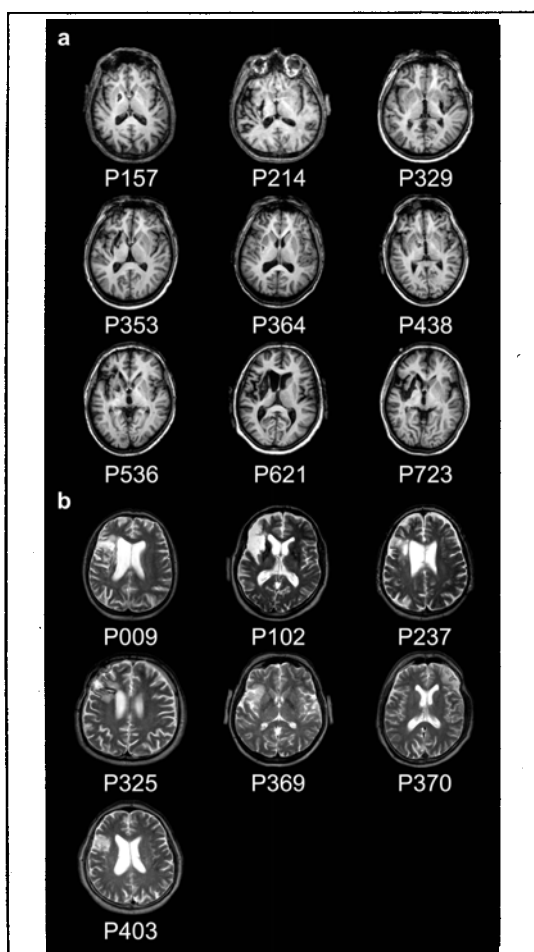


Figure 2. Representative anatomical MR slices of each patient. Anatomical convention. (A) Basal ganglia lesions, (B) lateral prefrontal cortex lesions.

regression method described by Gratton, Coles, and Donchin (1983).

Data Analysis

The time difference between target onset and button press was defined as response time. When an error was corrected by a second button press, the time difference between first (erroneous) and second (corrective) response was defined as correction time. Responses were analyzed when they occurred within 2000 msec after target onset.

Response-locked ERP epochs were averaged separately for incompatible correct and incompatible erro-

neous trials starting 100 msec before the response and continuing 500 msec after the response. Compatible trials were excluded from ERP analyses because of an insufficient number of error trials (<1%), as were responses delivered after the response deadline. The average voltage in the 100 msec preceding the onset of the flanker arrows served as baseline.

For the quantification of the ERN, peak-to-peak measurements were calculated to determine baseline-independent amplitudes of negative deflections by subtracting the amplitude of the preceding positive peak from the negative peak of this component (Falkenstein, Hoormann, et al., 2000). Based on the literature, time search windows of the ERN were chosen a priori: Two early time windows were defined from -100 to 0 msec for the positive peak preceding the ERN and from 0 to 120 msec for the ERN component. The negative peak for the ERN was also used to determine its latency. Because the Pe is a more sustained positive deflection, peak search was not possible in many participants' data. Therefore, the mean amplitude in two time windows covering the early (120–300 msec) and the late parts (300–500 msec) of this deflection were chosen (van Veen & Carter, 2002). The early Pe time window would also cover the time range of the CoRN. For better readability, the results are reported for the ERN time window, the CoRN time window, and the late Pe time window.

Statistical effects were determined at representative electrodes at the electrodes that spanned the region where the ERN and Pe are largest (F3, FCz, F4, C3, Cz, C4, P3, Pz, P4). For the two patients with right-sided lesions, lateral electrodes were switched such that F3, C3, and P3 corresponded to the side ipsilateral to the lesion (Gehring & Knight, 2000). All effects with more than one degree of freedom in the numerator were adjusted for violations of sphericity according to the formula of Huynh and Feld (1970). To avoid reporting large amounts of statistical results not relevant for the issues under investigation, only main effects or interactions, including the factors Response Type (correct, incorrect) and Group (BG, controls; LPFC, controls), are reported here. Topographical scalp potential maps were generated using a two-dimensional spherical spline interpolation and a radial projection from Cz, which respects the length of the median arcs. For graphical display, a low-pass filter with a cutoff frequency of 15 Hz was applied.

Results are listed as mean \pm standard error of the mean, unless otherwise specified.

Lesion Data Analysis

The lesions of the patients were segmented manually based on high-resolution 3-D T1-weighted anatomical MR data sets. These volume data sets were aligned and normalized to standard stereotactic space (Talairach and

Toumoux, 1988) by affine transformation. The rotational and translational parameters were subsequently used to transform lesion segments using trilinear interpolation, such that the resulting segments were aligned with the stereotactic coordinate system. Data sets for patients with lesions in the right hemisphere (329, 370) were flipped to allow lesion overlap analyses. For visualization purposes, the lesion data of the patients were overlapped for each patient group to form density maps (Figure 1C) (Rorden & Karnath, 2004). In order to extract the lesion parts unique to the three LPFC patients whose error correction abilities were impaired, a stepwise masking and overlapping procedure was used. First, for each of the three patients the lesion part exceeding the union (conjunction) of the lesions of the four LPFC patients with intact error correction was determined by masking. Second, the region of intersection (i.e., region of maximal overlap) of the resulting subtraction maps was determined. The formula for this procedure is as follows:

$$(009 \text{ m U}) \cap (102 \text{ m U}) \cap (237 \text{ m U}),$$

where U is the lesion union of the four remaining LPFC patients ($U = 325 \cup 369 \cup 370 \cup 403$), and m stands for "masked by."

RESULTS

Basal Ganglia Group

Behavioral Data

Response times and error rates obtained in the BG group and their controls are shown in Table 2. Both patients and controls show compatibility effects typical for flanker tasks, that is, longer response times and higher error rates for incompatible trials than for compatible trials. This was confirmed by repeated measures analyses of variance (ANOVAs) with the within-subject factor Compatibility (two levels) and the between-subjects factor Group (two levels), revealing a main effect of Compatibility: response times, $F(1,16) = 344.6, p < .0001$; error rates, $F(1,16) = 94.4, p < .0001$. For response times, also a main effect of Group was observed, $F(1,16) = 8.4, p < .05$, reflecting that BG patients responded more slowly. This is also reflected in the increase in mean response deadline for the patients, 616 ± 38 vs. 484 ± 18 msec; $t(16) = 3.08, p < .01$. The rate of incompatible errors committed before the deadline did not differ significantly between groups (patients $14.2 \pm 1.8\%$ vs. controls $11.3 \pm 1.8\%$, $p > .28$). For incompatible trials, response times were shorter for errors than for correct responses in both groups (Table 2). An ANOVA with the factors Response

Table 2. Mean Proportions and Reaction Times of Correct and Erroneous Responses in Patients and Controls Broken Down by Compatibility

| | Compatible Trials | | Incompatible Trials | |
|---|--------------------|-----------------------|---------------------|-----------------------|
| | Response Rates (%) | Response Times (msec) | Response Rates (%) | Response Times (msec) |
| <i>Basal ganglia group</i> | | | | |
| Correct | 94.7 (1.4) | 451.8 (25.7) | 83.1 (2.4) | 547.7 (23.5) |
| Erroneous | 3.5 (1.0) | – | 15.1 (2.1) | 440.8 (20.3) |
| <i>Control group for basal ganglia patients</i> | | | | |
| Correct | 99.0 (0.4) | 370.0 (12.1) | 88.1 (2.0) | 468.2 (15.5) |
| Erroneous | 0.5 (0.2) | – | 11.5 (1.9) | 419.2 (26.2) |
| <i>Lateral prefrontal cortex group</i> | | | | |
| Correct | 86.7 (9.5) | 490.8 (37.9) | 76.3 (8.6) | 581.0 (38.5) |
| Erroneous | 8.2 (6.6) | – | 18.2 (6.5) | 509.1 (46.7) |
| <i>Control group for lateral prefrontal cortex patients</i> | | | | |
| Correct | 98.2 (0.5) | 379.4 (12.0) | 83.9 (2.0) | 481.3 (14.4) |
| Erroneous | 1.1 (0.4) | – | 15.7 (1.8) | 387.5 (28.5) |

Responses recorded before and after the response deadline were collapsed. Standard errors of the means are shown in parentheses. In most participants, the number of compatible errors was insufficient to obtain reliable response times for this condition.

and Group revealed a main effect of Response, $F(1,16) = 45.0$, $p < .0001$, and a Response \times Group interaction, $F(1,16) = 6.2$, $p < .05$. This interaction was elucidated by Tukey tests showing that error response times did not differ significantly, whereas response times for correct responses were prolonged in the patients. In other words, relative to correct responses the errors were more premature in the BG patients than in the control group (response time difference, incompatible correct – incompatible error; 107 ± 19 vs. 49 ± 13 msec, patients vs. controls).

The rate of immediate error corrections in BG patients ($81.7 \pm 10.6\%$) and the control group ($75.1 \pm 12.4\%$) did not differ significantly ($p > .71$). Correction times (the time difference of the corrective response relative to the erroneous response) were not significantly different between groups (391 ± 48 vs. 412 ± 67 msec, patients vs. controls; $p > .8$).

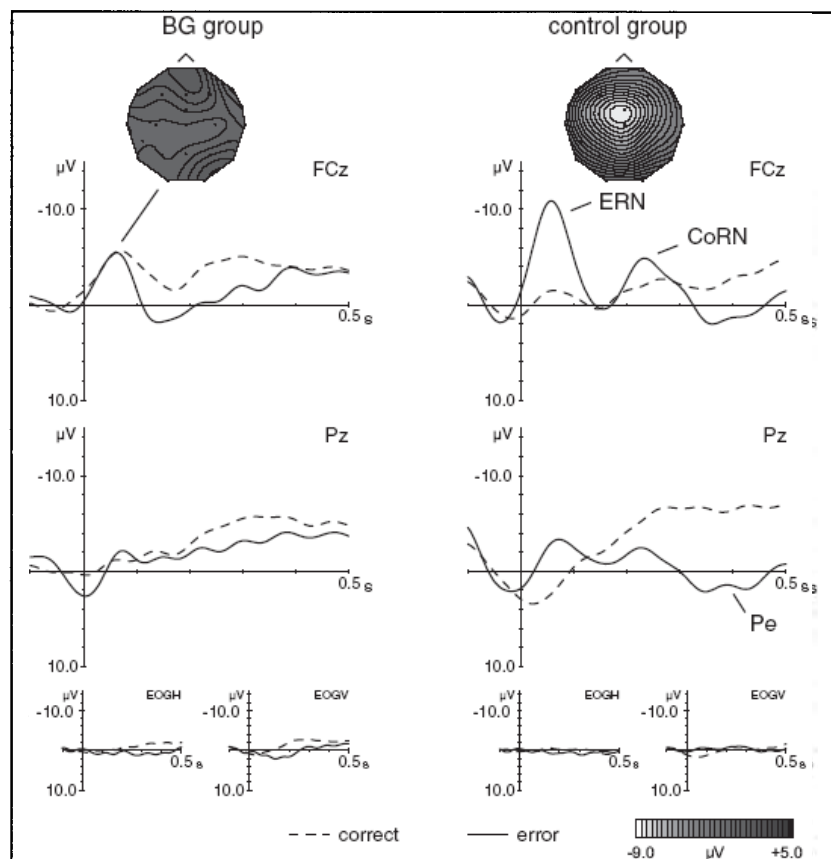
To test for post-error effects, error rates and response times were submitted to ANOVAs with the factors Compatibility (two levels), Previous response type (two

levels), and Group. However, neither a significant main effect of Previous response type nor an interaction with this factor was found ($ps > .24$). This may be a result of the time pressure and is consistent with previous studies in which post-error slowing was unstable for speeded flanker tasks (Ullsperger & von Cramon, 2004; Ullsperger et al., 2002). Moreover, it seems conceivable that post-error slowing effects are disturbed by the presence of timing feedback on every trial.

ERP Data

Figure 3 depicts the response-locked mean ERPs for hits and errors in the BG group and their corresponding controls at two midline electrodes. The waveform for the control group shows a clear ERN at FCz, followed by a CoRN, peaking around 230 msec, and a more posteriorly located Pe reaching its maximum between 300 and 500 msec. In contrast, in the patients no clear difference between the waveforms is visible in the early time window in which an ERN would be expected. Between

Figure 3. Response-locked grand average ERPs at two midline electrodes for the basal ganglia patients and the corresponding control group for correct (dashed lines) and incorrect (solid lines) responses on incompatible trials. Top: topographical distributions of the ERP difference between incorrect and correct trials in the time window 40–80 msec (i.e., time at which ERN is expected). BG = basal ganglia; ERN = error-related negativity; CoRN = correction-related negativity; Pe = error positivity; EOGH = horizontal electrooculogram; EOGV = vertical electrooculogram.



100 and 400 msec, the waveforms for incorrect responses seem to be more positive-going at frontal electrodes than for correct responses, and no CoRN is visible. Moreover, at parietal electrodes, no Pe is seen in the patients.

To test these observations, the peak-to-peak amplitude data of the ERN time window for correct and incorrect responses were submitted to a repeated measures ANOVA with the between-subjects factor Group (two levels; patients, controls) and the within-subjects factors Response (two levels; correct, incorrect), Anterior–Posterior Dimension (three levels; anterior, central, posterior sites) and Lateral Dimension (three levels; left, midline, right sites), revealing a main effect of Response, $F(1,16) = 17.58$, $p < .001$, and a significant Response \times Group interaction, $F(1,16) = 7.12$, $p < .05$. Moreover, the interactions Response \times Lateral Dimension, $F(2,32) = 5.01$, $p < .05$, and Response \times Group \times Lateral Dimension, $F(2,32) = 3.45$, $p < .05$, were significant.¹ A subordinate ANOVA for correct responses revealed neither main effects, $F(1,16) = 0.63$, nor interactions of the factor Group, $F(2,32) < 1.24$, whereas the same ANOVA for errors gave rise to a main effect of Group, $F(1,16) = 5.56$, $p < .05$, and a tendency for a Group \times Lateral Dimension interaction, $F(2,32) = 2.71$, $p = .082$. In the BG group, no effect of Response was found, $F(1,16) = 3.36$, $p > .11$, but an interaction of Response \times Anterior–Posterior Dimension, $F(2,32) = 4.68$, $p < .05$. Interestingly, a follow-up ANOVA revealed no effects of Response at anterior and central electrodes where the ERN would be expected, but a significant main effect of Response at posterior electrodes, $F(1,8) = 7.94$, $p < .05$. In contrast, in the healthy controls a main effect of Response, $F(1,16) = 13.56$, $p < .01$, and a Response \times Lateral Dimension interaction, $F(1,16) = 5.21$, $p < .05$, was found. This confirms that in the BG group the ERN amplitude was greatly reduced and the topography was changed such that at frontal electrodes the ERPs did not differ between correct and erroneous responses.

The latency of the ERN at FCz did not differ significantly between groups ($t(16) = -0.23$, $p > .82$).

In the CoRN time window, the four-way ANOVA revealed the significant interactions Response \times Group \times Anterior–Posterior Dimension, $F(2,32) = 6.60$, $p < .05$, and Response \times Lateral dimension, $F(2,32) = 5.46$, $p < .05$. A subordinate ANOVA for incorrect trials revealed a nearly significant Group \times Anterior–Posterior Dimension interaction, $F(2,32) = 2.94$, $p < .087$. Although the weak statistical power precludes firm conclusions, this pattern of results suggests that the BG patients did not show a CoRN on errors although they corrected errors as efficiently as the controls. Instead they showed a frontal positivity on error trials as previously observed (van Veen & Carter, 2002), reflected in a Response \times Anterior–Posterior Dimension interaction in an ANOVA restricted to the patients, $F(2,16) = 4.71$, $p < .05$.

In the late Pe time window, the four-way ANOVA revealed a main effect of Response, $F(1,16) = 4.58$, $p < .05$, a significant Response \times Lateral Dimension interaction, $F(2,32) = 4.51$, $p < .05$, and a nearly significant Group \times Response \times Anterior–Posterior Dimension triple interaction, $F(2,32) = 2.71$, $p < .10$. Groupwise ANOVAs revealed no significant effects or interactions of Response for the BG group ($F_s < 1.03$, $p_s > .35$), whereas a significant Response \times Lateral Dimension interaction, $F(2,32) = 4.31$, $p < .05$, was found for the control group. These findings confirm that in contrast to the controls, the BG patients had no Pe.

Visually evoked potentials. To test whether BG lesions have a general detrimental effect on ERPs we investigated the visually evoked N1 on stimulus presentation in compatible correct trials (Figure 4, left). To this end, the amplitudes of the most negative peak between 50 and 100 msec after target onset (note that the visually more salient onset of the flankers preceded the target by 80 msec) were compared between groups. Neither the ANOVA including the representative electrodes used for the analyses above nor t tests at occipital electrodes revealed group differences ($p_s > .47$).

Lateral Prefrontal Cortex Group

Behavioral Data

Response times and error rates obtained in the LPFC group and their controls are shown in the lower part of Table 2. Again, both patients and controls showed typical compatibility effects. This was confirmed by repeated measures ANOVAs with the factors Compatibility and Group, revealing a main effect of Compatibility: response times, $F(1,12) = 70.3$, $p < .0001$; error rates, $F(1,12) = 13.5$, $p < .01$. For response times, also a main effect of Group was observed, $F(1,16) = 7.4$, $p < .05$, reflecting that LPFC patients responded more slowly. This is also reflected in tendentially increased response deadlines in the patients, 742.6 ± 107 vs. 520 ± 18 msec; $t(16) = 2.04$, $p = .083$. The rate of incompatible errors committed before the deadline did not differ significantly between groups ($17.6 \pm 6.5\%$ vs. $15.4 \pm 1.8\%$, patients vs. controls; $p > .74$).

For incompatible trials, response times were shorter for errors than for correct responses in both groups. An ANOVA with the factors Response and Group revealed a main effect of Response, $F(1,12) = 21.7$, $p < .001$. There was no interaction with Group. The main effect of Group, $F(1,12) = 6.0$, $p < .05$, reflects that both incorrect as well as correct responses were delayed in the patients as compared to the control group.

The rate of immediate error corrections was reduced in the patients ($59.6 \pm 14.8\%$) vs. in the controls ($88.7 \pm 3.1\%$). This effect was marginally significant, $t(12) = 1.93$, $p = .078$. Correction time was longer in patients

(719 ± 210 msec; median = 533 msec) than in the controls (327 ± 32 msec; median = 315); due to high variance in the patient group, this effect only approached significance, $t(12) = 1.85, p = .089$. Further investigation revealed that three patients (P009, P102, P237) showed less than 30% (mean 19.6%) immediate error corrections, whereas the other patients corrected 89.6% (similar to controls). Patients with impaired error correction did not differ from the other LPFC patients with respect to error rates (17.8% errors on incompatible trials). Response times were prolonged (incompatible correct, 641 msec; incompatible error, 572 msec). Similarly, patients with impaired error correction had a mean error correction time of 1091 msec (note that only few error corrections occurred, thus weakening reliability of this data point). Patients with normal error correction needed, on average, 417 msec to correct errors.

We tested for post-error effects by submitting error rates and response times to ANOVAs with the factors Compatibility, Previous Response Type, and Group. Neither a significant main effect of Previous Response Type nor an interaction with this factor was found for the accuracy data ($ps > .27$). In the response time data, a main effect of Previous Response Type, $F(1,12) = 23.17, p < .001$, but no interaction with Group was found, suggesting comparable post-error slowing in both groups.

ERP Data

Figure 5 depicts the response-locked mean ERPs for correct and erroneous responses in the LPFC group and their controls at two midline electrodes. Again, the waveform for the control group shows a clear ERN at FCz, followed by a CoRN and a more posteriorly located Pe reaching its maximum between 300 and 400 msec. In

contrast, in the patients no clear difference between the waveforms is visible in the early time window in which an ERN would be expected. Between 100 and 300 msec, the waveforms for incorrect responses seem to be more positive-going at frontal electrodes, but neither a CoRN at FCz nor a Pe at Pz are seen.

To test these observations, amplitude data of the ERN time window were submitted to a four-way repeated measures ANOVA with the factors Group, Response, Anterior-Posterior Dimension, and Lateral Dimension, revealing a significant Response \times Group interaction, $F(1,12) = 5.13, p < .05$. Moreover, the main effect of Response approached significance, $F(1,12) = 3.76, p < .076$. A subordinate ANOVA for correct responses revealed no significant main effects, $F(1,12) = 0.02, p > .9$, or interactions of the factor Group, $F(2,24) < 1.08, ps > .34$, whereas the same ANOVA for errors gave rise to a main effect of Group, $F(1,12) = 7.58, p < .05$, and a Group \times Lateral Dimension interaction, $F(2, 24) = 7.18, p < .01$. In the LPFC group, neither a main effect of Response was found, $F(1,6) = 0.32, p > .59$, nor an interaction with this factor, $F(2, 12) < 1.54, p > .25$. In contrast, in the healthy controls a main effect of Response, $F(1,6) = 6.18, p < .05$, was found. This confirms that in the LPFC group the amplitudes of the ERN are greatly reduced such that the ERPs did not differ between correct and erroneous responses in the early time window.

The latency of the ERN at FCz did not differ significantly between groups, $t(12) = -0.3, p > .7$.

In the CoRN time window, the four-way ANOVA revealed a significant main effect of Response, $F(1,12) = 5.84, p < .05$. The interaction Group \times Response \times Lateral Dimension approached significance, $F(2, 24) = 2.81, p < .08$. A subordinate ANOVA for errors revealed a significant Group \times Lateral Dimension interaction, $F(2, 24) = 5.21, p < .05$, suggesting that the LPFC patients

Figure 4. Stimulus-locked visually evoked potentials for patients (dashed lines) and controls (solid lines). Left, basal ganglia (BG) group; right, lateral prefrontal cortex (LPFC) group.

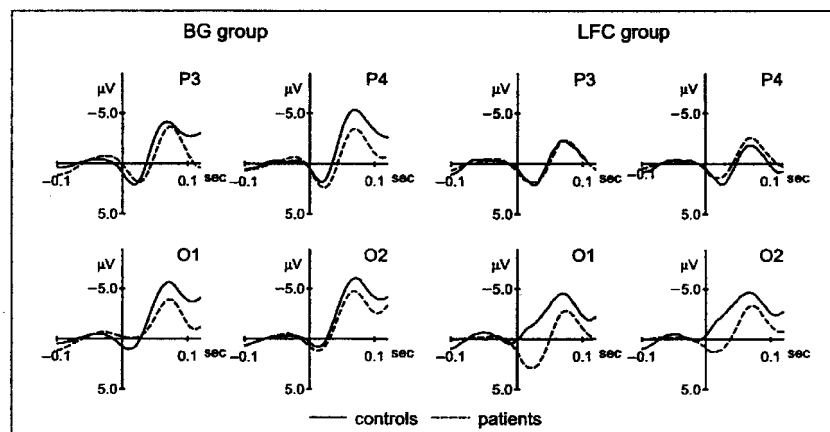
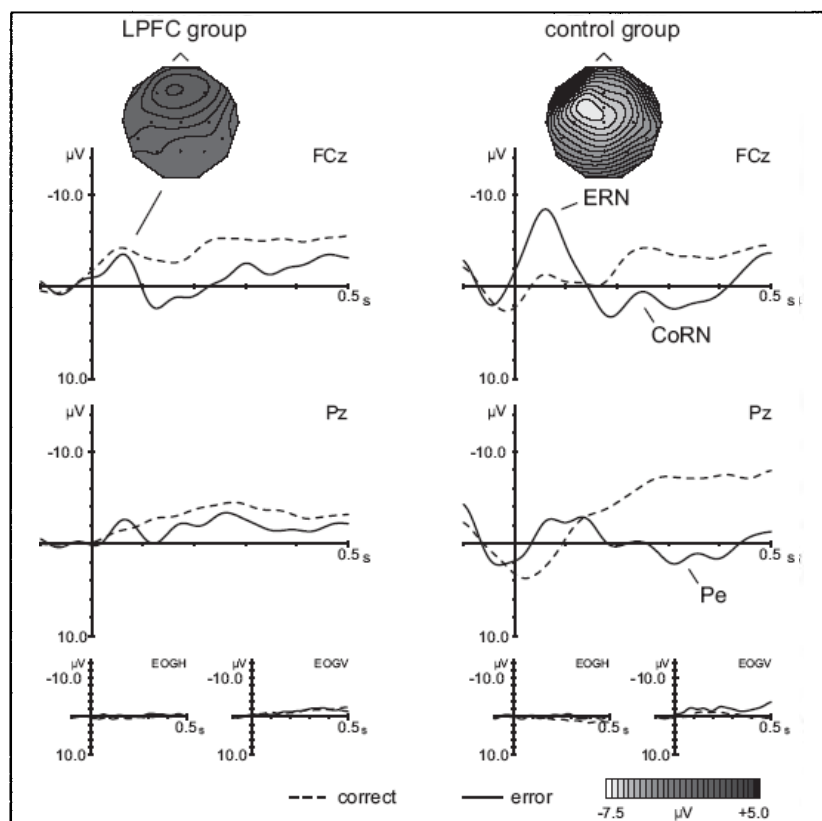


Figure 5. Response-locked grand average ERPs at two midline electrodes for the LPFC patients and the corresponding control group for correct (dashed lines) and incorrect (solid lines) responses on incompatible trials. Top: topographical distributions of the ERP difference between incorrect and correct trials in the time window 40–80 msec (i.e., time at which ERN is expected). LPFC = lateral prefrontal cortex; ERN = error-related negativity; CoRN = correction-related negativity; Pe = error positivity; EOGH = horizontal electrooculogram; EOGV = vertical electrooculogram.



did not show a CoRN. Similarly to the BG patients, they showed a positivity on error trials, reflected in a nearly significant main effect of Response, $F(1,6)$, $p < .099$.

In the late Pe time window, the four-way ANOVA revealed a main effect of Response, $F(1,12) = 9.87$, $p < .01$, and a tendency for a Group \times Response interaction, $F(1,12) = 3.18$, $p < .099$. Groupwise ANOVAs revealed no significant effects or interactions of Response for the LPFC group ($F_s < 1.28$, $p_s > .30$), whereas a main effect of Response, $F(1,6) = 9.48$, $p < .05$, and a Response \times Lateral Dimension interaction, $F(2, 12) = 4.43$, $p < .05$, were found for the control group. These findings confirm that the LPFC patients had no Pe.

In order to explore the ERP data for differences related to impairments in error correction, we performed a subgroup analysis (Figure 6). Interestingly, the general ERP pattern of the three patients with impaired error correction was quite similar to that of the other LPFC patients.

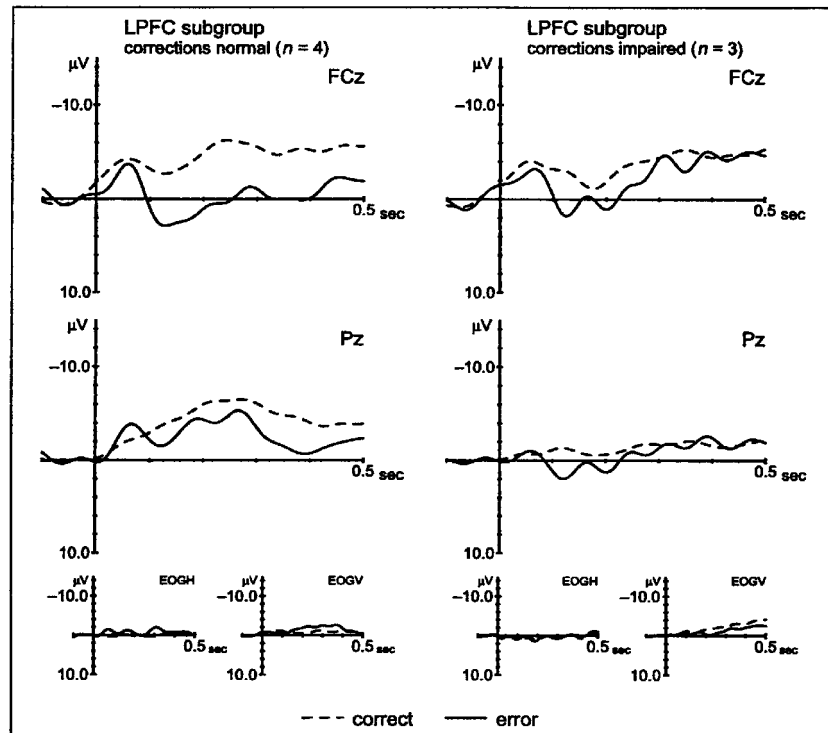
Visually evoked potentials. Similarly to the BG patients, for the LPFC group, neither the ANOVA including the representative electrodes used for the analyses

above nor t tests at occipital electrodes revealed group differences in the visually evoked N1 ($p_s > .54$; Figure 4, right). It should be noted that previous studies using lateralized target presentations in patients with lateral frontal lesions revealed reductions of early visually evoked potentials ipsilateral to the lesions (Barcelo, Suwazono, & Knight, 2000). The fact that in the present study stimuli were presented centrally might explain why no reduction of the visually evoked N1 was found.

DISCUSSION

To investigate the role of the BG and the LPFC in performance monitoring, we examined the ERP correlates of error processing as well as immediate corrective behavior in patients with focal lesions in these structures. Both patients with BG lesions and patients with LPFC lesions show an impaired ERN, which is greatly reduced and distorted or even absent. The centroparietal Pe and the CoRN are also absent, whereas a more frontal positivity on errors seems to be preserved in the patients. A further observation is that the ERN-like negativity on correct responses (sometimes called cor-

Figure 6. Response-locked grand average ERPs at two midline electrodes for the LPFC patients with unimpaired (left side) and impaired (right side) error corrections. The general pattern is similar for both groups; visual inspection suggests that the error-related frontal positive-going effect is more pronounced in the correction-unimpaired group. LPFC = lateral prefrontal cortex; EOGH = horizontal electrooculogram; EOGV = vertical electrooculogram.



rect-related negativity; Vidal, Burle, Bonnet, Grapperon, & Hasbroucq, 2003; Ford, 1999) is preserved if not enhanced in both patient groups, suggesting that this negativity is likely generated by a partly different network than the ERN and may reflect a different function, such as persisting uncertainty regarding the optimal response strategy (Bartholow et al., 2005). Notably, these changes in error-related ERPs are unlikely to result from a lesion effect on ERPs in general, as the visually evoked potentials are unimpaired in the patient groups. Moreover, preserved target P300 and N400 components were demonstrated for patient groups with comparable lesion patterns in the BG (Friederici, Kotz, Werheid, Hein, & von Cramon, 2003; Frisch, Kotz, von Cramon, & Friederici, 2003) and LPFC (Knight & Scabini, 1998; Yamaguchi & Knight, 1991).

Thus, ERP findings suggest that the lesions disturbed and prolonged performance monitoring processes. In both patient groups, the cortico-striato-thalamocortical loops via the pallidum and ventrolateral thalamus are damaged. Thus, the integration of contextual information about the task, the predicted serial order of events, and motor activity may be disturbed or mistimed. The notion that the pallidal inputs to the RCZ via the thalamus are necessary for the generation of the ERN is supported by the finding that thalamic lesions abol-

ished the ERN (Stemmer & Witzke, 2003). Second, the ongoing assessment of whether an event is better or worse than expected may be less exactly timed than in healthy persons, such that the proposed dopaminergic error signal is desynchronized. If this signal to the RCZ is weaker and/or scattered over time, the response at the RCZ neurons will be less synchronized such that the summation and propagation of electrical activity will result in abnormal ERPs. A hint that motor-related activity is less well synchronized in patients is provided by the findings that, in the BG group, within-subject reaction time variance is significantly larger than in controls ($p < .05$). In the LPFC group, this effect was also present numerically but only approached significance ($p = .1$).

However, in most patients, particularly those with lesions confined to the BG or to the LPFC, immediate error correction was unimpaired, although the ERP data suggest an impairment of the performance monitoring system. How to reconcile this apparent paradox? It has been suggested that incidental error corrections may reflect a delayed correct response that is delivered independently of error processing (Rabbitt, 2002). These incidental (spontaneous) error corrections occur in about 20–40% of errors (Fiehler et al., 2004, 2005). However, the intention to correct errors increases the

number of slow corrections assumed to depend on error processing and involving the RCZ. The correction rates found for the patients and controls are comparable to those reported previously for studies on intentional error corrections (above 80%; Fiehler et al., 2004, 2005), suggesting that most patients were able to intentionally correct errors. Furthermore, it could be argued that the ERN may be an epiphenomenon. A number of considerations make this simplified view seem unlikely. First, in healthy participants the ERN has been shown to be related to attempts to remediate the error (e.g., reflected in force reduction on errors and post-error slowing; Gehring et al., 1993), and reduced ERN-like activity on correct trials predicts the occurrence of errors (Allain, Carbonnell, Falkenstein, Burle, & Vidal, 2004; Ridderinkhof, Nieuwenhuis, & Bashore, 2003). Second, the absence of the ERN in patients does not necessarily mean that the generating structure does not show error-related activity. As elaborated above, desynchronized activity of neurons in the RCZ may result in reduced or even absent waveforms. The sustained midfrontal positivity beginning around 100 msec after the error may hint at preserved neuronal activity in the frontomedian cortex. Thus, we propose that, in patients, the ERN is a sensitive indicator of the integrity of the performance monitoring network. Our findings as well as previous patient studies investigating focal brain lesions in relevant structures suggest that damage of one relay in this network seems to be accompanied by massive reduction of the ERP difference between errors and correct responses in the time window where the ERN would be expected (Stemmer, Segalowitz, Witzke, & Schonle, 2004; Swick & Turken, 2002; Ullsperger et al., 2002; Gehring & Knight, 2000). It should be noted that the ERN is not impaired when lesions affect brain regions not directly involved in the frontostriatal performance monitoring network, such as frontopolar and temporal cortical lesions (Ullsperger et al., 2002). Why is this electrophysiological signature of impaired integrity of the performance monitoring network not accompanied by major behavioral deficits? Could ERPs be a more sensitive indicator of functional integrity than behavior? In the present study (as well as in previous studies), the lesions in the patients were chronic; at test, at least 1.5 years had elapsed since the damage occurred. Thus, time had been sufficient for the brain's plasticity to allow circumventing the damage functionally. This seems even more plausible, because lesions were unilateral and relatively small. Other brain regions may have taken over functionality to some extent and strategies may have changed. One should consider that these changes can compensate for behavioral deficits, but do not need to recover the electrophysiological correlates of error processing. Thus, behavioral deficits can be expected to be more apparent and persistent in patients with bilateral lesions of the performance monitoring network. A important question to be addressed in future

research is whether more pronounced behavioral performance monitoring deficits are found in patients with acute lesions. Furthermore, the stability of the ERN impairment should be addressed in longitudinal studies encompassing acute and chronic lesion stages.

It could be assumed that the brain contains multiple error processing and correction systems that orchestrate optimal motor behavior. For example, the posterior parietal cortex has been implicated in the detection and correction of errors resulting from target perturbations in tracking tasks (Grea et al., 2002; Desmurget et al., 1999). It seems possible that the error correction in the flanker task may also depend on the posterior parietal cortex system for motor corrections, and that this system may largely compensate for deficits in the RCZ network.

In contrast to all other patients, three LPFC patients had strongly reduced error correction rates (P009, P102, P237), although showing similar ERP patterns as the other LPFC patients. Whereas all patients reported to have well recognized their errors in a postexperiment survey, one patient from the noncorrector subgroup (P237) reported not to have recognized errors. The survey furthermore confirmed that all patients, including those impaired in error corrections, had understood and followed the task instructions, in particular the request to immediately correct errors. What is it that hampers the ability of these patients to correct errors? By a masking and overlaying procedure we extracted the lesion parts of the three noncorrectors that were unique to them compared to the four patients whose error correction abilities were normal. This part of the lesions is primarily located in the white matter at the base of the middle and inferior frontal gyri and the superior and anterior level of the external capsule system (Figure 1C). Based on the topography of this unique lesion part we suggest that fiber connections between the RCZ and the remaining intact parts of the LPFC as well as input from these regions to the striatum are disrupted. The data suggest these lesions in the frontal white matter get strategic relevance when they are combined with LPFC damage. Similarly as a direct lesion of the RCZ (Swick & Turken, 2002), they lead to severe error correction impairments. Note that this lesion analysis cannot prove the role of the fiber connections between RCZ, LPFC, and BG, as the MR scans had to be normalized and aligned. However, it provides a strong hypothesis to be tested in future studies in patients with isolated white matter lesions in the relevant region.

In sum, the data provide strong support that the LPFC as well as prefrontal and motor cortico-striato-thalamo-cortical circuits are important for performance monitoring. The function of the RCZ seems to critically depend on its connectivity with the LPFC and the BG via the ventrolateral thalamus. Moreover, the ERN has proven to be a sensitive measure to assess the integrity of the entire network including its circuits, even in the absence

of behavioral deficits. Large decrement or the absence of the ERN is an electrophysiological signature of impaired integrity of the performance monitoring system. However, ERN impairments do not need to map directly on behavioral deficits, as these different measures seem to be differentially susceptible to brain plasticity.

Acknowledgments

The authors thank T. Klein for help in data collection and M. Tittgemeyer and S. Seifert for support in lesion segmentation.

Reprint requests should be sent to Markus Ullsperger, Max Planck Institute for Human Cognitive and Brain Sciences, Stephanstrasse 1A, 04103 Leipzig, Germany, or via e-mail: ullsperg@cbs.mpg.de.

Note

1. Note that interactions of the Lateral dimension factor do not imply lateralization of the ERP; it can also be driven by an effect focused to midline electrodes.

REFERENCES

- Alexander, G. E., Crutcher, M. D., & DeLong, M. R. (1990). Basal ganglia-thalamocortical circuits: Parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. *Progress in Brain Research*, 85, 119–146.
- Allain, S., Carbonnell, L., Falkenstein, M., Burle, B., & Vidal, F. (2004). The modulation of the Ne-like wave on correct responses foreshadows errors. *Neuroscience Letters*, 372, 161–166.
- Barcelo, F., Suwazono, S., & Knight, R. T. (2000). Prefrontal modulation of visual processing in humans. *Nature Neuroscience*, 3, 399–403.
- Bar-Gad, I., Morris, G., & Bergman, H. (2003). Information processing, dimensionality reduction and reinforcement learning in the basal ganglia. *Progress in Neurobiology*, 71, 439–473.
- Bartholow, B. D., Pearson, M. A., Dickter, C. L., Sher, K. J., Fabiani, M., & Gratton, G. (2005). Strategic control and medial frontal negativity: Beyond errors and response conflict. *Psychophysiology*, 42, 33–42.
- Barto, A. G. (1995). Adaptive critics in the basal ganglia. In J. Houk, J. Davis, & D. Beiser (Eds.), *Models of information processing in the basal ganglia* (pp. 215–232). Cambridge: MIT Press.
- Bates, J. F., & Goldman-Rakic, P. S. (1993). Prefrontal connections of medial motor areas in the rhesus monkey. *Journal of Comparative Neurology*, 336, 211–228.
- Brass, M., & von Cramon, D. Y. (2004). Decomposing components of task preparation with functional magnetic resonance imaging. *Journal of Cognitive Neuroscience*, 16, 609–620.
- Coles, M. G., Scheffers, M. K., & Holroyd, C. B. (2001). Why is there an ERN/Ne on correct trials? Response representations, stimulus-related components, and the theory of error-processing. *Biological Psychology*, 56, 173–189.
- Dehaene, S., Posner, M. I., & Tucker, D. M. (1994). Localization of a neural system for error detection and compensation. *Psychological Science*, 5, 303–305.
- Derrfuss, J., Brass, M., & von Cramon, D. Y. (2004). Cognitive control in the posterior frontolateral cortex: Evidence from common activations in task coordination, interference control, and working memory. *Neuroimage*, 23, 604–612.
- Desmurget, M., Epstein, C. M., Turner, R. S., Prablanc, C., Alexander, G. E., & Grafton, S. T. (1999). Role of the posterior parietal cortex in updating reaching movements to a visual target. *Nature Neuroscience*, 2, 563–567.
- Dum, R. P., & Strick, P. L. (1993). Cingulate motor areas. In B. A. Vogt & M. Gabriel (Eds.), *Neurobiology of cingulate cortex and limbic thalamus* (pp. 415–441). Boston: Birkhäuser.
- Falkenstein, M. (2004). ERP correlates of erroneous performance. In M. Ullsperger & M. Falkenstein (Eds.), *Errors, conflicts, and the brain. Current opinions on performance monitoring* (pp. 5–14). Leipzig: MPI for Human Cognitive and Brain Sciences.
- Falkenstein, M., Hielischer, H., Dziobek, I., Schwarzenau, P., Hoormann, J., Sunderman, B., & Hohnsbein, J. (2001). Action monitoring, error detection, and the basal ganglia: An ERP study. *NeuroReport*, 12, 157–161.
- Falkenstein, M., Hohnsbein, J., Hoormann, J., & Blanke, L. (1990). Effects of errors in choice reaction tasks on the ERP under focused and divided attention. In C. H. M. Brunia, A. W. K. Gaillard, & A. Kok (Eds.), *Psychophysiological brain research* (vol. 1, pp. 192–195). Tilburg University Press.
- Falkenstein, M., Hoormann, J., Christ, S., & Hohnsbein, J. (2000). ERP components on reaction errors and their functional significance: A tutorial. *Biological Psychology*, 51, 87–107.
- Fiehler, K., Ullsperger, M., & von Cramon, D. Y. (2004). Neural correlates of error detection and error correction: Is there a common neuroanatomical substrate? *European Journal of Neuroscience*, 19, 3081–3087.
- Fiehler, K., Ullsperger, M., & Von Cramon, D. Y. (2005). Electrophysiological correlates of error correction. *Psychophysiology*, 42, 72–82.
- Ford, J. M. (1999). Schizophrenia: The broken P300 and beyond. *Psychophysiology*, 36, 667–682.
- Friederici, A. D., Kotz, S. A., Werheid, K., Hein, G., & von Cramon, D. Y. (2003). Syntactic comprehension in parkinson's disease: Investigating early automatic and late integrational processes using event-related brain potentials. *Neuropsychologia*, 17, 133–142.
- Frisch, S., Kotz, S. A., von Cramon, D. Y., & Friederici, A. D. (2003). Why the P600 is not just a P300: The role of the basal ganglia. *Clinical Neurophysiology*, 114, 336–340.
- Gehring, W. J., Goss, B., Coles, M. G., Meyer, D. E., & Donchin, E. (1993). A neural system for error detection and compensation. *Psychological Science*, 4, 385–390.
- Gehring, W. J., & Knight, R. T. (2000). Prefrontal-cingulate interactions in action monitoring. *Nature Neuroscience*, 3, 516–520.
- Gerfen, C. R. (1992). The neostriatal mosaic: Multiple levels of compartmental organization in the basal ganglia. *Annual Review of Neuroscience*, 15, 285–320.
- Gillies, A., & Arbutnot, G. (2000). Computational models of the basal ganglia. *Movement Disorders*, 15, 762–770.
- Gratton, G., Coles, M. G., & Donchin, E. (1983). A new method for off-line removal of ocular artifact. *Electroencephalography and Clinical Neurophysiology*, 55, 468–484.
- Graybiel, A. M., Aosaki, T., Flaherty, A. W., & Kimura, M. (1994). The basal ganglia and adaptive motor control. *Science*, 265, 1826–1831.
- Grea, H., Pisella, L., Rossetti, Y., Desmurget, M., Tilikete, C., Grafton, S., Prablanc, C., & Vighetto, A. (2002). A lesion of the posterior parietal cortex disrupts on-line adjustments during aiming movements. *Neuropsychologia*, 40, 2471–2480.

- Haber, S. N. (2003). The primate basal ganglia: Parallel and integrative networks. *Journal of Chemical Neuroanatomy*, 26, 317–330.
- Hatanaka, N., Tokuno, H., Hamada, I., Inase, M., Ito, Y., Imanishi, M., Hasegawa, N., Akazawa, T., Nambu, A., & Takada, M. (2003). Thalamocortical and intracortical connections of monkey cingulate motor areas. *Journal of Comparative Neurology*, 462, 121–138.
- Holroyd, C. B., & Coles, M. G. (2002). The neural basis of human error processing: Reinforcement learning, dopamine, and the error-related negativity. *Psychological Review*, 109, 679–709.
- Holroyd, C. B., Praamstra, P., Plat, E., & Coles, M. G. (2002). Spared error-related potentials in mild to moderate parkinson's disease. *Neuropsychologia*, 40, 2116–2124.
- Houk, J. C., Adams, J. L., & Barto, A. G. (1995). A model of how the basal ganglia generate and use neural signals that predict reinforcement. In J. C. Houk, J. Davis, & D. Beiser (Eds.), *Models of information processing in the basal ganglia* (pp. 249–270). Cambridge: MIT Press.
- Huynh, H., & Feld, L. S. (1970). Conditions under which mean square ratios in repeated measurements designs have exact F distributions. *Journal of the American Statistical Association*, 65, 1582–1589.
- Knight, R. T., & Scabini, D. (1998). Anatomic bases of event-related potentials and their relationship to novelty detection in humans. *Journal of Clinical Neurophysiology*, 15, 3–13.
- Koski, L., & Paus, T. (2000). Functional connectivity of the anterior cingulate cortex within the human frontal lobe: A brain-mapping meta-analysis. *Experimental Brain Research*, 133, 55–65.
- MacDonald, A. W., III, Cohen, J. D., Stenger, V. A., & Carter, C. S. (2000). Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science*, 288, 1835–1838.
- Nieuwenhuis, S., Ridderinkhof, K. R., Blom, J., Band, G. P., & Kok, A. (2001). Error-related brain potentials are differentially related to awareness of response errors: Evidence from an antisaccade task. *Psychophysiology*, 38, 752–760.
- O'Doherty, J., Dayan, P., Schultz, J., Deichmann, R., Friston, K., & Dolan, R. J. (2004). Dissociable roles of ventral and dorsal striatum in instrumental conditioning. *Science*, 304, 452–454.
- Paus, T., Castro-Alamancos, M. A., & Petrides, M. (2001). Cortico-cortical connectivity of the human mid-dorsolateral frontal cortex and its modulation by repetitive transcranial magnetic stimulation. *European Journal of Neuroscience*, 14, 1405–1411.
- Petrides, M., & Pandya, D. N. (1999). Dorsolateral prefrontal cortex: Comparative cytoarchitectonic analysis in the human and the macaque brain and corticocortical connection patterns. *European Journal of Neuroscience*, 11, 1011–1036.
- Rabbitt, P. (2002). Consciousness is slower than you think. *Quarterly Journal of Experimental Psychology*, A, 55, 1081–1092.
- Ridderinkhof, K. R., Nieuwenhuis, S., & Bashore, T. R. (2003). Errors are foreshadowed in brain potentials associated with action monitoring in cingulate cortex in humans. *Neuroscience Letters*, 348, 1–4.
- Ridderinkhof, K. R., Ullsperger, M., Crone, E. A., & Nieuwenhuis, S. (2004). The role of the medial frontal cortex in cognitive control. *Science*, 306, 443–447.
- Rorden, C., & Karnath, H. O. (2004). Using human brain lesions to infer function: A relic from a past era in the fMRI age? *Nature Reviews Neuroscience*, 5, 813–819.
- Schultz, W. (2002). Getting formal with dopamine and reward. *Neuron*, 36, 241–263.
- Stemmer, B., Segalowitz, S. J., Witzke, W., & Schonle, P. W. (2004). Error detection in patients with lesions to the medial prefrontal cortex: An ERP study. *Neuropsychologia*, 42, 118–130.
- Stemmer, B., & Witzke, W. (2003). *The effects of brain damage on the error negativity (Ne/ERN)*. Paper presented at the Errors, Conflicts, and The Brain. Current Opinions on Performance Monitoring Conference, Dortmund, Germany.
- Swick, D., & Turken, A. U. (2002). Dissociation between conflict detection and error monitoring in the human anterior cingulate cortex. *Proceedings of the National Academy of Sciences, U.S.A.*, 99, 16354–16359.
- Takada, M., Tokuno, H., Hamada, I., Inase, M., Ito, Y., Imanishi, M., Hasegawa, N., Akazawa, T., Hatanaka, N., & Nambu, A. (2001). Organization of inputs from cingulate motor areas to basal ganglia in macaque monkey. *European Journal of Neuroscience*, 14, 1633–1650.
- Talairach, P., & Tournoux, J. (1988). *A stereotactic coplanar atlas of the human brain*. Stuttgart: Thieme.
- Ullsperger, M., Volz, K. G., & von Cramon, D. Y. (2004). A common neural system signaling the need for behavioral changes. *Trends in Cognitive Sciences*, 8, 445–446.
- Ullsperger, M., & von Cramon, D. Y. (2001). Subprocesses of performance monitoring: A dissociation of error processing and response competition revealed by event-related fMRI and ERPs. *Neuroimage*, 14, 1387–1401.
- Ullsperger, M., & von Cramon, D. Y. (2004). Neuroimaging of performance monitoring: Error detection and beyond. *Cortex*, 40, 593–604.
- Ullsperger, M., von Cramon, D. Y., & Müller, N. G. (2002). Interactions of focal cortical lesions with error processing: Evidence from event-related brain potentials. *Neuropsychologia*, 16, 548–561.
- van Veen, V., & Carter, C. S. (2002). The timing of action-monitoring processes in the anterior cingulate cortex. *Journal of Cognitive Neuroscience*, 14, 593–602.
- Vidal, F., Burle, B., Bonnet, M., Grapperon, J., & Hasbroucq, T. (2003). Error negativity on correct trials: A reexamination of available data. *Biological Psychology*, 64, 265–282.
- Williams, Z. M., Bush, G., Rauch, S. L., Cosgrove, G. R., & Eskandar, E. N. (2004). Human anterior cingulate neurons and the integration of monetary reward with motor responses. *Nature Neuroscience*, 7, 1370–1375.
- Yamaguchi, S., & Knight, R. T. (1991). Anterior and posterior association cortex contributions to the somatosensory P300. *Journal of Neuroscience*, 11, 2039–2054.
- Yeung, N., Cohen, J. D., & Botvinick, M. M. (2004). The neural basis of error detection: Conflict monitoring and the error-related negativity. *Psychological Review*, 111, 931–959.

Chapter 9

Performance monitoring in neurological and psychiatric patients

Until very recently, performance monitoring impairments were not in the focus of classical neuropsychology. Usually these impairments were subsumed under the term "executive dysfunction". In fact, different types of errors (e.g., perseveration on one hand, and spontaneous rule breaking on the other) have often been interpreted in the framework of planning deficits and dysexecutive syndrome. However, it should be considered that these errors could sometimes result from performance monitoring dysfunction.

Interestingly, it is well-known that some patients with frontal brain lesions, particularly of the orbitofrontal cortex, suffer from the inability to draw consequences from previous errors (Bechara et al., 1994; Bechara et al., 1998). In a subset of these patients, a "knowing-doing" dissociation is observed: they are able to detect and report erroneous responses and to predict negative action outcomes, but they are unable to avoid these actions in the future.

In recent years, many researchers have attempted to differentiate between different functions which together enable goal-directed and flexible behavior. Therefore, over the last decade a large body of publications reporting performance monitoring studies in neurological and psychiatric patients. So far, the picture is mixed, in part due to small group sizes and methodological problems. There is a need for a more standardized approach in these studies. While the first studies necessarily needed to be exploratory, we are now in a position to integrate the experiences and to suggest standards for the study of performance monitoring. This Chapter reviews the current knowledge on performance monitoring in a variety of neurological and psychiatric disorders. It furthermore attempts to address the questions, which measures are useful and informative in patient studies, and how to standardize clinical performance monitoring research. A long-term aim must be to build up patient-friendly and robust paradigms that can be used in single cases to aid diagnostics and the documentation of therapeutic effects.



Available online at www.sciencedirect.com

SCIENCE @ DIRECT®

International Journal of Psychophysiology 59 (2006) 59–69

INTERNATIONAL
JOURNAL OF
PSYCHOPHYSIOLOGY

www.elsevier.com/locate/ijpsycho

Performance monitoring in neurological and psychiatric patients

Markus Ullsperger*

Max Planck Institute for Human Cognitive and Brain Sciences, Stephanstr. 1a, D-04103 Leipzig, Germany

Received 23 February 2005; accepted 21 June 2005

Available online 8 November 2005

Abstract

Performance monitoring, an indispensable prerequisite of goal-directed, flexible behavior has attracted the interest of many researchers. Performance monitoring impairment may result in major daily-life problems in neurological and psychiatric patients. In this paper, I review the recent advances in clinical studies on performance monitoring in different populations of neurological and psychiatric patients. The findings are discussed with respect to current models of performance monitoring that have mostly arisen from correlational approaches. Moreover, perspectives for clinical use are given and methodological issues for patient studies of performance monitoring will be discussed.
© 2005 Elsevier B.V. All rights reserved.

Keywords: Error processing; Conflict; Neuropsychology; ERP; fMRI

1. Introduction

The last decade has revealed a considerable body of new knowledge about functional and anatomical correlates and the underlying processes of goal-directed flexible behavior. Performance monitoring, i.e., continuous checking whether the action goals have been reached, is crucial for adjustments needed to optimize action outcome. Its impairment may result in major daily-life problems in neurological and psychiatric patients. However, until not long ago, patient studies had a more general view on flexible cognitive control (“executive functions”) rather than directly addressing performance monitoring. In this paper, I review the recent advances that have been made in clinical studies on performance monitoring. After a brief overview on the knowledge gathered in healthy participants and animal work, I will focus on the impairments that can be expected when performance monitoring is dysfunctional. Further on, I will review the findings that have been observed in a number of neurological and psychiatric diseases. In the discussion I will summarize the currently investigated performance monitoring network and still open questions with respect to possible clinical use. Finally, important methodological issues for patient studies of performance monitoring will be discussed.

1.1. Correlates of performance monitoring

On the behavioral level, performance monitoring is reflected in the consequences resulting from errors, contextual feedback evaluation, and situations in which action outcome is at risk (e.g., decision uncertainty, response conflict). Performance-monitoring-induced behavioral adjustments are most obvious after error commission which is sometimes accompanied by verbal and emotional responses. In experimental situations, even if not instructed, participants often immediately correct errors by a second key press (Rabbitt, 1966). On subsequent trials, behavioral adjustments can occur, such as post-error slowing (Rabbitt, 1966) and post-error reduction of interference (Ridderinkhof et al., 2002; see below) which can result in lower error rates subsequent to an error. In some instances, e.g., with short inter-trial intervals, however, error detection can also interfere with performance on subsequent trials thus increasing error rates on subsequent trials (Rabbitt and Rodgers, 1977; Fiehler et al., 2005).

Since the early nineties error-related event-related brain potentials (ERPs) have been in the focus of performance monitoring research. The error-related negativity (ERN or Ne) is elicited by executing prepotent but incorrect responses in choice reaction time tasks, peaks about 50 to 100 ms after the erroneous response, and has a frontocentral scalp distribution (Falkenstein et al., 1990; Gehring et al., 1993). It is assumed to reflect the mismatch between representations of the executed

* Tel.: +49 341 9940 262; fax: +49 341 9940 221.

E-mail address: ullsp@cps.mpg.de.

response and the response tendency resulting from full stimulus evaluation (Falkenstein et al., 2000; Coles et al., 2001). Alternatively, the ERN has been suggested to reflect post-response conflict between executed and competing response tendencies (Yeung et al., 2004). A neurobiological hypothesis suggests that the ERN is elicited based on a dopaminergic reinforcement signal from the mesencephalon, when action outcome is worse than expected (Holroyd and Coles, 2002). A second error-related ERP, the error positivity (Pe) has a centroparietal distribution and occurs about 300 to 500 ms after the erroneous response (Falkenstein et al., 2000). Its functional significance is still unclear (Falkenstein, 2004); it may be related to the conscious awareness of errors (Nieuwenhuis et al., 2001).

Recent observations of a negativity associated with correct responses that is similar to the ERN with respect to latency and scalp distribution but of smaller amplitude, sometimes called correct-related negativity (CRN; Ford, 1999), led to the notion of a permanently active response evaluation function of the brain structures generating the ERN (Vidal et al., 2000, 2003). This view was supported by recent findings that the CRN amplitude can predict performance on subsequent trials (Ridderinkhof et al., 2003; Allain et al., 2004). The CRN seems not directly to depend on response conflict but rather on the discrepancy between prepared and implemented strategy to solve the task (Bartholow et al., 2005). Finally, on immediate error corrections, a small frontocentral negativity time-locked to the corrective response, the correction-related negativity (CoRN) has been observed (Fiehler et al., 2005). It is also present on error-signaling responses (Ullsperger et al., 2005). Similarly to the CRN it appears to reflect a reevaluating function of the mesial cortical (pre)motor areas, although CRN and CoRN do not need to occur within the same task (Fiehler et al., 2005).

Source localization studies and functional neuroimaging suggest that the ERN is generated in the posterodorsal mesial frontal cortex (pmFC), specifically in the rostral cingulate zone (RCZ; note that this region is located in caudal and not rostral anterior cingulate cortex [ACC]) (Dehaene et al., 1994; Ullsperger and Von Cramon, 2001, 2004a,b). Functional magnetic resonance imaging suggests on a more general perspective that the pmFC is involved when the state of the individual or the outcome of an action are undesired (e.g., errors, pain, loss), or when the outcome is at risk (e.g., response conflict, decision uncertainty), thus signaling the need for behavioral adjustments (Ullsperger et al., 2004; Ridderinkhof et al., 2004). Subspecialization of areas in the pmFC and the models of performance monitoring are a matter of ongoing debate (Rushworth et al., 2004; Botvinick et al., 2004). In any case, correlational studies (ERP, neuroimaging, single- and multiunit recordings) strongly suggest the RCZ, pre-SMA, and mesial cortical area 8 to play key roles in performance monitoring functions. Correlational studies, although commonly accepted as providing strong suggestive evidence, by themselves cannot prove the *necessity* of specific brain regions for specific cognitive functions. Therefore, loss-of-function studies, e.g., in patients are needed for confirmation and hypothesis testing.

1.2. Anatomical connectivity of the rostral cingulate zone

A schematic overview of the connections of the RCZ is shown in Fig. 1. Evidence from nonhuman primates suggests that the RCZ receives inputs from the adjacent pre-SMA and dorsal premotor cortex as well as the thalamic ventroanterior nucleus (pars caudalis) and the oral part of the ventrolateral nucleus (Hatanaka et al., 2003). These thalamic nuclei in turn are sites of termination of pallidal efferents (Dum and Strick, 1993). The RCZ projects to premotor and caudal motor areas as well as the striatum, particularly in the putamen and the striatal cell bridges (Haber, 2003; Takada et al., 2001). Furthermore, reciprocal connections of the RCZ and lateral prefrontal cortex (LPFC) have been described (Bates and Goldman-Rakic, 1993; Petrides and Pandya, 1999). Tachibana et al. (2004) recently suggested that most of these connections go via the dorsal premotor cortex. In humans, RCZ and pre-SMA are functionally connected with LPFC (Koski and Paus, 2000; Paus et al., 2001; Derrfuss et al., 2004). The LPFC itself also projects to the BG, specifically to the rostral striatum. While original models suggested segregated parallel information processing in cortico-striato-thalamocortical circuits (Alexander et al., 1990), more recent views advocate an additional integrative function of the BG (Haber, 2003; Bar-Gad et al., 2003). In particular, the structure of the BG-thalamus-cortex connections appears to “mediate information flow from higher cortical ‘association’ areas of the prefrontal cortex to rostral motor areas” (p.325; Haber, 2003).

Furthermore, the striatal patch compartments project to the mesencephalic dopaminergic nuclei (substantia nigra pars

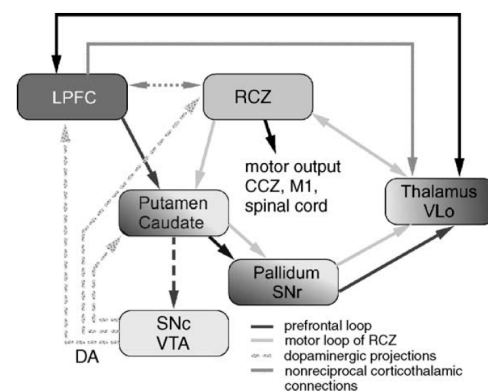


Fig. 1. Simplified schematic of the performance monitoring network connected to the rostral cingulate zone (RCZ). The RCZ and the lateral prefrontal cortex (LPFC) are each parts of segregated cortico-striato-thalamo-cortical loops, the (pre)motor (light grey arrows) and prefrontal loops (dark grey arrows), respectively. These loops interact at several stages, e.g., via non-reciprocal cortico-thalamic connections (hatched grey arrow). A connection between RCZ and LPFC (grey dotted arrow) is under debate, possibly going indirectly via dorsal premotor cortex and pre-supplementary motor area. Modulatory dopaminergic projections from the midbrain are shown as hatched dashed light grey arrows. Direct and indirect pathways of the basal ganglia are collapsed. Abbreviations: CCZ = caudal cingulate zone, DA = dopamine, M1 = primary motor cortex, SNr = substantia nigra pars reticularis, SNc = substantia nigra pars compacta, VLo = nucleus ventrolateralis pars oralis of the thalamus, VTA = ventral tegmental area.

compacta (SNc), ventral tegmental area (VTA), retrorubral area). Dopaminergic neurons project back to the striatum but also to the frontal cortex including the RCZ. These latter connections form the anatomical basis of reinforcement learning models explaining the function of the BG as well as the generation of the ERN (Barto, 1995; Holroyd and Coles, 2002).

1.3. Signs and symptoms of impaired performance monitoring

Impaired monitoring for situations in which action outcome is at risk or worse than expected and impaired signaling the need for behavioral adjustments can lead to a number of behavioral deficits. The function of the performance monitoring system can be tested by investigating behavioral consequences of errors. Impairments should result in decreased and delayed error correction. Post-error slowing (Rabbitt, 1966) is often interpreted as a measure of post-error adjustments as a consequence of error detection. This is probably true in a large number of studies; and it has been shown that it is modulated by error significance (Ullsperger and Szymanowski, 2004; Fiehler et al., 2005). However, it should be noted that a response on a trial after an error could be slow because of the persistence of the processing problem that caused the error (Gehring et al., 1993). In addition, when tasks are performed with high emphasis on response speed, post-error slowing can be absent. Thus, the functionality of the performance monitoring cannot be assessed merely relying on post-error slowing. A more specific measure of behavioral adjustments subsequent to errors seems to be post-error reduction of interference effects (Ridderinkhof et al., 2002). Similarly, impaired conflict-adaptation effects subsequent to increased response conflict may reveal performance monitoring deficits (Ullsperger et al., *in press*). Furthermore, when errors and reduced rewards do not result in a signal to change behavior, impairments in the implementation of alternative actions may be expected, generally reflected in perseveration. In contrast, when the signaling system is dysfunctional, this could also lead to spontaneous switches from successful to less appropriate actions (e.g., decay of task contingencies and rule breaking as described, e.g., in Burgess et al., 2000). As the implementation of alternative actions requires updating of task representation and increases of top-down control, damage to the brain systems involved in these functions would result in similar impairments as would direct dysfunctions of the performance monitoring system. Finally, dysfunction of the performance monitoring system may be expected to result in lower performance in complex and new tasks. However, it should be pointed out that in well-learned tasks, problems with performance monitoring do not necessarily result in generally increased error rates.

With the increased use of ERP and fMRI investigations, additional dependent variables that can hint at impairments of the performance monitoring system have been identified. Particular attention has been paid to modulations of the ERN and of fMRI signals in the pmFC.

2. Studies in neurological patients

Studies on performance monitoring changes mostly focused to the influence of acquired focal lesions on electrophysiological measures of performance monitoring, particularly the ERN. In the following, studies are reviewed ordered by lesion topology.

2.1. The anterior cingulate cortex (mesial frontal cortex)

Isolated, focal lesions in the ACC are very rare. Swick and colleagues reported extensive behavioral and ERP results on two patients with focal unilateral lesions of the RCZ (Turken and Swick, 1999; Swick and Jovanovic, 2002; Swick and Turken, 2002, 2004). One patient (D.L.) had a lesion in the right posterior RCZ reaching into the caudal cingulate zone, whereas the other patient (R.N.) had a lesion in the left anterior RCZ extending superiorly into the adjacent region where areas 32 and 8 adjoin. Patient D.L. with the posterior RCZ lesion showed normal levels of interference and accurate performance on incongruent trials in a Stroop task, but lower facilitation effects on congruent trials and no modulation of the interference effect by probability of incongruent trials (high vs. low conflict). It seems that this patient was incapable of modulating performance and “economizing” response selection by use of supportive stimulus features, as healthy subjects usually do on congruent trials. In other words, “patient D.L. adopted a conservative compensatory strategy [...] to reduce her susceptibility to [response] conflict” (p. 1251, Swick and Jovanovic, 2002). In contrast, patient R.N. with the anterior RCZ lesion showed consistently lower accuracy on incongruent trials and increased interference effects. Moreover, R.N.’s capability to modulate performance based on response conflict probability was reduced. Similarly, in a cued task-switching version of a word-arrow Stroop task R.N. showed increased interference in the mixed blocks requiring fast and flexible updating of task representations (Swick and Turken, 2004). The ERP findings were rather intriguing. R.N. showed a post-response negativity in the time range of the ERN on both errors and correct responses, but the ERN was attenuated and not different in amplitude from the CRN (Swick and Turken, 2002). Several interpretations are possible. First, the generator of the ERN was damaged by the unilateral lesion, but the contralateral side was still able to elicit a negativity, although not distinguishing between correct and incorrect anymore. Second, a number of studies suggest that ERN and CRN are related but not identical (Ford, 1999; Bartholow et al., 2005), i.e., the ERN may be superimposed on the CRN. Then, the generator of the CRN may still have been intact, while the generator of the ERN has been sufficiently damaged to prevent it from eliciting an error-related response. Regarding response conflict monitoring on correct trials, R.N. showed unimpaired congruency modulation of the stimulus-locked N2, which suggests that N2 and ERN have at least in part dissociable generators. The preserved N2, however, is difficult to reconcile with the obvious conflict-adaptation deficits found in the patient’s performance. It is necessary to investigate a larger

number of similar patients to make final conclusions about the functional relevance of the N2 modulation by response conflict.

The role of the RCZ in reward-guided behavior and performance monitoring has found support in a number of intracranial recording studies in patients who underwent pre-operative diagnosis for epilepsy (Brazdil et al., 2002; Wang et al., 2005). These studies revealed error- and negative-feedback-related electrical activity in the RCZ. Moreover, Wang et al. (2005) demonstrated error-related theta-band phase-locking of RCZ activity and other cortical areas in the brain, supporting the notion of a signal indicating the need to adjust behavior. A recent reward-processing study in patients who underwent cingulotomy in the RCZ combined correlative single-cell recordings (during the pre-cingulotomy phase of surgery) with a post-surgery loss-of-function examination (Williams et al., 2004). Activity in RCZ neurons not only responded to reward reductions but also predicted subsequent response alternations. Specifically the latter performance adjustments were impaired after partial ablation of the rostral cingulate zone.

A recent study challenged the view that the pMFC is necessary to signal the need for cognitive control. Fellows and Farah (2005) investigated four patients with extensive lesions involving the majority of pMFC and RCZ. One of them had bilateral lesions to the RCZ and adjacent cortical areas. In both, Stroop and Go–NoGo tasks, all four patients showed normal performance adjustments to manipulations of response conflict. Post-error slowing as well as the ability to adjust performance to speed or accuracy instructions was not different from healthy controls. The authors therefore concluded that the pMFC may not be necessary for cognitive adjustments in response to errors or increased conflict. They argued that its activity found in neuroimaging studies may be rather epiphenomenal and more related to autonomic control (Fellows and Farah, 2005; Critchley et al., 2003). The findings of preserved flexible adjustments in behavior are intriguing, particularly given the large lesion size. However, as has been shown previously, impairments subsequent to ACC lesions are at least in part transient in nature and disappear in chronic stages (Cohen et al., 1999), thus suggesting a high plasticity of the performance monitoring system. It might be that the patients in the Fellows & Farah study have recovered from impairments that were larger in the acute postlesional phase. Second, as pointed out previously, post-error slowing alone may be an insufficient measure to assess adjustments resulting from error processing. In sum, although evidence from loss-of-function studies is scarce and not entirely unequivocal, they appear to provide initial support for the view (derived from correlative studies) that the pMFC is essential for cognitive control by monitoring for and signaling the need to adjust behavior.

Neuroimaging and ERP studies have also suggested involvement of more rostral regions of the ACC in performance monitoring, particularly in affective processing of errors (Kiehl et al., 2000a; Luu and Pederson, 2004). Stemmer et al. (2004) investigated five patients with bilateral lesions of the anterior mesial frontal cortex involving the pregenual and

subcallosal ACC. They found largely impaired or absent ERN and Pe responses on errors in all patients, except for one who had a more inferior lesion, which was less extensive on the left side. The reinforcement-learning theory (Holroyd and Coles, 2002) suggests that dopaminergic input to the RCZ is necessary to elicit the ERN, and Paus (2001) pointed out the importance of cholinergic inputs for ACC function. Both, the dopaminergic projections from the midbrain and the cholinergic fibers from the septal region can be assumed to be largely impaired in the bilaterally lesioned patients. Thus, the absence of ERP responses to errors may result from the deprivation of the generator from modulating neurotransmitters. Interestingly, some of the patients seemed to show signs of error awareness (vocal responses, grimaces), suggesting that the activity of the ERN generator in the RCZ is not necessary to consciously detect errors. Taken together with the study by Nieuwenhuis et al. (2001) it appears that the error signaling process involving the RCZ is completely dissociated from the processing route enabling conscious error awareness.

2.2. The lateral prefrontal cortex

The LPFC has been shown to be involved in maintenance and updating of task representations (MacDonald et al., 2000; Derrfuss et al., 2004; Brass and Von Cramon, 2004; Brass et al., 2005). Contextual information about the task is necessary to make outcome predictions for an action. In addition, the LPFC seems to be involved in the increase in cognitive control as a consequence of detected errors or response conflict on preceding trials (Kerns et al., 2004; Garavan et al., 2002). Thus, bidirectional information flow between LPFC and the performance monitoring system can be expected.

Gehring and Knight (2000) investigated performance monitoring in patients with focal lesions of the lateral frontal cortex using ERPs. They reported that electrical brain activity—particularly the frontocentral negativity—was the same after errors as after correct responses. Moreover, the peak force elicited on error trials showed less inhibition in the LPFC group than in controls. Error correction rate was reduced as compared to the age-matched controls, but not in comparison to younger control subjects. Similarly, Ullsperger et al. (2002) found that in the time range of the ERN the difference between the response-locked ERPs on errors and correct responses vanishes when the LPFC is damaged. It was suggested that in these patients information about the task at hand was not properly conveyed to the performance monitoring system. Thus, for patients response selection remained underdetermined implying high uncertainty during and after the response, hindering the patients to properly process their errors. To investigate error compensation in detail, in a follow-up study, a similar group of LPFC patients was examined performing a flanker task in which all encountered errors should be corrected by an immediate key press (Ullsperger and Von Cramon, *in press*). The ERP findings replicated previous studies by showing an ERN reduction in LPFC patients such that the amplitude difference between the ERPs on correct and incorrect trials disappeared. Moreover, in contrast to healthy controls, no

parietal Pe and no CoRN were found. Interestingly, at frontocentral electrodes errors elicited a slow positive-going deflection between 100 and 200 ms after the response, being similar to the early Pe as described by Van Veen and Carter (2002) in healthy subjects (the same deflection was present for the controls in the patient study, but in part masked by the CoRN). Error correction time was prolonged in all LPFC patients. The errors correction rate, however, was massively reduced only in three out of seven patients. The lesions of these three patients extended into the frontal white matter presumably disrupting fiber connections between RCZ and LPFC as well as the input from these regions into the striatum. Taken together, current evidence suggests that LPFC lesions mostly confined to the cortex itself impairs the generation of the ERP correlates of performance monitoring, but can still be compensated behaviorally. Error-related electrocortical activity in the RCZ is presumably desynchronized and scattered in time, such that no ERN can be recorded at the scalp, but the later frontocentral positivity on errors suggests that error processing still takes place in the pMFC. Only larger lesions disrupting mutual connections of unlesioned parts of the performance monitoring network result in behavioral problems.

2.3. Other cortical areas

Patients with bilateral lesions in the *orbitofrontal cortex* (OFC) are impaired in using external feedback about positive and negative action outcomes (reward and punishment) and uncertainty (Bechara et al., 1997). A further study showed that lesions of the anterior OFC were sufficient to produce hypersensitivity to rewards and insensitivity to punishments (Bechara et al., 1998). Neuroimaging literature suggests that the lateral OFC in particular is involved in monitoring “punishers which when detected may lead to a change in current behavior” (p. 361; Kringelbach and Rolls, 2004), reminiscent of the above-mentioned functions proposed for the RCZ. A recent study showed complementary roles of the RCZ and OFC in the interaction between decision making and performance monitoring (Walton et al., 2004). Interestingly, a study in patients with bilateral frontopolar and anterior orbitofrontal lesions did not find any changes of the ERN, and the maximum of the Pe was only shifted anteriorly but not significantly reduced (Ullsperger et al., 2002). Based on these findings it was recently speculated that the OFC is more involved in processing of external stimuli (outcomes) that may have influence on future strategies, whereas the RCZ particularly monitors self-initiated performance to guide current behavior (Ullsperger and Von Cramon, 2004a,b).

Ullsperger et al. (2002) also investigated patients with lesions of the *temporal* cortex and did not find any changes in error-related ERPs.

2.4. The basal ganglia and dopamine

The reinforcement-learning theory (Holroyd and Coles, 2002) and the anatomical connectivity of the RCZ suggest that the vertical loops through the BG and ventrolateral thalamus are

at a central position of the performance monitoring network. To address the role of the BG and of dopaminergic transmission, two studies examining the ERN in patients with mild-to-moderate Parkinson's disease (PD) were conducted, but yielded equivocal results. In one study, medicated PD patients showed reduced ERN amplitudes, particularly in demanding tasks (Falkenstein et al., 2001). Holroyd et al. (2002) investigated patients with unilateral PD symptoms off-medication and did not reveal any ERN abnormalities. It can only be speculated on the reasons for this discrepancy. First, it may be that in early stages of PD, the performance monitoring system can still work normally, as the mesolimbic and mesocortical dopamine projections are affected in later stages of the disease. Furthermore, dopaminergic medication may have a detrimental effect. Cools and colleagues (Cools et al., 2001, 2003) showed that dopaminergic treatment impairs probabilistic reversal learning and increases impulsivity of response selection in PD patients. One can further speculate that dopaminergic medication tonically increases DA activity, but blunts the phasic responses (T.W. Robbins, personal communication). According to the model by Holroyd and Coles (2002) this could explain why the ERN was reduced in the study by Falkenstein et al. (2001).

In a study directly addressing BG function, nine patients with unilateral lesions confined to the BG (mostly putamen and globus pallidus) who performed a flankers task revealed similar ERP findings as in LPFC patients (Ullsperger and Von Cramon, *in press*). In the time window of the ERN the ERP amplitudes did not discriminate between hits and errors. Moreover, the CoRN and parietal Pe were absent, whereas a sustained frontocentral positivity occurred on errors. The BG patients corrected their errors as efficiently as the controls. Again, it seems that a lesion confined to one part of the performance monitoring system results in disturbed error-related ERPs, but behavior remains intact.

The Gilles-de-la-Tourette syndrome (TS) has been proposed to reflect dysfunction of the frontostriatal circuits resulting in enhanced cortical excitability in the frontal cortex. Johannes and colleagues (Johannes et al., 2002, 2003) demonstrated increased ERN amplitudes to errors and frontocentral N2 modulations to response conflicts, respectively. These findings are similar to reports on obsessive compulsive disorder (OCD; reviewed below), a disease that overlaps with TS in terms of co-morbidity and assumptions about underlying mechanisms. The studies support the view that the frontostriatal circuits play a central role in performance monitoring. Findings of *increased* error rates in Stroop, vigilance and response flexibility tasks (Muller et al., 2003) suggest that the increased ERN reflects a dysfunctional rather than hyperactive performance monitoring system. Investigations of post-error adjustments are lacking so far.

3. Studies in psychiatric patients

3.1. Obsessive-compulsive disorder (OCD)

A number of studies has addressed performance monitoring in OCD patients. They were motivated by neuroimaging and

neurosurgical findings suggesting that excessive activity in the frontostriatal circuits including the ACC contributes to the symptoms of OCD (Saxena et al., 1998). Moreover, it was proposed that OCD symptoms in part result from “hyperactive error signals”, which could be the reason for the patients’ feelings of incomplete performance (Schwartz, 1997).

Two studies investigated the ERN in reaction time tasks and found increased ERN amplitudes in OCD patients (Gehring et al., 2000; Johannes et al., 2001). The magnitude of the ERN enhancement was correlated with symptom severity (Gehring et al., 2000). A subsequent study on undergraduate students showing OCD symptoms additionally found increased CRN amplitudes suggesting that OCD patients excessively engage performance monitoring even on correct trials (Hajcak and Simons, 2002). Johannes et al. (2003) additionally reported an increased frontocentral N2 modulation by response conflict. In line with these ERP findings (Ursu et al., 2003) found increased fMRI responses in pmFC in OCD patients during errors as well as correct trials involving high response conflict. A recent study investigating response and feedback ERN in a probabilistic learning task, however, did not replicate the finding of a larger response ERN in OCD patients (Nieuwenhuis et al., 2005). The authors discussed the discrepancy of their findings with previous studies with respect to medication effects (only the Johannes et al., 2001, study was performed in unmedicated patients), to larger depressive symptoms in their patient group, and to the higher uncertainty and lower learning performance of the OCD patients in the probabilistic learning task. The feedback ERN showed a small, non-significant trend to be larger in OCD patients. Its amplitude was correlated with OCD symptom severity. Future studies including larger patient numbers will be needed to prove whether the feedback ERN is increased in OCD patients.

3.2. Attention deficit hyperactivity disorder (ADHD)

ADHD is a psychiatric disorder that has been related to dopaminergic and noradrenergic dysfunction. A number of gene polymorphisms (e.g., for the dopamine transporter and D4 receptor genes) have been associated with ADHD, and radioligand studies have suggested reduced or dysfunctional activity in the prefrontal cortex and the basal ganglia. The assumed dopaminergic dysfunction and increased behavioral impulsivity (often resulting in higher error rates) have motivated behavioral, ERP and fMRI studies of performance monitoring in ADHD patients.

Post-error slowing was examined in a large sample of children with ADHD ($N=151$) using the stop-signal task (Schachar et al., 2004). ADHD children showed significantly reduced post-error slowing than controls and a small but significant correlation of post-error slowing with total ADHD symptoms. Interestingly, the stop-signal-reaction time (which itself was prolonged in the patients) was not correlated with post-error slowing in the patients, indicating that the post-error slowing deficit did not simply reflect deficient response inhibition. A first ERP study in a large population of children indicated an increased ERN amplitude in children with ADHD

as compared to non-ADHD children in a target-detection task (Burgio-Murphy et al., 2001). In contrast, in a recent stop-signal task study ten ADHD children indicated a reduced ERN (Liotti et al., 2005). Two potential confounds make this result difficult to interpret. First, the children were on chronic methylphenidate medication and off-medication for just one night. Second, error rates differed significantly between ADHD patients and controls, and the ERN is known to decrease with increasing error rates (Falkenstein et al., 2000). In the same sample, a reduced right inferior N2 on successful stops was observed (Pliszka et al., 2000). In contrast, a study in 16 unmedicated boys with ADHD did not reveal any differences in the NoGo N2 (Fallgatter et al., 2004), a component that has been implicated with response conflict monitoring (Nieuwenhuis et al., 2003).

A study in eleven unmedicated, adult patients with ADHD (7 combined, 4 inattentive subtype) using the flanker task revealed impulsive response behavior (more errors, fewer late responses than in healthy controls), but neither a difference of error-related ERPs nor of error correction behavior in comparison to the controls, even when the difference in error rates was controlled for (Ullsperger, Siegert, and Colla, unpublished observations). Two fMRI studies in unmedicated adolescent (Rubia et al., 1999) and adult (Bush et al., 1999) ADHD patients revealed reduced hemodynamic responses in the pmFC in the patients in stop-signal and Stroop tasks, respectively.

In sum, the picture is still far from clear. Although neurobiological theories and imaging studies suggest an involvement of the performance monitoring network in the pathology of ADHD, the ERP findings are too inconsistent to support the notion of a performance monitoring deficit.

3.3. Schizophrenia

Defective self-monitoring leading to misattribution of thoughts and actions to external sources has been suggested to underlie some positive symptoms in schizophrenia (Frith, 1987). This view has motivated the hypothesis that performance monitoring may be affected in schizophrenic patients. Furthermore, evidence for subcortical dopamine excess and cortical dopamine deficit has been reported (Abi-Dargham, 2004). In addition, reductions in baseline cerebral blood flow as well as abnormal responses to dopaminergic challenge in the RCZ of unmedicated schizophrenia patients (Dolan et al., 1995) make dysfunctions of the performance monitoring system conceivable.

Early behavioral studies reported a deficit in immediate error corrections in schizophrenic patients (Malenka et al., 1982, 1986). A later study ruling out possible lack of compliance in the patients replicated this finding and showed that reaction time correlates of response conflict did not differ between patients and controls (Turken et al., 2003). Interestingly, in an ERP study employing the flankers task (Kopp and Rist, 1999) schizophrenic patients corrected errors as efficiently as healthy controls. This study furthermore demonstrated that the ERN was greatly reduced in paranoid patients, a

finding that has been replicated by Bates et al. (2002). Ford (1999) and Mathalon et al. (2002) reported in addition to a smaller ERN an enlarged CRN, which were indistinguishable with regard to amplitude. This finding was pronounced in patients with the paranoid subtype. Interestingly, the patients had an unimpaired Pe and normal post-error slowing (Mathalon et al., 2002). The NoGo N2 as a measure of conflict monitoring and inhibition appeared to be smaller in two studies, but this trend did not reach significance (Kiehl et al., 2000b; Ford et al., 2004).

A positron-emission tomography (PET) study showed decreased activity in pMFC during response conflict in schizophrenic patients when compared to controls (Carter et al., 1997). Similarly, in patients the error-related fMRI signal in the RCZ was reduced in a continuous performance task (Carter et al., 2001). In these patients post-error slowing was diminished. In contrast, an fMRI study using a Go–NoGo task revealed reduced error-related signal increases in the rostral (pregenual) ACC in patients, but equal activity in the RCZ for patients and controls (Laurens et al., 2003). Furthermore, post-error slowing was preserved in the patients of this study. The rostral ACC activation has been interpreted as reflecting the motivational and affective response to errors (Kiehl et al., 2000a; Luu and Pederson, 2004), which might be disturbed in schizophrenic patients.

Taken together, the results hint at a performance monitoring deficit in schizophrenic patients. However, the evidence is not entirely unequivocal, particularly with regard to most affected regions in MFC and to post-error compensatory processes. This may have a number of reasons. First, schizophrenia is a heterogeneous disease, and only one study has focused on subtypes in detail (Kopp and Rist, 1999). Second, in all studies patients were on medication, raising the issue that the observed effects might result from drug action rather than from the disease itself. This is particularly relevant, as antipsychotic drugs act on the dopamine system and have been shown to attenuate ERN and post-error slowing after acute administration (Zirnheld et al., 2004). Moreover, antipsychotic drugs may influence cerebral blood flow and thus make neuroimaging studies difficult to interpret.

3.4. Depression

The rostral (pregenual) and subcallosal ACC has been shown to have abnormal structure and metabolism in patients with major depression (Drevets, 2001). A direct link between reinforcers and normal emotions has been suggested, thus it can be hypothesized that processing of reinforcers, a prerequisite of performance monitoring, is impaired in depression. This view found support by a recent ERP study indicating larger ERN-like responses to all feedback types (indicating no, small, or large loss) in unmedicated depressed patients than in controls (Tucker et al., 2003). Whereas in healthy subjects ERN amplitude did not differ between the two loss conditions (while being larger than for no-loss feedback), in the depressed group ERN amplitude increased with magnitude of loss. This effect was most pronounced in moderately depressed subjects

and attenuated in more severely depressed patients. Thus, the modulation of feedback ERN amplitude by loss magnitude, usually not found in healthy subjects (Yeung and Sanfey, 2004), seems to be influenced by depression in an inverted u-shaped manner. An fMRI study investigating feedback-related activity in a gambling paradigm by modeling error signals using Kalman filter theory (Steele et al., 2004) found increased hemodynamic activity in the rostral ACC and parahippocampal gyrus in medicated depressed patients. The increased signal in these regions positively correlated with Hamilton depression score. The rostral ACC region of interest was located pregenually, close to the region found to be less activated in schizophrenic patients by Laurens et al. (2003). Thus, ERP and fMRI studies conducted so far suggest larger responses of the performance monitoring system to feedback, in particular to negative ones. An ERP study investigating response errors and feedback-related activity in a flanker task reported no difference in ERN amplitudes between healthy and medicated depressed subjects and a reduced negativity on the second feedback in double error sequences in depressed patients (Ruchow et al., 2004). These findings have to be interpreted with caution, as neither error rates nor the number of double errors have been reported, and inspection of the waveforms suggests high noise in the double-error-related ERPs. Moreover, the negativity after the feedback has an unusual shape and latency and usually does not occur in flanker tasks (De Bruijn et al., 2004).

The findings suggest so far that in depression the performance monitoring system has an increased sensitivity to negative feedback. The data provide hints for a specific change in affective processing of signals from the performance monitoring system. However, further studies are needed to address whether the increased response to errors results in changed and possibly dysfunctional behavioral adjustments after errors.

4. Conclusions

The present review revealed a number of results. *First*, patient studies largely—but not entirely unequivocally in all cases—support the views about the networks and transmitter systems involved in performance monitoring which were mostly based on correlative single-unit, ERP and neuroimaging studies. The importance of the pMFC, LPFC, the fronto-striato-thalamo-cortical circuitry and the reward system are stressed by a number of findings. Particularly important seem the findings on the LPFC and subcortical structures, as neuroimaging findings have only in some cases pointed at an involvement of these regions in performance monitoring. The findings in psychiatric patients support the relevance of dopamine for error processing. Moreover, they may hint at the involvement of other monoamines, such as norepinephrine and serotonin in performance monitoring in the service of behavior optimization and the concomitant modulation of affect. *Second*, overt and latent performance monitoring dysfunctions are present in a rather large variety of neurological and psychiatric diseases. It should, therefore, be a goal of future studies to establish diagnostic tools

for performance monitoring examination that can be used in single patients with the aim to better characterize their cognitive abilities and to quantify functional recovery and therapeutic effects. *Third*, the ERN has proven to be a very sensitive measure giving information on the integrity of the performance monitoring system. It is a large and easy-to-evoke component. It seems specific to lesions and dysfunctions of the performance monitoring network, as it was shown to be preserved in patients with lesions to other parts of the brain (Ullsperger et al., 2002). However, given the finding that many patients can still detect and sometimes even correct their errors despite showing ERN abnormalities one needs to keep in mind that it is more an epiphenomenon indicating the integrity of the whole system than a direct measure of error processing. *Fourth*, in line with studies in healthy subjects the patient data suggest that ERN on one hand, and Pe and error awareness on the other, may be based on two separate pathways of error processing.

Of course, many questions remain open. The relationship of the described dysfunctions measured in experimental settings to daily-life problems still needs to be established. For example, is the knowing-doing-dissociation often observed in frontal lobe patients related to measures of performance monitoring? Further, the plasticity of performance monitoring is an important issue for clinical applications. In basic research, involvement and interaction of transmitter systems in performance monitoring should become a question of detailed studies.

The gathered experience in patient studies on performance monitoring shall be used to make suggestions on how to optimize gain in information in future patient studies. *First*, in addition to ERP and neuroimaging data behavioral measures clearly associated with performance monitoring and its consequences (e.g., error correction, better yet error signaling responses, post-error and post-conflict reduction of interference) should be collected. *Second*, in studies investigating errors, sufficient numbers of error trials need to be recorded to guarantee reliable analyses, without encouraging subjects to make errors. *Third*, performance (error, feedback frequencies) should be kept as similar across groups as possible. In case error rates differ between patients and controls, statistical methods need to be applied to partial out the confounding factor. *Fourth*, drug effects state an important problem in patient studies, which is difficult to address. Although unmedicated patients would be best for investigations, this is often not feasible. At least, medication should be stable for a sufficient time period prior to the experiment (depending on drug properties, it varies from a day to several weeks). In fMRI studies, indirect drug effects on the results by influencing hemodynamics pose an additional problem. Here, control experiments (checkerboard stimulation, motor tapping) can be helpful. If in such control experiments fMRI signals in patients and controls do not differ, this hints at negligible unspecific drug effects on the BOLD response. In elderly subjects and patients with vascular diseases, general deficits in cerebral vasoreactivity potentially influencing perfusion and BOLD should also be addressed (Heinke et al., 2005; Hund-Georgiadis et al., 2003).

All in all, studies of performance monitoring in patients are an important new-arising domain of cognitive neurology and neuropsychiatry. They help to understand the performance monitoring functions and to learn about the pathophysiology of cognitive symptoms. I am convinced that examination of performance monitoring will become an essential part of diagnosis of cognitive dysfunction even in clinical settings.

Acknowledgments

The author thanks K. G. Volz and D. Y. von Cramon for helpful comments on this manuscript.

References

- Abi-Dargham, A., 2004. Do we still believe in the dopamine hypothesis? New data bring new evidence. *Int. J. Neuropsychopharmacol.* 7 (Suppl 1), S1–S5.
- Alexander, G.E., Crutcher, M.D., DeLong, M.R., 1990. Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, “pre-frontal” and “limbic” functions. *Prog. Brain Res.* 85, 119–146.
- Allain, S., Carbonnell, L., Falkenstein, M., Burle, B., Vidal, F., 2004. The modulation of the Ne-like wave on correct responses foreshadows errors. *Neurosci. Lett.* 372, 161–166.
- Bar-Gad, I., Morris, G., Bergman, H., 2003. Information processing, dimensionality reduction and reinforcement learning in the basal ganglia. *Prog. Neurobiol.* 71, 439–473.
- Bartholow, B.D., Pearson, M.A., Dickter, C.L., Sher, K.J., Fabiani, M., Gratton, G., 2005. Strategic control and medial frontal negativity: beyond errors and response conflict. *Psychophysiology*, 42.
- Barto, A.G., 1995. Adaptive critics and the basal ganglia. In: Houk, J.C., Davis, J.L., Beiser, D.G. (Eds.), *Models of Information Processing in the Basal Ganglia*. Cambridge, Massachusetts.
- Bates, J.F., Goldman-Rakic, P.S., 1993. Prefrontal connections of medial motor areas in the rhesus monkey. *J. Comp. Neurol.* 336, 211–228.
- Bates, A.T., Kiehl, K.A., Laurens, K.R., Liddle, P.F., 2002. Error-related negativity and correct response negativity in schizophrenia. *Clin. Neurophysiol.* 113, 1454–1463.
- Bechara, A., Damasio, H., Tranel, D., Damasio, A.R., 1997. Deciding advantageously before knowing the advantageous strategy. *Science* 275, 1293–1295.
- Bechara, A., Damasio, H., Tranel, D., Anderson, S.W., 1998. Dissociation Of working memory from decision making within the human prefrontal cortex. *J. Neurosci.* 18, 428–437.
- Botvinick, M.M., Cohen, J.D., Carter, C.S., 2004. Conflict monitoring and anterior cingulate cortex: an update. *Trends Cogn. Sci.* 8, 539–546.
- Brass, M., Von Cramon, D.Y., 2004. Decomposing components of task preparation with functional magnetic resonance imaging. *J. Cogn. Neurosci.* 16, 609–620.
- Brass, M., Ullsperger, M., Knösche, T.R., Von Cramon, D.Y., Phillips, N.A., 2005. Who comes first? The role of prefrontal and parietal cortex in cognitive control. *J. Cogn. Neurosci.* 17, 1367–1375.
- Brazdil, M., Roman, R., Falkenstein, M., Daniel, P., Jurak, P., Rektor, I., 2002. Error processing-evidence from intracerebral ERP recordings. *Exp. Brain Res.* 146, 460–466.
- Burgess, P.W., Veitch, E., De Lacy Costello, A., Shallice, T., 2000. The cognitive and neuroanatomical correlates of multitasking. *Neuropsychologia* 38, 848–863.
- Burgio-Murphy, A., Klorman, R., Thatcher, J., Shaywitz, S., Fletcher, J., Marchione, K., Holahan, J., Stuebing, K., Shaywitz, B., 2001. ERN in attention-deficit hyperactivity, oppositional-defiant, reading, and math disorder. *Psychophysiology* 38, S30.
- Bush, G., Frazier, J.A., Rauch, S.L., Seidman, L.J., Whalen, P.J., Jenike, M.A., Rosen, B.R., Biederman, J., 1999. Anterior cingulate cortex dysfunction in attention-deficit/hyperactivity disorder revealed by fMRI and the Counting Stroop. *Biol. Psychiatry* 45, 1542–1552.

- Carter, C.S., Mintun, M., Nichols, T., Cohen, J.D., 1997. Anterior cingulate gyrus dysfunction and selective attention deficits in schizophrenia: [¹⁵O]H₂O PET study during single-trial Stroop task performance. *Am. J. Psychiatry* 154, 1670–1675.
- Carter, C.S., Macdonald, R., A.W., Ross, L.L., Stenger, V.A., 2001. Anterior cingulate cortex activity and impaired self-monitoring of performance in patients with schizophrenia: an event-related fMRI study. *Am. J. Psychiatry* 158, 1423–1428.
- Cohen, R.A., Kaplan, R.F., Moser, D.J., Jenkins, M.A., Wilkinson, H., 1999. Impairments of attention after cingulotomy. *Neurology* 53, 819–824.
- Coles, M.G., Scheffers, M.K., Holroyd, C.B., 2001. Why is there an ERN/Ne on correct trials? Response representations, stimulus-related components, and the theory of error-processing. *Biol. Psychol.* 56, 173–189.
- Cools, R., Barker, R.A., Sahakian, B.J., Robbins, T.W., 2001. Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. *Cereb. Cortex* 11, 1136–1143.
- Cools, R., Barker, R.A., Sahakian, B.J., Robbins, T.W., 2003. L-Dopa medication remedies cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease. *Neuropsychologia* 41, 1431–1441.
- Critchley, H.D., Mathias, C.J., Josephs, O., O'Doherty, J., Zanini, S., Dewar, B.K., Cipolotti, L., Shallice, T., Dolan, R.J., 2003. Human cingulate cortex and autonomic control: converging neuroimaging and clinical evidence. *Brain* 126, 2139–2152.
- De Bruijn, E.R.A., Mars, R.B., Hulstijn, W., 2004. It wasn't me...or was it? How false feedback affects performance. In: Ullsperger, M., Falkenstein, M. (Eds.), *Errors, Conflicts, and the Brain. Current Opinions on Performance Monitoring. MPI for Human Cognitive and Brain Sciences, Leipzig*.
- Dehaene, S., Posner, M.I., Tucker, D.M., 1994. Localization of a neural system for error detection and compensation. *Psychol. Sci.* 5, 303–305.
- Derrfuss, J., Brass, M., Von Cramon, D.Y., 2004. Cognitive control in the posterior frontolateral cortex: evidence from common activations in task coordination, interference control, and working memory. *Neuroimage* 23, 604–612.
- Dolan, R.J., Fletcher, P., Frith, C.D., Friston, K.J., Frackowiak, R.S., Grasby, P.M., 1995. Dopaminergic modulation of impaired cognitive activation in the anterior cingulate cortex in schizophrenia. *Nature* 378, 180–182.
- Drevets, W.C., 2001. Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. *Curr. Opin. Neurobiol.* 11, 240–249.
- Dum, R.P., Strick, P.L., 1993. Cingulate motor areas. In: Vogt, B.A., Gabriel, M. (Eds.), *Neurobiology of Cingulate Cortex and Limbic Thalamus*. Birkhäuser, Boston.
- Falkenstein, M., 2004. ERP correlates of erroneous performance. In: Ullsperger, M., Falkenstein, M. (Eds.), *Errors, Conflicts, and the Brain. Current Opinions on Performance Monitoring. MPI for Human Cognitive and Brain Sciences, Leipzig*.
- Falkenstein, M., Hohnsbein, J., Hoormann, J., Blanke, L., 1990. Effects of errors in choice reaction tasks on the ERP under focused and divided attention. *Psychophysiological Brain Research. Tilburg University Press*.
- Falkenstein, M., Hoormann, J., Christ, S., Hohnsbein, J., 2000. ERP components on reaction errors and their functional significance: a tutorial. *Biol. Psychol.* 51, 87–107.
- Falkenstein, M., Hielscher, H., Dziobek, I., Schwarzenau, P., Hoormann, J., Sunderman, B., Hohnsbein, J., 2001. Action monitoring, error detection, and the basal ganglia: an ERP study. *Neuroreport* 12, 157–161.
- Fallgatter, A.J., Ehlis, A.C., Seifert, J., Strik, W.K., Scheuerpflug, P., Zillesen, K.E., Herrmann, M.J., Warnke, A., 2004. Altered response control and anterior cingulate function in attention-deficit/hyperactivity disorder boys. *Clin. Neurophysiol.* 115, 973–981.
- Fellows, L.K., Farah, M.J., 2005. Different underlying impairments in decision-making following ventromedial and dorsolateral frontal lobe damage in humans. *Cereb. Cortex* 15, 58–63.
- Fiehler, K., Ullsperger, M., Von Cramon, D.Y., 2005. Electrophysiological correlates of error correction. *Psychophysiology* 42, 72–82.
- Ford, J.M., 1999. Schizophrenia: the broken P300 and beyond. *Psychophysiology* 36, 667–682.
- Ford, J.M., Gray, M., Whitfield, S.L., Turken, A.U., Glover, G., Faustman, W.O., Mathalon, D.H., 2004. Acquiring and inhibiting prepotent responses in schizophrenia: event-related brain potentials and functional magnetic resonance imaging. *Arch. Gen. Psychiatry* 61, 119–129.
- Frith, C.D., 1987. The positive and negative symptoms of schizophrenia reflect impairments in the perception and initiation of action. *Psychol. Med.* 17, 631–648.
- Garavan, H., Ross, T.J., Murphy, K., Roche, R.A., Stein, E.A., 2002. Dissociable executive functions in the dynamic control of behavior: inhibition, error detection, and correction. *Neuroimage* 17, 1820–1829.
- Gehring, W.J., Knight, R.T., 2000. Prefrontal-cingulate interactions in action monitoring. *Nat. Neurosci.* 3, 516–520.
- Gehring, W.J., Goss, B., Coles, M.G., Meyer, D.E., Al, E., 1993. A neural system for error detection and compensation. *Psychol. Sci.* 4, 385–390.
- Gehring, W.J., Himle, J., Nisenson, L.G., 2000. Action-monitoring dysfunction in obsessive-compulsive disorder. *Psychol. Sci.* 11, 1–6.
- Haber, S.N., 2003. The primate basal ganglia: parallel and integrative networks. *J. Chem. Neuroanat.* 26, 317–330.
- Hajcak, G., Simons, R.F., 2002. Error-related brain activity in obsessive-compulsive undergraduates. *Psychiatry Res.* 110, 63–72.
- Hatanaka, N., Tokuno, H., Hamada, I., Inase, M., Ito, Y., Imanishi, M., Hasegawa, N., Akazawa, T., Nambu, A., Takada, M., 2003. Thalamocortical and intracortical connections of monkey cingulate motor areas. *J. Comp. Neurol.* 462, 121–138.
- Heinke, W., Zysset, S., Hund-Georgiadis, M., Olthoff, D., Von Cramon, D.Y., 2005. The effect of esmolol on cerebral blood flow, cerebral vasoreactivity, and cognitive performance: a functional magnetic resonance imaging study. *Anesthesiology* 102, 41–50.
- Holroyd, C.B., Coles, M.G., 2002. The neural basis of human error processing: reinforcement learning, dopamine, and the error-related negativity. *Psychol. Rev.* 109, 679–709.
- Holroyd, C.B., Praamstra, P., Plat, E., Coles, M.G., 2002. Spared error-related potentials in mild to moderate Parkinson's disease. *Neuropsychologia* 40, 2116–2124.
- Hund-Georgiadis, M., Mildner, T., Georgiadis, D., Weih, K., Von Cramon, D.Y., 2003. Impaired hemodynamics and neural activation? A fMRI study of major cerebral artery stenosis. *Neurology* 61, 1276–1279.
- Johannes, S., Wieringa, B.M., Nager, W., Rada, D., Dengler, R., Emrich, H.M., Munte, T.F., Dietrich, D.E., 2001. Discrepant target detection and action monitoring in obsessive-compulsive disorder. *Psychiatry Res.* 108, 101–110.
- Johannes, S., Wieringa, B.M., Nager, W., Müller-Vahl, K.R., Dengler, R., Munte, T.F., 2002. Excessive action monitoring in Tourette syndrome. *J. Neurol.* 249, 961–966.
- Johannes, S., Wieringa, B.M., Nager, W., Rada, D., Müller-Vahl, K.R., Emrich, H.M., Dengler, R., Munte, T.F., Dietrich, D., 2003. Tourette syndrome and obsessive-compulsive disorder: event-related brain potentials show similar mechanisms [correction of mechanisms] of frontal inhibition but dissimilar target evaluation processes. *Behav. Neurol.* 14, 9–17.
- Kerns, J.G., Cohen, J.D., Macdonald, R., A.W., Cho, R.Y., Stenger, V.A., Carter, C.S., 2004. Anterior cingulate conflict monitoring and adjustments in control. *Science* 303, 1023–1026.
- Kiehl, K.A., Liddle, P.F., Hopfinger, J.B., 2000a. Error processing and the rostral anterior cingulate: an event-related fMRI study. *Psychophysiology* 37, 216–223.
- Kiehl, K.A., Smith, A.M., Hare, R.D., Liddle, P.F., 2000b. An event-related potential investigation of response inhibition in schizophrenia and psychopathy. *Biol. Psychiatry* 48, 210–221.
- Kopp, B., Rist, F., 1999. An event-related brain potential substrate of disturbed response monitoring in paranoid schizophrenic patients. *J. Abnorm. Psychology* 108, 337–346.
- Koski, L., Paus, T., 2000. Functional connectivity of the anterior cingulate cortex within the human frontal lobe: a brain-mapping meta-analysis. *Exp. Brain Res.* 133, 55–65.
- Kringelbach, M.L., Rolls, E.T., 2004. The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. *Prog. Neurobiol.* 72, 341–372.
- Laurens, K.R., Ngan, E.T., Bates, A.T., Kiehl, K.A., Liddle, P.F., 2003. Rostral anterior cingulate cortex dysfunction during error processing in schizophrenia. *Brain* 126, 610–622.

- Liotti, M., Pliszka, S.R., Perez, R., Kothmann, D., Woldorff, M.G., 2005. Abnormal brain activity related to performance monitoring and error detection in children with ADHD. *Cortex* 41, 377–388.
- Luu, P., Pederson, S.M., 2004. The anterior cingulate cortex. Regulating actions in context. In: Posner, M.I. (Ed.), *Cognitive Neuroscience of Attention*. The Guilford Press, New York.
- MacDonald III, A.W., Cohen, J.D., Stenger, V.A., Carter, C.S., 2000. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science* 288, 1835–1838.
- Malenka, R.C., Angel, R.W., Hampton, B., Berger, P.A., 1982. Impaired central error-correcting behavior in schizophrenia. *Arch. Gen. Psychiatry* 39, 101–107.
- Malenka, R.C., Angel, R.W., Thiemann, S., Weitz, C.J., Berger, P.A., 1986. Central error-correcting behavior in schizophrenia and depression. *Biol. Psychiatry* 21, 263–273.
- Mathalon, D.H., Fedor, M., Faustman, W.O., Gray, M., Askari, N., Ford, J.M., 2002. Response-monitoring dysfunction in schizophrenia: an event-related brain potential study. *J. Abnorm. Psychology* 111, 22–41.
- Muller, S.V., Johannes, S., Wieringa, B., Weber, A., Muller-Vahl, K., Matzke, M., Kolbe, H., Dengler, R., Munte, T.F., 2003. Disturbed monitoring and response inhibition in patients with Gilles de la Tourette syndrome and co-morbid obsessive compulsive disorder. *Behav. Neurol.* 14, 29–37.
- Nieuwenhuis, S., Ridderinkhof, K.R., Blom, J., Band, G.P., Kok, A., 2001. Error-related brain potentials are differentially related to awareness of response errors: evidence from an antisaccade task. *Psychophysiology* 38, 752–760.
- Nieuwenhuis, S., Yeung, N., Van Den Wildenberg, W., Ridderinkhof, K.R., 2003. Electrophysiological correlates of anterior cingulate function in a go/no-go task: effects of response conflict and trial type frequency. *Cogn. Affect. Behav. Neurosci.* 3, 17–26.
- Nieuwenhuis, S., Nielen, M.M., Mol, N., Hajcak, G., Veltman, D.J., 2005. Performance monitoring in obsessive–compulsive disorder. *Psychiatry Res.* 134, 111–122.
- Paus, T., 2001. Primate anterior cingulate cortex: where motor control, drive and cognition interface. *Nat. Rev., Neurosci.* 2, 417–424.
- Paus, T., Castro-Alamancos, M.A., Petrides, M., 2001. Cortico-cortical connectivity of the human mid-dorsolateral frontal cortex and its modulation by repetitive transcranial magnetic stimulation. *Eur. J. Neurosci.* 14, 1405–1411.
- Petrides, M., Pandya, D.N., 1999. Dorsolateral prefrontal cortex: comparative cytoarchitectonic analysis in the human and the macaque brain and corticocortical connection patterns. *Eur. J. Neurosci.* 11, 1011–1036.
- Pliszka, S.R., Liotti, M., Woldorff, M.G., 2000. Inhibitory control in children with attention-deficit/hyperactivity disorder: event-related potentials identify the processing component and timing of an impaired right-frontal response-inhibition mechanism. *Biol. Psychiatry* 48, 238–246.
- Rabbitt, P.M., 1966. Error correction time without external error signals. *Nature* 212, 438.
- Rabbitt, P., Rodgers, B., 1977. What does a man do after he makes an error? An analysis of response programming. *Q. J. Exp. Psychol.* 29, 727–743.
- Ridderinkhof, K.R., De Vlugt, Y., Bramlage, A., Spaan, M., Elton, M., Snel, J., Band, G.P., 2002. Alcohol consumption impairs detection of performance errors in mediofrontal cortex. *Science* 298, 2209–2211.
- Ridderinkhof, K.R., Nieuwenhuis, S., Bashore, T.R., 2003. Errors are foreshadowed in brain potentials associated with action monitoring in cingulate cortex in humans. *Neurosci. Lett.* 348, 1–4.
- Ridderinkhof, K.R., Ullsperger, M., Crone, E.A., Nieuwenhuis, S., 2004. The role of the medial frontal cortex in cognitive control. *Science* 306, 443–447.
- Rubia, K., Overmeyer, S., Taylor, E., Brammer, M., Williams, S.C., Simmons, A., Bullmore, E.T., 1999. Hypofrontality in attention deficit hyperactivity disorder during higher-order motor control: a study with functional MRI. *Am. J. Psychiatry* 156, 891–896.
- Ruchow, M., Herrnberger, B., Wiesend, C., Gron, G., Spitzer, M., Kiefer, M., 2004. The effect of erroneous responses on response monitoring in patients with major depressive disorder: A study with event-related potentials. *Psychophysiology* 41, 833–840.
- Rushworth, M.F.S., Walton, M.E., Kennerley, S.W., Bannerman, D.M., 2004. Action sets and decisions in the medial frontal cortex. *Trends Cogn. Sci.* 8, 410–417.
- Saxena, S., Brody, A.L., Schwartz, J.M., Baxter, L.R., 1998. Neuroimaging and frontal-subcortical circuitry in obsessive–compulsive disorder. *Br. J. Psychiatry*, 26–37.
- Schachar, R.J., Chen, S., Logan, G.D., Ornstein, T.J., Crosbie, J., Ickowicz, A., Pakulak, A., 2004. Evidence for an error monitoring deficit in attention deficit hyperactivity disorder. *J. Abnorm. Child Psychol.* 32, 285–293.
- Schwartz, J.M., 1997. Cognitive-behavioral self-treatment for OCD systematically alters cerebral metabolism: a mind–brain interaction paradigm for psychotherapists. In: Hollander, E., Stein, D.J. (Eds.), *Obsessive–Compulsive Disorders: Diagnosis, Etiology, Treatment*. Marcel Dekker, New York.
- Steele, J.D., Meyer, M., Ebmeier, K.P., 2004. Neural predictive error signal correlates with depressive illness severity in a game paradigm. *Neuroimage* 23, 269–280.
- Stemmer, B., Segalowitz, S.J., Witzke, W., Schonle, P.W., 2004. Error detection in patients with lesions to the medial prefrontal cortex: an ERP study. *Neuropsychologia* 42, 118–130.
- Swick, D., Jovanovic, J., 2002. Anterior cingulate cortex and the Stroop task: neuropsychological evidence for topographic specificity. *Neuropsychologia* 40, 1240–1253.
- Swick, D., Turken, A.U., 2002. Dissociation between conflict detection and error monitoring in the human anterior cingulate cortex. *Proc. Natl. Acad. Sci. U. S. A.* 99, 16354–16359.
- Swick, D., Turken, A.U., 2004. Errors can be dissociated from conflict: Implications for theories of performance monitoring. In: Ullsperger, M., Falkenstein, M. (Eds.), *Errors, Conflicts, and the Brain. Current Opinions on Performance Monitoring. MPI for Human Cognitive and Brain Sciences, Leipzig*.
- Tachibana, Y., Nambu, A., Hatanaka, N., Miyachi, S., Takada, M., 2004. Input–output organization of the rostral part of the dorsal premotor cortex, with special reference to its corticostriatal projection. *Neurosci. Res.* 48, 45–57.
- Takada, M., Tokuno, H., Hamada, I., Inase, M., Ito, Y., Imanishi, M., Hasegawa, N., Akazawa, T., Hatanaka, N., Nambu, A., 2001. Organization of inputs from cingulate motor areas to basal ganglia in macaque monkey. *Eur. J. Neurosci.* 14, 1633–1650.
- Tucker, D.M., Luu, P., Frishkoff, G., Quiring, J., Poulsen, C., 2003. Frontolimbic response to negative feedback in clinical depression. *J. Abnorm. Psychology* 112, 667–678.
- Turken, A.U., Swick, D., 1999. Response selection in the human anterior cingulate cortex. *Nat. Neurosci.* 2, 920–924.
- Turken, A.U., Vuilleumier, P., Mathalon, D.H., Swick, D., Ford, J.M., 2003. Are impairments of action monitoring and executive control true dissociative dysfunctions in patients with schizophrenia? *Am. J. Psychiatry* 160, 1881–1883.
- Ullsperger, M., Szymanski, F., 2004. ERP Correlates of error relevance. In: Ullsperger, M., Falkenstein, M. (Eds.), *Errors, Conflicts, and the Brain. Current Opinions on Performance Monitoring. MPI for Human Cognitive and Brain Sciences, Leipzig*.
- Ullsperger, M., Von Cramon, D.Y., 2001. Subprocesses of performance monitoring: a dissociation of error processing and response competition revealed by event-related fMRI and ERPs. *Neuroimage* 14, 1387–1401.
- Ullsperger, M., Von Cramon, D.Y., 2004a. Decision making, performance and outcome monitoring in frontal cortical areas. *Nat. Neurosci.* 7, 1173–1174.
- Ullsperger, M., Von Cramon, D.Y., 2004b. Neuroimaging of performance monitoring: error detection and beyond. *Cortex* 40, 593–604.
- Ullsperger, M., Von Cramon, D.Y., in press. The role of intact frontostriatal circuits in error processing. *J. Cogn. Neurosci.*
- Ullsperger, M., Von Cramon, D.Y., Müller, N.G., 2002. Interactions of focal cortical lesions with error processing: evidence from event-related brain potentials. *Neuropsychology* 16, 548–561.
- Ullsperger, M., Volz, K.G., Von Cramon, D.Y., 2004. A common neural system signaling the need for behavioral changes. *Trends Cogn. Sci.* 8, 445–446.
- Ullsperger, M., Fiehler, K., von Cramon, D.Y., 2005. How does error correction differ from error signaling? An ERP study. 11th International Conference on Functional Mapping of the Human Brain, Toronto, Canada, June 2005, *NeuroImage*. Elsevier (available on CD).

- Ullsperger, M., Bylsma, L.M., Botvinick, M.M., in press. The conflict-adaptation effect: it's not just priming. *Cogn. Affect. Behav. Neurosci.*
- Ursu, S., Stenger, V.A., Shear, M.K., Jones, M.R., Carter, C.S., 2003. Overactive action monitoring in obsessive–compulsive disorder: evidence from functional magnetic resonance imaging. *Psychol. Sci.* 14, 347–353.
- Van Veen, V., Carter, C.S., 2002. The timing of action-monitoring processes in the anterior cingulate cortex. *J. Cogn. Neurosci.* 14, 593–602.
- Vidal, F., Hasbroucq, T., Grapperon, J., Bonnet, M., 2000. Is the 'error negativity' specific to errors? *Biol. Psychol.* 51, 109–128.
- Vidal, F., Burle, B., Bonnet, M., Grapperon, J., Hasbroucq, T., 2003. Error negativity on correct trials: a reexamination of available data. *Biol. Psychol.* 64, 265–282.
- Walton, M.E., Devlin, J.T., Rushworth, M.F., 2004. Interactions between decision making and performance monitoring within prefrontal cortex. *Nat. Neurosci.* 7, 1259–1265.
- Wang, C., Ulbert, I., Schomer, D.L., Marinkovic, K., Halgren, E., 2005. Responses of human anterior cingulate cortex microdomains to error detection, conflict monitoring, stimulus-response mapping, familiarity, and orienting. *J. Neurosci.* 25, 604–613.
- Williams, Z.M., Bush, G., Rauch, S.L., Cosgrove, G.R., Eskandar, E.N., 2004. Human anterior cingulate neurons and the integration of monetary reward with motor responses. *Nat. Neurosci.* 7, 1370–1375.
- Yeung, N., Sanfey, A.G., 2004. Independent coding of reward magnitude and valence in the human brain. *J. Neurosci.* 24, 6258–6264.
- Yeung, N., Cohen, J.D., Botvinick, M.M., 2004. The neural basis of error detection: conflict monitoring and the error-related negativity. *Psychol. Rev.* 111, 931–959.
- Zirnheld, P.J., Carroll, C.A., Kieffaber, P.D., O'donnell, B.F., Shekhar, A., Hetrick, W.P., 2004. Haloperidol impairs learning and error-related negativity in humans. *J. Cogn. Neurosci.* 16, 1098–1112.

Part IV

Adjustments and Remedial Actions Based on Performance Monitoring

Chapter 10

Neural correlates of error detection and error correction: is there a common anatomical substrate?

When errors have occurred, compensatory actions are required. These compensatory actions take place in different time frames. Immediate compensatory actions aim at amelioration of the erroneous action outcome, whereas adjustments often have a prolonged effect and may help avoiding similar errors in the future. Part IV of this volume addresses immediate remedial actions (Chapters 10-12) and more prolonged adjustments reflected in sequential trial-by-trial effects (Chapter 13).

Immediate error corrections have been investigated since the nineteen sixties (Rabbitt, 1966a, 1966b; Rabbitt, 1967; Rabbitt and Phillips, 1967). It was found that participants tend to correct errors in speeded reaction time tasks by immediately pressing the correct response button. Around 20 to 40% of the errors are corrected this way, even when participants were not instructed to do so.

The present Chapter investigates the functional anatomical network involved in error processing and in immediate error correction. Using a flanker task in a between-subjects design uncorrected and corrected errors were compared in an fMRI study. One group of participants was instructed to immediately correct every encountered error (correction-instructed group), whereas another group of participants was not instructed about the possibility to correct errors (non-instructed group). Brain activity associated with corrected errors was compared to activity associated with uncorrected errors, revealing increased fMRI responses in the RCZ, pre-SMA, SMA and secondary somatosensory areas. This finding suggests that the RCZ is not only involved in error processing but also in the initiation of immediate corrections. This is consistent with the view that this region plays a role in signaling the need for adjustments when the action outcome is worse than expected. We interpreted the engagement of the mesial premotor areas (pre-SMA, SMA) as a result of the additional motor response needed to correct the error. Secondary somatosensory areas may indicate the increased processing of the somatosensory feedback during error correction.

Neural correlates of error detection and error correction: is there a common neuroanatomical substrate?

Katja Fiehler, Markus Ullsperger and D. Yves von Cramon

Max Planck Institute for Human Cognitive and Brain Sciences, Stephanstr. 1A, D-04103 Leipzig, Germany

Keywords: error processing, fMRI, human, pre-supplementary motor area, rostral cingulate zone

Abstract

Successful behaviour requires error detection resulting in remedial actions, such as immediate error correction. The present event-related functional magnetic resonance imaging study in humans examined the neural correlates of error detection and error correction using a speeded modified flankers task. In order to investigate corrective behaviour, participants were randomly divided into two groups. The correction instructed group was asked to correct all encountered errors immediately. The correction not instructed group was unaware that corrective responses were recorded. The intention to correct errors significantly increased the correction rate. Brain activations correlating with error detection were isolated in the rostral cingulate zone and in the pre-supplementary motor area, supporting their important role in error processing. Error correction activated similar brain regions, suggesting a common neuroanatomical substrate. Additional activations were found in the parietal cortex, representing an interconnected cortical network, which processes somatosensory information of tactile stimuli.

Introduction

Error detection is an important domain of performance monitoring. It enables a person to correct his/her errors in order to reach the intended goal. In current research, subsequent behavioural effects of errors have been considered to a lesser extent than the error detection process itself. Two kinds of corrective behaviour can be distinguished: immediate error corrections and long-term adjustments, such as post-error slowing. Behavioural studies have reported that volunteers tended to correct their responses immediately after they had committed an error (Rabbitt, 1966). Error correction is suggested to be centrally generated and can occur as rapidly as around 30–150 ms after the error (Higgins & Angel, 1970; Angel, 1976; Cooke & Diggles, 1984).

It has been proposed that the posterior portion of the anterior cingulate cortex (ACC) and the adjacent frontomedian cortex (FMC) play a crucial role in error detection as well as in the detection of response conflict (Carter *et al.*, 1998; Kiehl *et al.*, 2000; MacDonald *et al.*, 2000; Botvinick *et al.*, 2001; Mathalon *et al.*, 2003; Yeung *et al.*, 2004). Recently published data suggested a regional dissociation along the midline between the two processes. Whereas error detection preferentially activated the rostral cingulate zone (RCZ; cf. Picard & Strick, 1996), response conflict was accompanied by activations of the pre-supplementary motor area (pre-SMA) and mesial Brodmann area (BA) 8 (Ullsperger & von Cramon, 2001, 2004; Garavan *et al.*, 2002, 2003). Studies using single cell recording in monkeys revealed evidence that the monkey homologue of the RCZ, the rostral cingulate motor area (rCMA), is also related to an alternation in behaviour after detecting an error (Shima & Tanji, 1998; Ito *et al.*, 2003). Garavan *et al.* (2002) investigated prolonged effects of errors by means of functional

magnetic resonance imaging (fMRI), and revealed a higher activation in the RCZ and the pre-SMA bilaterally, the left inferior frontal and precentral gyri and the right putamen. To our knowledge, there are no fMRI studies examining the neural correlate of short-term adjustments.

The present study aimed to investigate the neural correlates of immediate error correction. We addressed the issue of whether both processes, error detection and error correction, rely on a common neuroanatomical substrate. Considering the cortical function of the RCZ in performance processing (Botvinick *et al.*, 2001; Ullsperger & von Cramon, 2001) and of the pre-SMA in motor planning (Tanji, 1994), we assumed that similar areas engaged in error detection are also needed for the implementation of immediate error correction.

Methods

Participants

Thirty-one individuals participated in the experiment. They were randomly divided into two groups: in one group participants were instructed to correct their errors immediately by pressing the correct button after an erroneous answer (correction instructed, CI), and in the second group the possibility to correct errors was not mentioned in the instruction (correction not instructed, CN). To guarantee homogeneous corrective behaviour within each group, exclusion criteria for the two samples were chosen. Participants in the CI group were excluded from analysis when they showed a correction rate below 50%, whereas in the CN group participants with a correction rate above 50% were excluded. Data from three volunteers met these exclusion criteria. Furthermore, one participant was excluded because of an error rate below 10%, resulting in an insufficient number of error trials to allow meaningful statistical analysis. The sample of 27 healthy volunteers (CI group: $n = 14$, six female; CN group: $n = 13$, five female) was

Correspondence: K. Fiehler, as above.

E-mail: fiehler@cbs.mpg.de

Received 24 March 2004, accepted 2 April 2004

3082 K. Fiehler *et al.*

right-handed and had normal or corrected-to-normal vision. Their age ranged from 21 to 35 years (mean 25 years). Written informed consent according to the declaration of Helsinki was obtained from each participant and the rights of the volunteers were protected. They were paid for their participation.

Procedure

A speeded modified flanker task known to yield high error rates was used in the study (Ullsperger & von Cramon, 2001). In the task, participants were presented with a fixation mark for 900 ms at the centre of a screen, after which four flanker arrows occurred for 150 ms. The arrows were 0.46° high and 1.08° wide, and appeared 0.52° and 1.04° above and below the screen centre. The target arrow was presented for 30 ms in the centre of the flanker arrows; its onset was delayed by 90 ms from the onset of the flanker arrow. In half of the trials (162 trials) the flankers pointed in the same direction as the target (compatible trial) and in the other half of the trials (162 trials) in the opposite direction (incompatible trial). Compatible and incompatible trials appeared in randomized order. Participants were instructed to respond with maximal speed and accuracy to the target arrow with the hand indicated by the direction, in which the target arrow pointed. Additionally, members of the CI group were instructed to correct errors, whenever they noticed one.

To yield a sufficient error rate, the response deadline was individually estimated based on the performance in two subsequent training sessions (160 trials each) prior to the experimental session. When the response deadline was exceeded, the response was followed by a feedback with the request to speed up responding.

Imaging

Imaging was performed at 3 T on a Bruker (Ettlingen, Germany) Medspec 30/100 system equipped with the standard bird-cage head coil. Twenty slices (thickness 4 mm, spacing 1 mm) were positioned parallel to the anterior commissure – posterior commissure (AC–PC) plane covering the whole brain. Prior to the functional runs, a set of two-dimensional (2D) anatomical images was acquired for each participant using an anatomical modified driven equilibrium Fourier transform (MDEFT) sequence (256×256 -pixel matrix). Functional images in plane with the anatomical images were acquired using a single-shot gradient echo-planar imaging (EPI) sequence ($T_R = 2$ ms; $T_E = 30$ ms; 64×64 -pixel matrix; flip angle 90° ; field of view 192 mm) sensitive to blood-oxygen level-dependent (BOLD) contrast. In order to improve temporal resolution for modelling of the haemodynamic response, an interleaved design was employed (Miezin *et al.*, 2000).

In a separate session, high-resolution whole brain images were acquired from each participant to improve the localization of activation foci using a T1-weighted 3D segmented MDEFT sequence covering the whole brain.

Data analysis

The fMRI data were processed using the software package LIPSIA (Lohmann *et al.*, 2001). In the pre-processing, low-frequency signals were suppressed by applying a $1/120$ Hz highpass filter. Spatial smoothing was applied by means of a Gaussian filter with 5.65 mm full width at half maximum (FWHM). The increased autocorrelation caused by the filtering was taken into account during statistical analysis by adjusting the degrees of freedom (Worsley & Friston, 1995). Functional data were corrected for slice-time acquisition differences using a sinc-interpolation algorithm based on the Nyquist–Shannon theorem (Stark & Bradley, 1992). In addition, the data were corrected for motion artefacts using a matching metric based

on linear correlation for geometrical alignment. Co-registration of the anatomical and functional data was performed in three steps. First, the anatomical slices (MDEFT) were geometrically aligned with the functional slices (EPI-T1). These were used to compute a transformation matrix, containing rotational and translational parameters, that register the anatomical slices with the 3D reference T1-data set. Second, each individual transformation matrix was scaled to the standard Talairach brain size (Talairach & Tournoux, 1988) by applying linear scaling. In the final step, these normalized transformation matrices were applied to the individual functional raw data. Slice gaps were scaled using a trilinear interpolation, generating output data with a spatial resolution of $3 \times 3 \times 3$ mm (27 mm³).

The statistical analysis was based on a least-squares estimation using the general linear model (GLM) for serially auto-correlated observations (random effects model; Friston *et al.*, 1995; Worsley & Friston, 1995; Zarahn *et al.*, 1997). The design matrix was generated with a synthetic haemodynamic response function (Friston *et al.*, 1998). Incompatible correct trials in-time and incompatible erroneous trials in-time (CI group, corrected errors; CN group, uncorrected errors) were used as predictors in the GLM to calculate contrasts (see below). Erroneous compatible trials were excluded from statistical analysis because of an insufficient trial number ($<4\%$). Late responses and compatible pre-deadline responses were used as additional predictors in the GLM. The model equation, including the observation data, the design matrix and the error term, was convolved with a Gaussian kernel of dispersion of 4 s FWHM. The model includes an estimate of temporal autocorrelation that is used to estimate the effective degrees of freedom (Worsley & Friston, 1995). As the individual functional data sets were all aligned to the same stereotactic reference space, a group analysis was subsequently performed.

The following contrasts were calculated. ‘Error-related brain activity’ is reflected by the contrast incompatible erroneous trials vs. incompatible correct trials. The resulting statistical parametric map was thresholded at $P < 0.001$ (uncorrected). Local maxima of the z -maps residing in activation areas of size smaller than 360 mm³ (= eight measured voxels) are not reported to minimize the probability of false positive results. In order to investigate the brain activity related to immediate ‘error correction’, a between-group analysis was employed contrasting the brain activity on corrected errors performed in the CI group vs. the brain activity on uncorrected errors performed in the CN group. The comparison was confined to regions that were significantly activated during errors in at least one of both groups. The between-group analysis consisted of a two-sample t -test to compare both groups against each other. Because of the anatomical variability of the observed cortical regions, a liberal threshold at $P < 0.05$ (uncorrected) was used for the resulting statistical parametric map of the group comparison. Results are given as mean \pm SEM below.

Results

Behavioural data

The behavioural data revealed instruction-based behaviour: volunteers in the CI group corrected their errors significantly more often ($82 \pm 4\%$) than volunteers in the CN group (21 ± 6 ; $t_{25} = 8.7$, $P < 0.0001$). The correction time was 104 ± 10 ms for the CN group and 161 ± 11 ms for the CI group and differed significantly between the two groups ($t_{24} = 3.7$, $P < 0.01$).

As depicted in Table 1, typical effects of incompatibility were found for both reaction times and error rates. Correct response times were submitted to an ANOVA with Compatibility as the within-factor and

TABLE 1. Proportions and reaction times of correct, erroneous and late responses for each stimulus type

| | CN group | | CI group | |
|--------------------|------------|--------------|------------|--------------|
| | Compatible | Incompatible | Compatible | Incompatible |
| Response rate (%) | | | | |
| Correct | 93 ± 2 | 43 ± 5 | 89 ± 2 | 42 ± 5 |
| Error | 2 ± 0.3 | 34 ± 3 | 4 ± 1 | 39 ± 3 |
| Correct late | 5 ± 1 | 22 ± 3 | 7 ± 1 | 17 ± 3 |
| Error late | 1 ± 0.3 | 2 ± 1 | 1 ± 0.3 | 2 ± 1 |
| Reaction time (ms) | | | | |
| Correct | 362 ± 6 | 421 ± 7 | 359 ± 5 | 414 ± 5 |
| Error | – | 334 ± 6 | – | 334 ± 6 |
| Correct late | 500 ± 9 | 489 ± 10 | 498 ± 9 | 491 ± 9 |
| Error late | – | – | – | – |

Data are presented as means ± SEM. CN, correction not instructed; CI, correction instructed; –, too few trials for meaningful analyses.

Group as the between-factor. The analysis revealed a significant main effect of Compatibility, reflecting longer reaction times for incompatible correct trials (416 ± 4 ms) than for compatible correct trials (360 ± 4 ms; $F_{1,25} = 1035.4$, $P < 0.0001$). Secondly, error rates were higher for incompatible trials ($37 \pm 2\%$) compared with compatible trials ($3 \pm 1\%$; $F_{1,25} = 290.4$, $P < 0.0001$). Consistent with previous findings, volunteers were significantly faster on incompatible erroneous trials (334 ± 4 ms) than on incompatible correct trials (417 ± 4 ms; $F_{1,25} = 651.8$, $P < 0.0001$). All three ANOVAs revealed no interaction with the factor Group ($P > 0.12$).

fMRI data

Error detection

The first question we addressed in the analysis of the fMRI data was the haemodynamic response related to error detection. A complete list of significant activations in the contrast 'incompatible correct trials' vs. 'incompatible erroneous trials' reflecting error-related signal increase is presented in Table 2.

The fMRI data revealed a clear activation pattern. On errors, the focus of the haemodynamic activity was localized on the frontomedian wall, specifically in two areas: the pre-SMA bilaterally and the right RCZ. As illustrated in Fig. 1, there was a widespread activation in the pre-SMA extending into BA 32. The error-related activation in the RCZ was located on the border BA 24/BA 32 and showed a more focal distribution.

TABLE 2. Anatomical specification, Brodmann area and Talairach coordinates (x, y, z) of voxels co-varying significantly ($P < 0.001$) with error detection (incompatible erroneous vs. incompatible correct)

| Brain region | Brodmann area | Talairach coordinates | | |
|--------------|---------------|-----------------------|----|----|
| | | x | y | z |
| L pre-SMA | 6 | –2 | 6 | 62 |
| L pre-SMA | 8 | –2 | 15 | 53 |
| R pre-SMA | 6 | 7 | 21 | 62 |
| R pre-SMA | 8 | 1 | 30 | 56 |
| R RCZ | 24/32 | 1 | 21 | 38 |

R, right; L, left; SMA, supplementary motor area; RCZ, rostral cingulate zone. The same activations were found using a Bayesian second-level analysis (Neumann & Lohmann, 2003) with a posterior probability above 99.9%, thus ruling out the possibility that the activations are false positive findings.

Error correction

To investigate haemodynamic correlates of immediate error correction, corrected errors occurring in the CI group were compared with uncorrected errors occurring in the CN group by using a two-sample *t*-test. Figure 2 shows the activation foci related to immediate error correction on the frontomedian wall based on common significant activation foci in at least one of the two groups (see Table 3). The trial-averaged time courses of the fMRI signal are depicted at the top of the displayed activation.

Consistent with the results reported for error detection, the fMRI data revealed activation foci in the left pre-SMA and the right RCZ associated with immediate error correction. Both areas showed a higher haemodynamic activation for corrected error trials than for uncorrected error trials (cf. trial averaged time courses in Fig. 2).

Additional activations associated with error correction were found in the right caudal part of the SMA (SMA proper) and in the left cuneus. An interesting activation pattern was also observed in the parietal cortex of the right hemisphere (cf. Fig. 3). The data revealed a higher haemodynamic response for corrected errors in the parietal operculum, an area located between the central sulcus and the posterior ascending branch of the Sylvian fissure, where an imaginary lateral extension of the postcentral sulcus points to the middle of the parietal operculum. Separated activation foci were also found in two areas superior to the parietal operculum: one on the crown of the postcentral gyrus, and a second focus in the supramarginal gyrus posterior to the parietal operculum and adjacent to the posterior ascending branch of the Sylvian fissure.

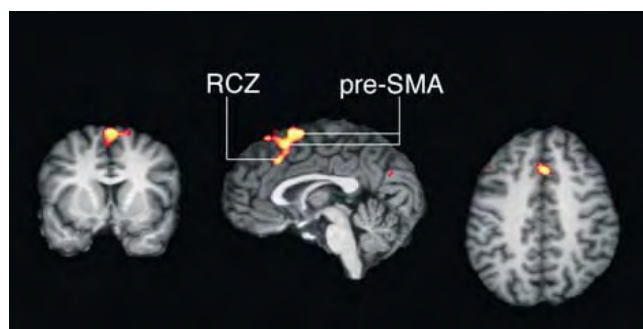


FIG. 1. Cortical activations of the contrast of incompatible erroneous trials vs. incompatible correct trials on coronal ($y = 8$), sagittal ($x = 1$) and axial ($z = 38$) slices of a 3D structural MRI; RCZ, rostral cingulate zone; SMA, supplementary motor area.

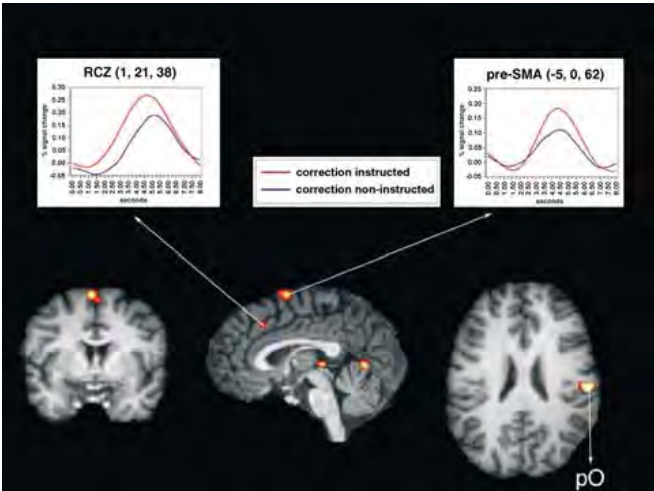


Fig. 2. Cortical activations of the contrast of corrected erroneous trials vs. uncorrected erroneous trials on coronal ($y = 0$), sagittal ($x = -2$) and axial ($z = 24$) slices of a 3D structural MRI; activations in the cisterna cerebelli superior and in the cisterna laminae tecti were probably caused by pulsation artefacts; pO, parietal operculum. Top: trial averaged time courses of the two significantly activated areas on the frontomedian wall: superior pre-supplementary motor area (pre-SMA) ($x = -5$, $y = 0$, $z = 62$) and rostral cingulate zone (RCZ) ($x = 1$, $y = 21$, $z = 38$).

TABLE 3. Anatomical specification, Brodmann area and Talairach coordinates (x , y , z) of voxels co-varying significantly ($P < 0.05$) with immediate error correction (corrected incompatible erroneous vs. uncorrected incompatible erroneous)

| Brain region | Brodmann area | Talairach coordinates | | |
|-------------------------|---------------|-----------------------|-----|-----|
| | | x | y | z |
| L pre-SMA | 6 | -5 | 0 | 62 |
| R SMA proper | 6 | 4 | -6 | 56 |
| R RCZ | 24/32 | 1 | 21 | 38 |
| R parietal operculum | 40 | 55 | -24 | 24 |
| R gyrus supramarginalis | 39 | 61 | -33 | 38 |
| R gyrus post-centralis | 1 | 58 | -15 | 35 |
| L cuneus | 18 | -5 | -87 | 12 |

R, right; L, left; SMA, supplementary motor area; RCZ, rostral cingulate zone. The same activations were found using a Bayesian second-level analysis (Neumann & Lohmann, 2003) with a posterior probability above 98.4%, thus ruling out the possibility that the activations are false positive findings.

Discussion

The present fMRI study aimed at investigating error processing and immediate error correction. The results provide several new insights into functional implementation of the two processes and their relationship.

The data revealed evidence for an increase in error correction rates by experimental instruction. In accordance with the literature, participants who were instructed to correct errors were able to detect and correct errors very efficiently without being given an external signal that indicates a committed error (Rabbitt, 1966; Higgins & Angel, 1970). In line with the results by Rabbitt (1967), participants who were not instructed to correct errors also showed immediate error corrections but only in 20% of the errors.

Error detection

We replicated the findings that error detection is reflected by a distributed cortical network of brain regions with a focus in RCZ and superior pre-SMA (Carter *et al.*, 1998; Kiehl *et al.*, 2000;

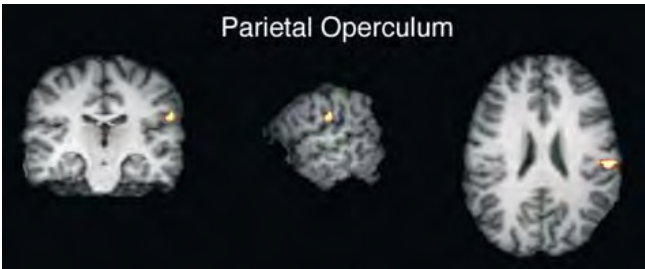


Fig. 3. Cortical activations of the contrast of corrected erroneous trials vs. uncorrected erroneous trials on coronal ($y = -24$), sagittal ($x = 55$) and axial ($z = 24$) slices of a 3D structural MRI.

Ullsperger & von Cramon, 2001; Garavan *et al.*, 2002, 2003). This result supports the notion that RCZ plays an important role in error detection. The role of pre-SMA in error detection is still questionable. Ullsperger & von Cramon (2004) speculated that the activation in pre-SMA is due to insufficient inhibition of the erroneous response. Following the response conflict model, Garavan *et al.* (2002) argued that activation of pre-SMA may also reflect post-response conflict (cf. Carter *et al.*, 1998; Botvinick *et al.*, 1999). However, the activation in pre-SMA reported in the present study was located posterior and superior to the activations associated with response conflict. In contrast to some previous studies (Kiehl *et al.*, 2000; Garavan *et al.*, 2002), no significant activation was found in lateral prefrontal cortex (LPFC). Regarding activation foci below spatial threshold, an activation maximum was observed in middle frontal gyrus (BA 9, coordinates: $x = -43$, $y = 23$, $z = 41$). It seems that error-related activation in LPFC is a more reliable finding for Go-NoGo tasks (Kiehl *et al.*, 2000; Garavan *et al.*, 2002) than for flanker tasks (see also Ullsperger & von Cramon, 2001, 2004). One may speculate that errors in Go-NoGo tasks result in more robust task-set-related adjustment processes reflected in lateral prefrontal activations (cf. Garavan *et al.*, 2004) than do flanker tasks.

Error correction

To investigate cortical areas related to immediate error correction, we contrasted corrected and uncorrected error trials. The major finding of this study is the increased activation in RCZ and in pre-SMA on both corrected and uncorrected errors. However, the common activated brain regions differed in strength of activation, showing a significantly greater haemodynamic response for corrected than for uncorrected errors.

The data suggest that cortical areas involved in error detection also play a role in the implementation of immediate error correction. According to the Talairach coordinates, the regional overlap of the maxima in RCZ was nearly perfect (cf. Tables 2 and 3). A clinical study reported a reduced error correction rate in a patient with an RCZ lesion assuming an involvement of RCZ in error correction (Swick & Turken, 2002). Taking the results by Garavan *et al.* (2002) into account, RCZ and pre-SMA seem not only to be involved in long-term adjustments as reported in their study, but also to be engaged in immediate corrective mechanisms as evidenced by the present data. Following this idea, both error detection and error correction activated cortical networks involving posterior fronto-medial cortex.

Neurons in the rCMA, the monkey homologue of the human RCZ, respond to alternations in motor behaviour (Shima & Tanji, 1998) after error detection in order to reach the intended goal (Ito *et al.*, 2003). The important role of the RCZ in corrective behaviour is strengthened by neuroanatomical findings in monkeys revealing direct projections from the rCMA to motor/premotor areas and the SMA to facilitate movement-related processes (Dum & Strick, 1991; Picard & Strick, 1996). Dum & Strick (1991) argued that rCMA has the potential to generate and control movements as necessary in corrective behaviour. Our findings fit very nicely with the monkey data. An increased activation in RCZ was found during error correction in terms of an alternation of motor behaviour after error detection.

An alternative view is provided by the response conflict monitoring hypothesis (Carter *et al.*, 1998; Botvinick *et al.*, 2001; Yeung *et al.*, 2004). In this view, an incompatible stimulus ensemble in a two-choice reaction time task initiates two competing response tendencies. The resulting competition between two response tendencies on correct trials is termed as pre-response conflict because it occurs before the response (Yeung *et al.*, 2004). Conflict following the response is

assumed only for error trials, the so-called post-response conflict (Yeung *et al.*, 2004). It arises between the executed (erroneous) response and the still evolving second (correct) response tendency. After premature execution of the erroneous response tendency, stimulus processing continues and may result in the execution of the second correct response tendency, the corrective response. If the second (correct) response tendency does not reach the response threshold, it does not result in the execution of the corrective response. The degree of post-response conflict depends on the relative activation level of two response tendencies: on corrected errors, the second response tendency would be stronger than on uncorrected errors, suggesting a larger post-response conflict for corrected errors (cf. Yeung *et al.*, 2004). fMRI studies suggest that ACC (Carter *et al.*, 1998; Botvinick *et al.*, 2001) or adjacent posterior frontomedian areas (Ullsperger & von Cramon, 2001, 2004; Garavan *et al.*, 2002, 2003) monitor response conflict. One could speculate that the increased activation in RCZ and pre-SMA during error correction found in the present data reflects an enhanced post-response conflict in the CI group caused by a stronger activation of the second correct response tendency. However, recently published data showed that RCZ is activated during errors even in the absence of response conflict, e.g. in feedback-based error processing (Ullsperger & von Cramon, 2003; Holroyd *et al.*, 2004). The question as to whether RCZ reflects post-response conflict or the initiation of remedial actions after errors cannot be determined on the basis of our current knowledge.

Furthermore, additional activation related to error correction was observed in the SMA proper, a region highly interconnected with the RCZ. Considering the dense projections from the SMA proper to the primary motor cortex and the spinal cord (Dum & Strick, 1991, 1993), this area is considered to be directly engaged in generating concrete motor commands, which is in accordance with its involvement in immediate error correction. By contrast, pre-SMA is more strongly connected to prefrontal cortices and more closely related to cognitive than to motor processes. Whereas pre-SMA operates at a more abstract level, activation of SMA proper reflects movement-related activation (Picard & Strick, 2001). In summary, from an anatomical point of view RCZ and pre-SMA are optimally qualified to be involved in the preparation of error correction. The higher activation in the SMA proper during error correction is likely to be related to the execution of the corrective response. This argument does not seem to be suitable for pre-SMA and RCZ, because these regions were also active in the error detection contrast when performed for the CN group alone, in which purely motor-related activations should be cancelled out.

Additional evidence comes from studies using event-related potential (ERP), which investigated the electrophysiological correlates of immediate error correction. Recently published data suggested a relation of the error-related negativity (ERN), a fronto-centrally distributed ERP component occurring 50–100 ms after the onset of an erroneous response (Falkenstein *et al.*, 1990; Gehring *et al.*, 1993), and corrective behaviour (Rodríguez-Fornells *et al.*, 2002). Dipole source modelling revealed evidence that the ERN is presumably generated in the RCZ (Dehaene *et al.*, 1994). Moreover, a recently published study reported a significant correlation between the ERN and fMRI activation in RCZ (Mathalon *et al.*, 2003). Very latest ERP findings have revealed a new ERP component associated with immediate error correction, the so-called correction-related negativity (CoRN), which also showed a fronto-central distribution over the scalp (K. Fiehler, M. Ullsperger and D. Y. von Cramon, unpublished observations). Taken together, one could speculate that the increased RCZ activity during error correction is a correlate either of the CoRN and/or of the ERN amplitude modulation.

The somatosensory network in error correction

The increased activation found for corrected errors in the posterior frontomedian cortex was accompanied by activations in the anterior parietal lobe. These activation foci represent an interconnected cortical network, which processes somatosensory information of tactile stimuli.

The activation in the post-central gyrus lies in the primary somatosensory cortex (SI) known as a cortical region for finger representation. Imaging studies indicated single and unique centres of mass for each finger (e.g. Francis *et al.*, 2000). The activation found in our data was located on the crown of the post-central gyrus (BA1). This area has been shown to represent the index finger, which was used by the participants to correct the errors in the present study.

The anatomical location of the activation in the parietal operculum coincides with the position of the secondary somatosensory cortex (SII) (Penfield & Boldrey, 1937). Activity in SII was reported, while volunteers performed motor tasks showing an enhanced response during active movements than during passive movements (Mima *et al.*, 1999). This motor-related modulation of SII activity suggests mechanisms for enhancing sensory information from a limb as a guide to behaviour involving that limb. During successive, targeted finger movements, enhanced sensory messages processed in SII are available to direct and control integrated sequential touching (Binkofski *et al.*, 1999). This area therefore appears to be qualified in the preparation and the initiation of the corrective response subsequent to the erroneous button press. Furthermore, Burton (2002) suggested that SII provides a conduit for information from cutaneous receptors to the motor cortex. Besides central error processing, this proprioceptive feedback mediated by SII can be used to enhance the error signal to initiate the corrective response.

The activation in the supramarginal gyrus represents the third cortical region of the somatosensory network and is best noted when participants receive discrete vibrotactile stimulation to a single fingertip (Burton, 2002). Considering the lack of visual motor response feedback in the scanner, vibrotactile information can be used to confirm a full button press (i.e. 'click-feeling').

Conclusions

The present study provides further evidence that the RCZ as well as the pre-SMA play a central role in error detection. Extending this finding, the data revealed that similar areas engaged in error detection are also involved in the implementation of immediate error correction, presumably reflecting a common neural substrate. Activations found in the parietal cortex represent an interconnected cortical network processing somatosensory information of tactile stimuli needed to perform the corrective behaviour successfully.

Abbreviations

ACC, anterior cingulate cortex; BA, Brodmann area; CoRN, correction-related negativity; EPI, echo-planar imaging; ERN, error-related negativity; ERP, event-related potential; FMC, frontomedian cortex; fMRI, functional magnetic resonance imaging; LPFC, lateral prefrontal cortex; MDEFT, modified driven equilibrium Fourier transform; pre-SMA, pre-supplementary motor area; rCMA, rostral cingulate motor area; RCZ, rostral cingulate zone.

References

- Angel, R.W. (1976) Efference copy in the control of movement. *Neurology*, **26**, 1164–1168.
- Binkofski, F., Buccino, G., Posse, S., Seitz, R., Rizzolatti, G. & Freund, H. (1999) A fronto-parietal circuit for object manipulation in man: evidence from an fMRI-study. *Eur. J. Neurosci.*, **11**, 3276–3286.

- Botvinick, M.M., Braver, T.S., Barch, D.M., Carter, C.S. & Cohen, J.D. (2001) Conflict monitoring and cognitive control. *Psychol. Rev.*, **108**, 624–652.
- Botvinick, M., Nystrom, L.E., Fissell, K., Carter, C.S. & Cohen, J.D. (1999) Conflict monitoring versus selection-for action in anterior cingulate cortex. *Nature*, **402**, 179–181.
- Burton, H. (2002) Cerebral cortical regions devoted to the somatosensory system: results from brain imaging studies in humans. In Nelson, R.J. (Ed.), *The Somatosensory System*. CRC Press, Boca Raton, FL, pp. 27–72.
- Carter, C.S., Braver, T.S., Barch, D.M., Botvinick, M.M., Noll, D. & Cohen, J.D. (1998) Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science*, **280**, 747–749.
- Cooke, J.D. & Diggles, V.A. (1984) Rapid error correction during human arm movements: evidence for central monitoring. *J. Motor Behav.*, **16**, 348–363.
- Dehaene, S., Posner, M.I. & Tucker, D.M. (1994) Localization of a neural system for error detection and compensation. *Psychol. Sci.*, **5**, 303–305.
- Dum, R. & Strick, P. (1991) The origin of corticospinal projections from the premotor areas in the frontal lobe. *J. Neurosci.*, **11**, 667–689.
- Dum, R. & Strick, P. (1993) Cingulate motor areas. In Vogt, B.A. & Gabriel, M. (Eds), *Neurobiology of Cingulate Cortex and Limbic Thalamus*. Birkhäuser, Boston, MA, pp. 415–441.
- Falkenstein, M., Hohnsbein, J., Hoormann, J. & Blanke, L. (1990) Effects of errors in choice reaction time tasks on the ERP under focussed and divided attention. In: Brunia, C.H.M., Gaillard, A.W.K. & Kok, A. (Eds), *Psychophysiol. Brain Research*. Tilburg University Press, Tilburg, pp. 192–195.
- Francis, S., Kelly, E., Bowtell, R., Dunseath, W., Folger, S. & McGlone, F. (2000) fMRI of the responses to vibratory stimulation of digit tips. *Neuroimage*, **11**, 188–202.
- Friston, K., Fletcher, P., Josephs, O., Holmes, A., Rugg, M.D. & Turner, R. (1998) Event-related fMRI: characterizing differential responses. *Neuroimage*, **7**, 30–40.
- Friston, K., Holmes, A.P., Worsley, K.J., Poline, J.-P., Frith, C.D. & Frackowiak, R.S.J. (1995) Statistical parametric maps in functional imaging: a general linear approach. *Hum. Brain Mapp.*, **2**, 189–210.
- Garavan, H., Hester, R. & Fassbender, C. (2004) The impact of individual differences and prefrontal control on action monitoring revealed through fMRI. In Ullsperger, M. & Falkenstein, M. (Eds), *Errors, Conflicts, and the Brain. Current Opinions on Performance Monitoring*. MPI for Human Cognitive and Brain Sciences, Leipzig, pp. 47–54.
- Garavan, H., Ross, T.J., Kaufman, J. & Stein, E.A. (2003) A midline dissociation between error-processing and response-conflict monitoring. *Neuroimage*, **20**, 1132–1139.
- Garavan, H., Ross, T.J., Murphy, K., Roche, R.A.P. & Stein, E.A. (2002) Dissociable executive functions in the dynamic control of behavior: inhibition, error detection, and correction. *Neuroimage*, **17**, 1820–1829.
- Gehring, W.J., Goss, B., Coles, M.G.H., Meyer, D.E. & Donchin, E. (1993) A neural system for error detection and compensation. *Am. Psychol. Soc.*, **4**, 385–390.
- Higgins, J.R. & Angel, R.W. (1970) Correction of tracking errors without sensory feedback. *J. Exp. Psychol.*, **84**, 412–416.
- Holroyd, C.B., Nieuwenhuis, S., Yeung, N., Nystrom, L., Mars, R.B., Coles, M.G.H. & Cohen, J.D. (2004) Dorsal anterior cingulate cortex shows fMRI response to internal and external error signals. *Nature Neurosci.*, **7**, 497–498.
- Ito, S., Stuphorn, V., Brown, J.W. & Schall, J.D. (2003) Performance monitoring by the anterior cingulate cortex during saccade countermanding. *Science*, **302**, 120–122.
- Kiehl, K.A., Liddle, P.F. & Hopfinger, J.B. (2000) Error processing and the rostral anterior cingulate: an event-related fMRI study. *Psychophysiology*, **37**, 216–223.
- Lohmann, G., Mueller, K., Bosch, V., Mentzel, H., Hessler, S., Chen, L., Zysset, S. & von Cramon, D.Y. (2001) Lipsia – a new software system for the evaluation of functional magnetic resonance images of the human brain. *Comput. Med. Imag. Grap.*, **25**, 449–457.
- MacDonald, A.W., III, Cohen, J.D., Stenger, V.A. & Carter, C.S. (2000) Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science*, **288**, 1835–1837.
- Mathalon, D.H., Whitfield, S.L. & Ford, J.M. (2003) Anatomy of an error: ERP and fMRI. *Biol. Psychol.*, **64**, 119–141.
- Miezin, F.M., Maccotta, L., Ollinger, J.M., Petersen, S.E. & Buckner, R.L. (2000) Characterizing the hemodynamic response: effects of presentation rate, sampling procedure, and the possibility of ordering brain activity based on relative timing. *Neuroimage*, **11**, 735–759.
- Mima, T., Sadato, N., Yazawa, S., Hanakawa, T., Fukuyama, H., Yonekura, Y. & Shibasaki, H. (1999) Brain structures related to active and passive finger movements in man. *Brain*, **122**, 1989–1997.

- Neumann, J. & Lohmann, G. (2003) Bayesian second-level analysis of functional magnetic resonance images. *Neuroimage*, **20**, 1346–1355.
- Penfield, W. & Boldrey, E. (1937) Somatic motor and sensory representation in the cerebral cortex of man studied by electrical stimulation. *Brain*, **60**, 389–443.
- Picard, N. & Strick, P.L. (2001) Imaging the premotor areas. *Curr. Opin. Neurobiol.*, **11**, 663–672.
- Picard, N. & Strick, P.L. (1996) Motor areas of the medial wall: a review of their location and functional activation. *Cereb. Cortex*, **6**, 342–353.
- Rabbitt, P.M.A. (1966) Error correction time without external error signals. *Nature*, **22**, 438.
- Rabbitt, P.M.A. (1967) Time to detect errors as a function affecting choice-response time. *Acta Psychol.*, **27**, 131–142.
- Rodriguez-Fornells, A., Kurzbuch, A. & Muentz, T. (2002) Time course of error detection and correction in humans: neurophysiological evidence. *J. Neurosci.*, **22**, 9990–9996.
- Shima, K. & Tanji, J. (1998) Role for cingulate motor area cells in voluntary movement selection based on reward. *Science*, **282**, 1335–1338.
- Stark, D.D. & Bradley, W.G. (1992) *Magnetic Resonance Imaging*. Mosby-Year Book, St Louis.
- Swick, D. & Turken, A. (2002) Dissociation between conflict detection and error monitoring in the human anterior cingulate cortex. *Proc. Natl Acad. Sci. USA*, **99**, 16354–16359.
- Talairach, J. & Tournoux, P. (1988) *Co-Planar Stereotaxis Atlas of the Human Brain*. Thieme, New York.
- Tanji, J. (1994) The supplementary motor area in the cerebral cortex. *Neurosci. Res.*, **19**, 251–268.
- Ullsperger, M. & von Cramon, D.Y. (2001) Subprocesses of performance monitoring: a dissociation of error processing and response competition revealed by event-related fMRI and ERPs. *Neuroimage*, **14**, 1387–1401.
- Ullsperger, M. & von Cramon, D.Y. (2003) Error monitoring using external feedback: specific roles of the habenular complex, the reward system, and the cingulate motor area revealed by fMRI. *J. Neurosci.*, **23**, 4308–4314.
- Ullsperger, M. & von Cramon, D.Y. (2004) Neuroimaging of performance monitoring: Error detection and beyond. *Cortex* (Special Issue on Neuroimaging Higher Cognitive Function), in press.
- Worsley, K. & Friston, K. (1995) Analysis of fMRI time-series revisited – Again. *Neuroimage*, **2**, 359–365.
- Yeung, N., Botvinick, M.M. & Cohen, J.D. (2004) The neural basis of error detection: conflict monitoring and the error-related negativity. *Psychophysiol. Rev.*, in press.
- Zarahn, E., Aguirre, G.K. & D'Esposito, M. (1997) Empirical analysis of BOLD fMRI statistics. I. Spatially smoothed data collected under null-hypothesis and experimental conditions. *Neuroimage*, **5**, 179–197.

Chapter 11

Electrophysiological correlates of error correction

The fMRI study presented in the previous Chapter suggests that the RCZ is more active when errors are corrected than during error processing alone. While a number of electrophysiological studies has examined the relationship of the ERN with subsequent error corrections, the results are equivocal. This Chapter reviews previous reports on this issue and presents the results of an ERP study investigating error correction in a between-subjects design equivalent to the fMRI study in Chapter 10.

The study replicated the finding that the instruction to correct errors results in a significant increase of immediate error corrections, such that almost all errors are corrected. Distributional analyses revealed that this increase in error corrections is – to a large degree – a result of a gain in slow error corrections. We suggest that slow intentional corrections result from performance monitoring – the error correction is executed as a result of error detection. In contrast, incidental (spontaneous) error corrections occurring even without explicit instructions to correct errors have been suggested not to require error processing but rather to result from the correct response tendency which still evolves while the premature erroneous response is being issued. Thus, the seemingly corrective response could be a delayed correct response instead (Rabbitt, 2002).

The pattern of ERP results is discussed with respect to the different models of performance monitoring. The ERN latency results are consistent with the response conflict monitoring theory. However, the ERN amplitude results do not appear to be consistent with any of the current models. At a within-group level, no significant amplitude modulations were found (e.g., comparing corrected and uncorrected errors in the non-instructed group). However, between groups a surprising difference was revealed: the ERN was larger in the group not instructed to correct errors than in the instructed group. One interpretation of this finding is that the instruction to correct errors may modulate subjective error significance. This notion is supported by autonomic response data which we recorded simultaneously (Fiehler et al., 2004). In the non-instructed group errors were associated with stronger heart rate decelerations than in the instructed group (Figure IV-01). An alternative interpretation suggesting that the intention to immediately correct errors results in lowering the motor threshold is discussed in Chapter 12.

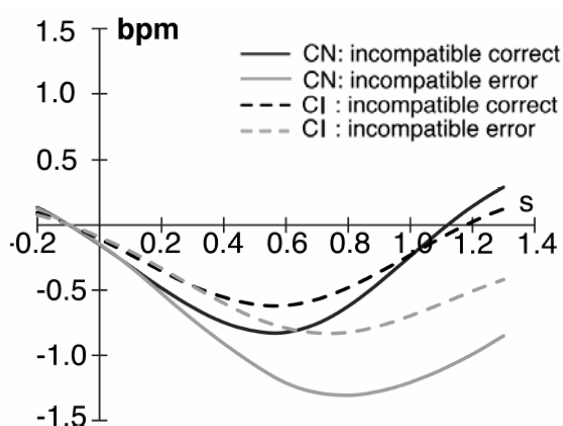


Figure IV-01.

Response-locked averages of HR changes in beats per minute (bpm) for incompatible correct trials (solid, black line) and uncorrected error trials (solid, gray line) in the non-instructed group (N=16) and for incompatible correct trials (dashed, black line) and corrected error trials (dashed, gray line) in the correction-instructed group (N=16). From Fiehler, Ullsperger, Grigutsch, and von Cramon (2004).

An important result reported in the present Chapter is the finding of an additional frontocentral negativity time-locked to the corrective response. With respect to the scalp topography and timing it is similar to the ERN and the CRN, but it seems to occur specifically after error corrections. Therefore, we have termed it correction-related negativity (CoRN). At the current stage, we can only speculate on the functional significance of the CoRN. It seems to reflect brain activity related to re-evaluation of the corrective action. We further speculate that the fMRI signal increase in the RCZ observed for corrected errors (see Chapter 10) could be a result of the activity reflected in the CoRN.

Electrophysiological correlates of error correction

KATJA FIEHLER, MARKUS ULLSPERGER, AND D. YVES VON CRAMON

Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany

Abstract

Evidence in the literature for the proposed relationship between the error-related negativity (ERN) and error correction is rather limited and inconsistent. We investigated corrective behavior and the ERN in two groups of participants who performed a flanker task. The correction-instructed group was asked to immediately correct all encountered errors. The noninstructed group was unaware that corrective responses were recorded. We found a negative deflection following corrected errors that peaked at 200–240 ms after the error. We refer to this negativity in the ERP waveform as correction-related negativity (CoRN). We assume that the correction-related negativity reflects evaluative functions of the motor system necessary for error corrections. ERN latency and amplitude were modulated by the occurrence and temporal characteristics of immediate corrections. These results are discussed within the framework of current models of performance monitoring.

Descriptors: Error correction, Error detection, Error-related negativity (ERN), Correction-related negativity (CoRN)

Whereas over the last decade research has mostly focused on error detection, the consequences of error detection—remedial actions—are less investigated and require further attention. The present study provides a first attempt to close this research gap by investigating the event-related potential (ERP) correlates of error correction. It builds on previous behavioral and ERP findings concerned with performance monitoring and extends these to the domain of error correction behavior.

ERP studies revealed a negative voltage component associated with errors, the error negativity (Ne; Falkenstein, Hohnsbein, Hoormann, & Blanke, 1990) or error-related negativity (ERN; Gehring, Goss, Coles, Meyer, & Donchin, 1993). It starts at the onset of the electromyographic (EMG) activity preceding the overt error response and peaks about 50 to 100 ms thereafter (Gehring et al., 1993; Kopp Rist, & Mattler, 1996). The ERN is fronto-centrally distributed over the scalp and presumably generated in the anterior cingulate cortex (ACC; Carter et al., 1998; Dehaene, Posner, & Tucker, 1994; Ullsperger & von Cramon, 2001, 2004), specifically in the human homolog of the monkey rostral cingulate motor area (rCMA), called the rostral cingulate zone (RCZ; cf. Picard & Strick, 1996).

It has been shown that the ERN is typically present when executed errors are easy to detect by the individual (action slip). An ERN-like wave is also elicited by external error feedback in reinforcement learning tasks (the feedback ERN; Badgaiyan & Posner, 1998; Holroyd & Coles, 2002; Miltner, Braun, & Coles, 1997), indicating at least the partial independence of error

processing from the motor system. Furthermore, the ERN is unaffected by perceptual properties of the stimuli (Bernstein, Scheffers, & Coles, 1995), stimulus modality (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991), and response modality (Falkenstein, Hoormann, Christ, & Hohnsbein, 2000; Gehring & Fencsik, 2001; Holroyd, Dien, & Coles, 1998; Miltner et al., 1997; Nieuwenhuis, Ridderinkhof, Blom, Band, & Kok, 2001); however, the ERN appears to be modulated by individual error salience (Bernstein et al., 1995; Gehring, Himle, & Nisenson, 2000; Luu, Collins, & Tucker, 2000; Pailing, Segalowitz, Dywan, & Davies, 2002; Ullsperger & Szymanowski, 2004).

A second ERP component has been described to be associated with errors, the error positivity (Pe; Falkenstein et al., 1990, 2000). It is a parietally distributed positivity occurring about 300–500 ms after the response, the functional significance of which is still rather unclear. As Falkenstein (2004) pointed out, three hypotheses for the Pe have been proposed. First, the Pe could reflect conscious error recognition (Falkenstein et al., 2000; Leuthold & Sommer, 1999; Nieuwenhuis et al., 2001); second, it could be an adaptation of response strategy (Leuthold & Sommer, 1999; Nieuwenhuis et al., 2001; but see Ullsperger & Szymanowski, 2004, for conflicting findings), or third, it could be subjective/emotional error processing (van Veen & Carter, 2002).

Error Correction

There is empirical evidence that errors result in adjustments to reach the intended goal and/or to prepare efficient behavior in similar subsequent situations. For example, participants slow down their responses following the occurrence of an error, the so-called post-error slowing effect (Rabbitt, 1966b). In addition, they mostly show overt corrective responses following errors. Behavioral studies reported that participants tended to correct their responses immediately after they had committed an error

This work was supported by the German Research Foundation (SPP 1107). K.F. and M.U. have equally contributed to this article. We thank M. Grigutsch for support in time-frequency decomposition.

Address reprint requests to: Katja Fiehler, Max Planck Institute for Human Cognitive and Brain Sciences, Stephanstr. 1A, D-04103 Leipzig, Germany. E-mail: fiehler@cbs.mpg.de.

without being given an external signal that an error had occurred (Cooke & Diggles, 1984; Rabbitt, 1966a, 1966b). These error-correcting responses were significantly faster than correct responses. A behavioral study by Rabbitt (2002) investigated error correction and error signaling in a serial-choice reaction-time task. In line with previous findings, participants quickly and accurately corrected most of their errors. Rabbitt (2002) argued that these very fast error corrections are “delayed correct responses,” initiated almost in parallel with the erroneous response and following briefly after them. Latest findings demonstrated that if participants are not instructed to correct errors, they allowed the majority of errors to remain uncorrected. In contrast, if they have been instructed to correct their errors, the percentage of error corrections can be raised up to nearly 100% (Fiehler, Ullsperger, & von Cramon, 2004). This gain in correction rate can be attributed to an intentional process and depends on the instructional context. Whether this intentional gain in error correction requires error detection remains an open question.

Few psychophysiological studies have systematically investigated the relationship between ERP components and error correction. These studies revealed inconsistent findings about whether ERN amplitude and latency vary as a function of whether errors are corrected or not. Concerning ERN amplitude, Gehring et al. (1993) observed a modulation of the ERN by error correction. The authors demonstrated that the larger the ERN, the greater the probability that the error would be corrected. Consistent with this result, Falkenstein, Hohnsbein, and Hoormann (1994) showed a larger ERN amplitude for corrected compared to uncorrected errors; however, this effect was only found after auditory and not after visual stimuli. In contrast, a later study of the same group reported an enhanced ERN amplitude for corrected than uncorrected errors after both auditory and visual stimuli (Falkenstein, Hohnsbein, & Hoormann, 1996). This finding was strengthened by recently published data showing a larger ERN for corrected than uncorrected errors (Rodríguez-Fornells, Kurzbuch, & Münte, 2002). Furthermore, this study revealed an increased ERN amplitude for fast compared to slow error corrections.

Inconsistent findings have also been reported with regard to ERN latency. Falkenstein et al. (1994) observed no latency differences of the ERN between corrected and uncorrected errors after either auditory or visual stimuli. In a later experiment of the same group, a modulation of ERN latency between corrected and uncorrected errors was exhibited revealing a later peak for uncorrected compared to corrected errors after both auditory and visual stimuli (Falkenstein et al., 1996). In contrast, a study by Rodríguez-Fornells et al. (2002) did not find latency differences of the ERN between corrected and uncorrected errors, nor between slow and fast error corrections.

Aims of the Study

Given the inconsistent picture of the relationship between the ERN and error correction provided by the literature, we investigated the time course of immediate error correction by means of behavioral data and ERPs. Furthermore, we studied whether correction speed modulates error-related ERP components.

To investigate corrective behavior, participants were randomly divided into two groups. One group was instructed to immediately correct all encountered errors (correction-instructed group), and a second group was unaware that corrective responses were recorded (noninstructed group). A similar design was used in the study by Rodríguez-Fornells et al. (2002) with an

important difference. Whereas in their study error correction was *forbidden* in one condition, we merely did not instruct immediate corrective behavior. Our design offers two noteworthy advantages: First, we can rule out additional processes of control or inhibition due to the prohibition of error correction, and second, we can conduct a supplementary comparison between incidental and intentional error correction to get a more detailed view of the error correction process.

Taking previous findings into account, the following predictions can be made. Both the correction-instructed group and the noninstructed group should show error correcting responses (e.g., Rabbitt, 1966a, 1966b); however, the correction-instructed group should commit significantly higher correction rates than the noninstructed group (e.g., Fiehler et al., 2004). Based on the majority of previous ERP studies one should expect a larger ERN amplitude for corrected than uncorrected errors (Falkenstein et al., 1996; Gehring et al., 1993; Rodríguez-Fornells et al., 2002; but see Falkenstein et al., 1994) and a similar ERN time course of these two conditions (Falkenstein et al., 1994; Gehring et al., 1993; Rodríguez-Fornells et al., 2002; but see Falkenstein et al., 1996). Moreover, ERN amplitude should be modulated by correction speed exhibiting a larger ERN for quickly compared to slowly corrected errors (Rodríguez-Fornells et al., 2002).

Methods

Participants

Forty-four individuals participated in the experiment. They were randomly divided into two groups: In one group, participants were instructed to correct their errors immediately by pressing the correct button after an erroneous response (correction-instructed group) and in the second group, the possibility to correct errors was not mentioned in the instruction (noninstructed group). It is important to note that all participants were naive to the experiment and did not participate in any previous experiment involving immediate error correction. Data from 4 participants were excluded from analyses, 2 participants for an error rate below 10% resulting in an insufficient number of error trials to form meaningful ERPs and 2 participants for disregarding the experimental instruction. The sample of 40 participants (21 female) was right-handed and had normal or corrected-to-normal vision. They ranged in age from 20 to 31 years ($M = 24$, $SEM = 0.4$). Written informed consent according to the Declaration of Helsinki was obtained from each participant and the rights of the participants were protected. They were paid for participation.

Procedure

A speeded modified flankers task known to elicit the ERN was used in the study (Ullsperger & von Cramon, 2001). The experiment comprised five experimental blocks of 10 min. After each block, participants had the possibility to relax for a short time before the next block started. In the task, participants were presented with a fixation mark for about 500 ms at the center of a screen, after which four flanker arrows occurred for 110 ms. The arrows were 0.46° tall and 1.08° wide, and appeared 0.52° and 1.04° above and below the screen center. The target arrow was presented for 30 ms in the center of the flanker arrows; its onset was delayed by 80 ms from the flanker's onset. In 45% of trials (540 trials) the flankers pointed in the same direction as the target (compatible trial) and in the other 55% of the trials (660 trials) in

the opposite direction (incompatible trial). Compatible and incompatible trials appeared in randomized order. Participants were instructed to respond with maximal speed and accuracy to the target arrow. The target arrow pointing to the left required a left-hand response and the target arrow pointing to the right required a right-hand response. Additionally, members of the correction-instructed group were instructed to correct any errors they detected. Each response was followed by a symbolic feedback (600 ms) about response speed, informing participants whether their answer was fast enough or should be speeded up. After the feedback a fixation cross was presented for 500 ms, such that the intertrial interval amounted to 2580 ms.

We introduced an adaptive algorithm, which dynamically adjusted the response time pressure based on the participant's performance. The algorithm aimed at an optimization of error rate (goal: 20% incompatible errors) and late response rates (as low as possible). This procedure helped to reduce drop-outs for a low number of error trials. The mean response deadlines were comparable between the noninstructed group ($M = 434$ ms, $SEM = 13$) and the correction-instructed group ($M = 444$ ms, $SEM = 9$), $t(38) = -0.6$, $p > .58$.

Psychophysiological Recording

The participants were seated comfortably in a dimly lit, electrically shielded chamber. The electroencephalogram (EEG) was recorded with Ag/AgCl electrodes from 51 electrode sites (the extended 10–20 system) referenced to left mastoid and off-line re-referenced to linked mastoids. Electrode impedance was kept below 5 k Ω . The vertical electrooculogram (EOG) was recorded from electrodes placed above and below the right eye. To monitor horizontal eye movements the EOG was collected from electrodes placed on the outer canthus of the left and right eye. EEG and EOG were recorded continuously with a low-pass filter of 70 Hz and AD converted with 22-bit resolution at a sampling rate of 250 Hz.

The ERP signals were response-locked averaged separately for incompatible correct and incompatible erroneous trials starting 100 ms before the response and continuing 600 ms post-response. Compatible trials were excluded from statistical analyses, because of an insufficient number of error trials (<1%). Late responses (delivered after the response deadline) were also excluded from analyses. The average voltage in the 100 ms preceding the onset of the flanker arrows served as baseline. The single trial EEG signals were corrected for horizontal and vertical EOG artifacts by means of an eye movement correction procedure (Pfeifer, 1993) based on a linear regression method described by Gratton, Coles, and Donchin (1983).

In the response-locked averages, peak-to-peak measurements were calculated to determine baseline-independent amplitudes of negative deflections by subtracting the amplitude of the preceding positive peak from the subsequent negative peak of the components of interest. The time search windows of the ERN and the Pe were chosen a priori (cf. Falkenstein et al., 2000). For the ERN, two early time windows were defined from -80 ms to 0 ms for the positive peak preceding the ERN and from 0 ms to 120 ms for the ERN component. Because the Pe is a more sustained positive deflection, peak search was not possible in many participants' data. Therefore, the mean amplitude in the late time window from 300 ms to 500 ms was used for statistical analysis. To investigate the observed negative deflection following the ERN (see Results section), two middle time windows centered around this negativity were chosen post hoc: first, a time window

from 100 ms to 180 ms for the positive peak preceding the negativity and, second, a time window from 120 ms to 300 ms for the negative deflection. Because this negativity only occurred on corrected error trials, peak search was not possible for uncorrected error trials. Therefore, the mean amplitude in the middle time window of 150–250 ms was used to compare corrected and uncorrected errors within the noninstructed group. The negative peaks in the early and middle time windows also served for obtaining latencies at the midline electrode FCz, where these deflections were maximal.

To avoid the loss of statistical power that occurs when repeated-measures ANOVAs are employed to quantify multichannel and multitime window data (Gevins et al., 1996; Oken & Chiappa, 1986), electrode sites were pooled to form six topographical regions. The following regions of interest were defined: left anterior (F5, FC3, FC5, C3), medial anterior (F3, Fz, F4, FCz), right anterior (F6, FC4, FC6, C4), left posterior (CP3, P5, P3, PO7), medial posterior (Pz, PO3, POz, PO4), and right posterior (CP4, P4, P6, PO8). For illustration purposes, a low-pass filter with a cutoff frequency of 15 Hz was applied.

Statistical Analyses

Response times were defined as the time between target onset and button press. Correction time was calculated as the response time difference between the erroneous and the subsequent corrective response.

The ERP statistics were based on a four-way repeated-measures ANOVA with the within-subject factors Response Type (two levels: correct and erroneous responses), Anterior-Posterior Dimension (two levels: anterior and posterior scalp regions), Lateral Dimension (three levels: right, middle, and left scalp region) and the between-subject factor Group (two levels: correction-instructed group and noninstructed group). Subsequently, lower order ANOVAs and t tests were computed to analyze resulting interactions. All effects with more than one degree of freedom in the numerator were adjusted for violations of sphericity according to the formula of Greenhouse and Geisser (1959). Reported effects revealed in lower order ANOVAs also reached significance using Bonferroni correction ($\alpha = .05/n$, where α is the probability of Type I error and n is the number of comparisons; Huberty & Morris, 1989). To avoid reporting large amounts of statistical results not relevant to the issues under investigation, only main effects or interactions including the Response Type, Correction Type, and Group factors are described. Scalp potential topographic maps were generated using a two-dimensional spherical spline interpolation (Perrin, Pernier, Bertrand, & Echallier, 1989) and a radial projection from Cz, which respects the length of the median arcs.

Results

Behavioral Data

As depicted in Table 1, typical effects of incompatibility were found for both reaction times and error rates. Correct response times, including in-time and late correct responses, and error rates were submitted to separate ANOVAs with the within-factor Compatibility and the between-factor Group. The analysis of correct response times revealed a significant main effect of Compatibility reflecting longer reaction times for incompatible correct trials than for compatible correct trials, $F(1,38) = 1653.2$, $p < .0001$. Error rates were higher for incompatible trials

Table 1. Mean Proportion and Reaction Times of Correct, Erroneous, and Late Responses for Each Stimulus Type

| | Noninstructed Group | | Correction-Instructed Group | |
|--------------|---------------------|--------------|-----------------------------|--------------|
| | Compatible | Incompatible | Compatible | Incompatible |
| Correct | 93.2 (1.5) | 59.6 (1.4) | 93.3 (1.4) | 61.4 (1.0) |
| Error | 0.7 (0.2) | 17.6 (1.2) | 1.0 (0.2) | 22.9 (1.9) |
| Correct late | 4.7 (0.7) | 20.9 (2.5) | 5.1 (1.4) | 15.1 (2.2) |
| Error late | 0.2 (0.1) | 0.5 (0.2) | 0.2 (0.03) | 0.2 (0.04) |
| Correct | 305 (5) | 369 (5) | 302 (5) | 368 (5) |
| Error | * | 270 (4) | * | 265 (3) |
| Correct late | 447 (14) | 438 (12) | 455 (14) | 437 (9) |
| Error late | * | * | * | * |

Notes: upper rows: response rates in percent; lower rows: reaction times in milliseconds. Standard error of the mean is presented in parentheses.

*Too few trials for meaningful analyses.

compared to compatible trials, $F(1,38) = 973.9$, $p < .0001$.¹ In addition, the noninstructed group showed lower error rates, $F(1,38) = 5.4$, $p < .05$, and a higher number of late responses, $F(1,38) = 4.7$, $p < .05$, compared to the correction-instructed group, suggesting a more cautious response behavior. Finally, an ANOVA with the within-factor Response Type (correct vs. erroneous) and the between-factor Group was performed for response times on incompatible trials. Consistent with previous findings, participants were faster on incompatible erroneous trials than on incompatible correct trials, $F(1,38) = 1909.6$, $p < .0001$.

To test whether performance on the trial immediately following an error differed between groups, we performed an ANOVA with the factors Previous Response Type (preceding correct vs. erroneous trial) and Group for dependent variables response time and error rate. The analysis of response time revealed a significant Previous Response Type \times Group interaction, $F(1,38) = 8.1$, $p < .01$. A subordinate within-group analysis showed a significant main effect of the factor Previous Response Type only in the noninstructed group, indicating longer reaction times of correct trials after errors ($M = 390$ ms, $SEM = 6$) than after correct responses ($M = 382$ ms, $SEM = 6$), $F(1,19) = 8.9$, $p < .01$.² The analysis of error rates also revealed a significant Previous Response Type \times Group interaction, $F(1,38) = 11.1$, $p < .01$, which was due to the fact that the noninstructed group produced more errors after erroneous responses ($M = 18\%$, $SEM = 2$) than after correct responses ($M = 13\%$, $SEM = 1$), whereas no such effect was present in the correction-instructed group ($M = 19$ vs. 19%).

Corrective Behavior

Participants in the correction-instructed group corrected their errors significantly more often ($M = 96\%$, $SEM = 1$) than participants in the noninstructed group ($M = 18\%$, $SEM = 3$), $t(38) = 7.3$, $p < .0001$. The mean correction time of 109 ms

($SEM = 8$) for the noninstructed group and of 200 ms ($SEM = 13$) for the correction-instructed group differed significantly, $t(38) = -6.0$, $p < .0001$.

Corrective behavior varied depending on the reaction times for erroneous responses. Figure 1A illustrates the percentage of corrected errors sorted into the reaction time quartiles of erroneous responses. These data were subjected to an ANOVA with the factors Quartile and Group revealing a significant interaction between these two factors, $F(3,78) = 29.7$, $p < .0001$, $\epsilon = .66$. This result suggests a different distribution of corrective behavior across reaction time quartiles. A subsequent within-group comparison showed an equivalent number of corrected errors within each quartile in the correction-instructed group, $F(3,39) = 1.4$, $p = .27$, $\epsilon = .50$, whereas the percentage of corrected errors significantly differed among the quartiles in the noninstructed group, $F(3,39) = 37.5$, $p < .0001$, $\epsilon = .70$. As illustrated in Figure 1A, the slower the reaction time for erroneous responses the larger was the percentage of corrected errors in the noninstructed group.

In addition, Figure 1A depicts the correction time for each error response time bin in the correction-instructed group (dotted line) showing that correction times decreased when error response time increased, resulting in a main effect of Quartile, $F(3,39) = 13.7$, $p < .0001$, $\epsilon = .69$. An analogous analysis was not possible for the noninstructed group due to an insufficient number of trials available. However, it appears that correction times associated with longest error response times (quartile 4) in the correction-instructed group (174 ms) were nearest to mean correction times in the noninstructed group (109 ms). Thus, it seems that fast corrections in the correction-instructed group were most comparable to incidental error corrections in the correction-instructed group.

This impression is further supported by the distribution of corrective responses across correction times in bins of 50 ms as depicted in Figure 1B. As reported above, there were more corrections in the correction-instructed group than in the noninstructed group across all correction time bins, $F(14,364) = 21.3$, $p < .0001$, $\epsilon = .22$. Incidental corrections in the noninstructed group fell mostly into the fastest correction time bins of the histogram whereas error corrections in the correction-instructed group showed mostly corrections in the slower correction time bins. The results suggest that the gain in error corrections in the correction-instructed group is mostly caused by an increase of slow error corrections. A large proportion of fast corrections seems to be independent of the intention to correct errors,

¹Response rate data were also tested after arcsine transformation. This and all subsequently reported statistical effects also reached significance by applying converted data to the ANOVA. The conversion was performed as follows: $X = \arcsin(\sqrt{Y/100})$. X indicates the normalized value; Y indicates the percentage value.

²Trials preceded by compatible trials were excluded from analysis of post-error adjustments so that the comparison was between trials preceded by incompatible hits and incompatible errors. This procedure ruled out confounds with the conflict sequence effect often observed in flanker tasks (Gratton, Coles, & Donchin, 1992).

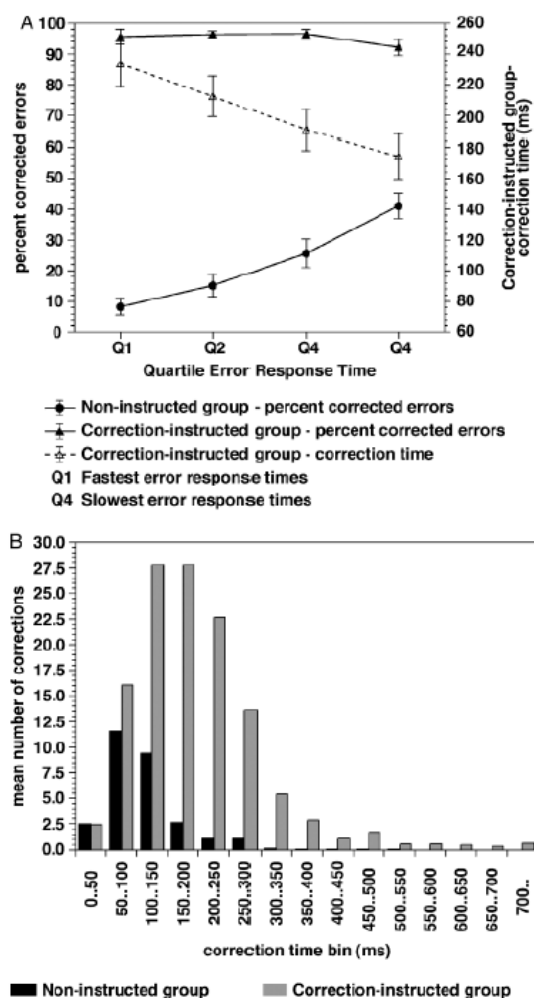


Figure 1. A: Quartile analysis of error response times. Solid lines depict correction rate as a function of error response time for both the correction-instructed group and the noninstructed group. The dashed line shows correction time (time between erroneous/first and corrective/second responses) as a function of error response time in the correction-instructed group. Q1–Q4 refer to the ascending RT quartile score of erroneous responses calculated separately for the two groups. B: Distributional analysis of error corrections across 50-ms bins of correction times. The y-axis shows the mean number of error corrections; the x-axis shows 15 correction time bins.

whereas the majority of slow corrections results from the instruction for error correction. Therefore, ERP data were analyzed separately for fast and slow error corrections in the correction-instructed group.

ERP Data

Incidental Error Correction

As mentioned before, participants from the noninstructed group incidentally corrected almost one fifth of their errors, although corrective behavior was not instructed. To investigate

incidental error corrections, a within-group analysis was carried out comparing incompatible noncorrected error trials and incompatible corrected error trials only *within the noninstructed group*. Fourteen participants (8 female) of this group had enough artifact-free corrected error trials to be included in the analysis. The time course of the response-locked ERP data for incompatible erroneous trials with and without correction is depicted in Figure 2 (solid lines). Compatible trials were excluded from statistical analyses, because of an insufficient number of error trials ($< 1\%$).

Early time window (0–120 ms). A three-way ANOVA with the factors Correction Type (incompatible noncorrected and incompatible corrected error trials), Lateral Dimension, and Anterior-Posterior Dimension was conducted revealing no significant difference of ERN amplitude between corrected and noncorrected errors, $F(1,13) = 0.2$, $p = .68$. Latency analysis demonstrated a later peak of the ERN for noncorrected errors than for corrected errors (15 ms difference), $t(13) = -4.3$, $p < .001$.

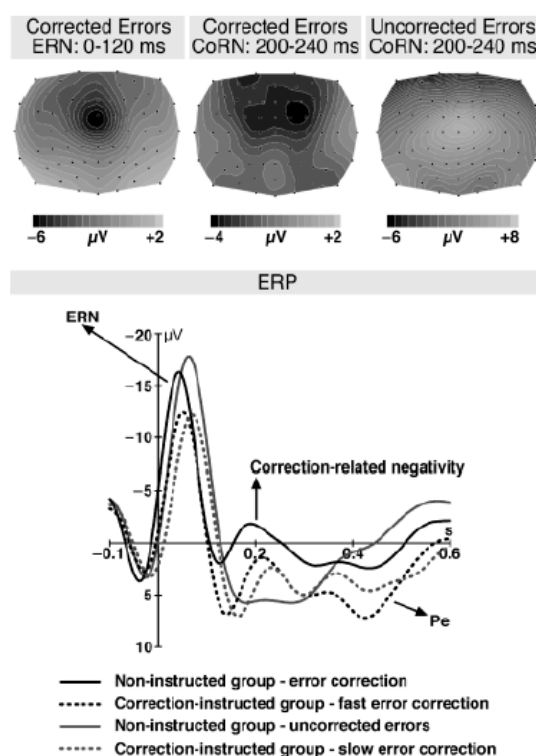


Figure 2. ERP findings. Response-locked grand averages for incidentally corrected (solid, black line) and uncorrected errors (solid, gray line) in the noninstructed group ($N = 14$) and for slow (dashed, gray line) and fast (dashed, black line) error corrections in the correction-instructed group ($N = 14$) at FCz. In the upper part, topographical scalp distributions for the ERN (leftmost panel) and the CoRN (middle panel) for error corrections in the correction-instructed group, as well as the time window of the CoRN for uncorrected errors in the noninstructed group (rightmost panel), are depicted. ERN: error-related negativity, CoRN: correction-related negativity, Pe: error positivity.

Middle time window (150–250 ms). In the middle time window, there was a negative-going deflection exclusively occurring on corrected errors. In the mean amplitude analysis, a significant Correction Type \times Lateral Dimension \times Anterior-Posterior Dimension triple interaction was observed, $F(2,26) = 4.5$, $p < .05$, $\epsilon = .94$, showing a smaller amplitude (i.e., a negativity) for corrected than noncorrected error trials at anterior electrodes, $F(1,13) = 35.6$, $p < .0001$. Because this negative-going deflection only occurred on corrected error trials we will henceforth refer to it as *correction-related negativity (CoRN)*. As visible in Figure 2, both ERP waveforms, the ERN and the correction-related negativity, are fronto-centrally distributed.

Late time window (300–500 ms). To test for differences in Pe amplitude, repeated-measures ANOVAs were conducted revealing neither a significant main effect of the factor Correction Type, $F(1,13) = 0.7$, $p = .43$, nor any significant interactions with this factor.

Summing up the results, the latency of the ERN was significantly delayed for incidentally corrected errors relative to noncorrected errors, whereas ERN amplitude showed no differences. The ERN was followed by a fronto-centrally distributed negative deflection, which only occurred on error corrections, the correction-related negativity. The amplitude of the Pe did not differ between incidentally corrected and noncorrected errors.

Incidental versus Intentional Error Correction

Response time and correction time distribution analyses suggested a similarity of fast error corrections in the correction-instructed group with incidental corrections in the noninstructed group (cf. Figure 1B). To disentangle different kinds of error corrections and to allow comparisons with the noninstructed group, corrected error trials were divided by the median of the correction time in each participant in the correction-instructed group. For subsequent comparisons between both groups and to rule out the influence of differences in error rates, we used a subsample of the correction-instructed group ($N = 14$; 6 female) whose error rates matched with the error rates of the noninstructed subgroup with a sufficient number of error corrections (as used for the within-group analysis reported above). For the correction-instructed group, the mean correction time for fast corrections amounted to 132 ms ($SEM = 9$) and for slow corrections to 274 ms ($SEM = 17$).

The response-locked ERPs for corrected and noncorrected errors in the noninstructed subgroup as well as for quickly and slowly corrected errors in the correction-instructed subgroup are illustrated in Figure 2.

Early time window (0–120 ms). To compare the amplitudes of the ERN for slowly and quickly corrected errors *within the correction-instructed group*, we conducted a three-way ANOVA with the within-subject factors Correction Speed, Lateral Dimension, and Anterior-Posterior Dimension. The analysis revealed no significant difference of ERN amplitude between slow and fast error corrections, $F(1,13) = 1.1$, $p = .31$. ERN peaked 20 ms later for slow as compared to fast corrections, $t(13) = -5.3$, $p < .0001$.

In a second step we contrasted amplitudes and peak latencies of the ERN of incidentally corrected errors in the noninstructed group with those of slow and fast corrections in the correction-instructed group. Although inspection of the waveforms suggested larger ERN amplitudes in the noninstructed group, these

differences did not reach statistical significance, $F_s < 1.3$, $p_s > .29$. The ERN for corrected errors in the noninstructed group peaked earlier than for both quickly, $t(26) = -2.1$, $p < .05$ (latency difference = 7 ms) and slowly, $t(26) = -7.2$, $p < .0001$ (latency difference = 27 ms) corrected errors in the correction-instructed group.

Middle time window (120–300 ms). First, we contrasted the amplitudes of the correction-related negativity of incidentally corrected errors in the noninstructed group and quickly corrected errors in the correction-instructed group. The ANOVA with the factors Anterior-Posterior Dimension, Lateral Dimension, and Group revealed only a main effect of the factor Group, $F(1,26) = 6.4$, $p < .05$, reflecting a smaller correction-related negativity for incidental corrections in the noninstructed group compared to fast corrections in the correction-instructed group. The analogous analysis for incidentally corrected errors in the noninstructed group and slowly corrected errors in the correction-instructed group revealed again a main effect of the factor Group exhibiting a smaller correction-related negativity for incidental corrections in the noninstructed group compared to slow corrections in the correction-instructed group, $F(1,26) = 4.7$, $p < .05$. The within-group comparison for fast and slow corrections revealed neither a significant main effect, $F(1,13) = 0.8$, $p = .40$, nor a significant interaction of the factor Correction Speed.

Concerning latency analyses, the correction-related negativity in the correction-instructed group peaked earlier for fast corrections than for slow corrections, $t(26) = -5.2$, $p < .001$. Similarly, the correction-related negativity for incidental corrections in the noninstructed group peaked earlier than for slow correction in the correction-instructed group, $t(26) = -3.4$, $p < .01$, but at about the same time as for fast corrections in the correction-instructed group, $t(26) = -0.4$, $p = .46$.

To examine whether the correction-related negativity is temporally dependent either on the first erroneous response or on the second corrective response, we computed an ERP image plot by using the software package EEGLAB (Delorme & Makeig, 2004). Figure 3A shows the ERN and the correction-related negativity components scaled to microvolt levels at channel FCz, aligned with the erroneous button press and sorted according to the participants' correction time. The ERP image plot demonstrates a distinct negative deflection in the time window of the ERN time-locked to the initial error. In the time window of the correction-related negativity, a negativity occurs after the corrective response and shows a distribution along the correction time.

Late time window (300–500 ms). The ANOVA testing for differences in Pe amplitude between fast and slow corrections in the correction-instructed group revealed a main effect of Correction Speed, $F(1,13) = 33.0$, $p < .001$, and two interactions, a Correction Speed \times Anterior-Posterior Dimension interaction, $F(1,13) = 5.2$, $p < .05$, and a Correction Speed \times Lateral Dimension interaction, $F(2,26) = 8.1$, $p < .01$, $\epsilon = .83$. Follow-up contrasts suggested that these interactions reflect a larger positivity at frontal electrodes for fast error corrections.

Pe differences were also found in the between-group comparison of incidental corrections in the noninstructed group and fast corrections in the correction-instructed group, revealing a triple interaction Group \times Anterior-Posterior Dimension \times Lateral Dimension, $F(2,52) = 6.0$, $p < .01$, $\epsilon = .92$. Follow-up

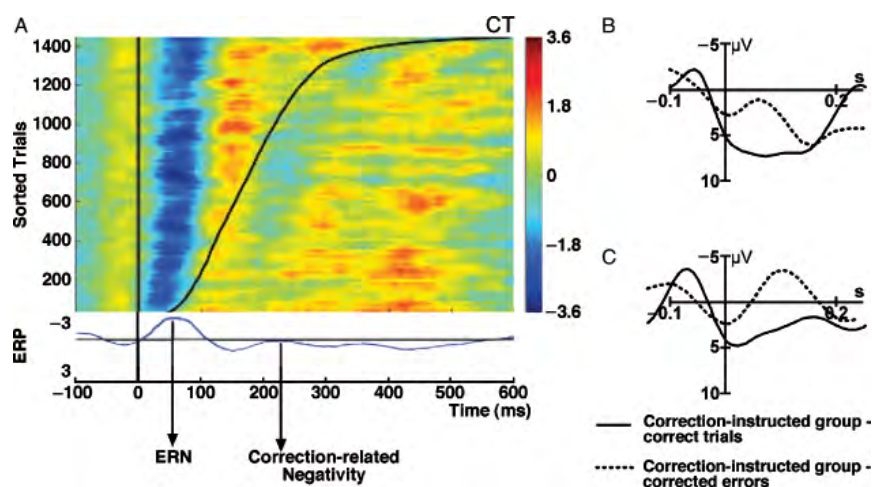


Figure 3. A: Response-locked ERP image plot for incompatible corrected error trials at channel FCz. Each vertically stacked thin color-coded horizontal bar represents a single trial in the event-related data set. Single trials are sorted according to the subjects' correction time (CT), smoothed across 50 neighboring trials in the sorting order, and plotted as a color-coded image. The trace below the ERP image shows the ERP average of the imaged data epochs. As data from all subjects of the correction-instructed group were collapsed, amplitudes of each trial were normalized for each subject. ERN: error-related negativity. B: Correct-response-locked and corrective-response-locked ERP averages, respectively, for incompatible correct trials (solid, black line) and incompatible corrected error trials (dashed, black line) for the correction-instructed group ($N = 14$) at channel FCz. C: Same ERPs as depicted in Figure 1B after 3.5 Hz high-pass filtering.

comparisons suggested that this difference is most pronounced at midline electrodes, particularly at frontal ones. Comparing incidental corrections in the noninstructed group and slow corrections in the correction-instructed group, a significant main effect of the factor Group was found, indicating a larger Pe for slow corrections in the correction-instructed group, $F(1,26) = 12.6$, $p < .01$.

To sum up the observed findings, the ERN peaked significantly earlier for incidentally corrected errors than for quickly and slowly corrected errors, whereas ERN amplitude showed no differences between these conditions. The correction-related negativity occurred on incidentally corrected error trials as well as quickly and slowly corrected trials. This deflection was fronto-centrally distributed and time-locked to the corrective response. The amplitude of the correction-related negativity was smallest for incidental corrections and did not differ between fast and slow corrections. Whereas the correction-related negativity of incidentally corrected and quickly corrected errors peaked at about the same time, slow corrections were significantly delayed relative to the other two conditions. At frontal electrode sites, Pe amplitude significantly differed between incidental, fast, and slow corrections.

Discussion

The present data provide a number of new findings regarding immediate error corrections and related ERP phenomena. First, we discuss the behavioral findings. Second, we will focus on the observed negative deflection associated with immediate error correction, the correction-related negativity, and we will offer preliminary suggestions about its functional role. Third, the temporal characteristics of the ERN depending on error correction will be discussed. Finally, the results of ERN amplitude and

the Pe will be elaborated within the framework of current models of performance monitoring.

Corrective Behavior

Consistent with previous findings, participants who were instructed to correct errors were able to do so very efficiently without being given an external signal that indicates a committed error (Higgins & Angel, 1970; Rabbitt, 1966a, 1966b, 1967). In line with the results by Rabbitt (1967), participants in the non-instructed group also showed immediate error corrections although to a lesser degree. These incidental corrections in the noninstructed group appeared in a similar time range as fast corrections in the correction-instructed group. The distributional analysis of correction times across response time quartiles of the erroneous responses showed that incidental corrections in the noninstructed group occurred mostly for slower errors. Similarly, fast error corrections in the correction-instructed group also occurred predominantly for slower errors; however, slow error corrections followed fast errors. These findings suggest that fast error corrections in the correction-instructed group are comparable to the incidental corrections in the noninstructed group.

In the following, the error correction behavior will be discussed in terms of the response conflict theory, which assumes that response conflict arises when more than one response tendencies compete (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Carter et al., 1998; Yeung, Botvinick, & Cohen, 2004). The short correction times for incidental corrections in the noninstructed group and for fast corrections in the correction-instructed group support the notion that these fast corrections occur when the correct response tendency very closely follows the erroneous one. Slow error corrections in the correction-instructed group, however, are based on a later correct response tendency, which leads to a larger time span between the correct and the erroneous response tendencies. The time span can be

modulated by the occurrence of the erroneous response tendency. Fast errors are associated with an early erroneous response tendency resulting in a large time span to the correct response tendency. Slower errors, however, are associated with a late erroneous response tendency leading to a shorter time span to the correct response tendency. The result that incidental corrections in the noninstructed group occurred predominantly for slower errors suggests that only during slow errors is the immediately following correct response tendency executed, even when no corrective behavior was instructed. In contrast, during fast errors the correct response tendency seems not to be executed in the majority of trials in the noninstructed group. Either the correct response tendency does not further evolve because stimulus processing is finished or its execution is blocked as soon as an efference copy of the first response has been received. This seems to be changed by the intention to correct errors, such that also late corrections become possible. The initiation of slow error correction can either be due to a general prolongation of stimulus processing after the first response and/or a change in the response mode of the motor system allowing multiple responses.

Besides this continuous stimulus processing account, one could also assume a phasic intentional process triggered by error detection that actively enhances the evolving correct response tendency. The fact that intentional "error signaling responses" reported by Rabbitt (2002) were much slower than slow error corrections revealed in the present study: 650–750 ms compared to ~240 ms (correction time in the fastest error RT quartile) seems to question this account. It is important to note, however, that the intention to produce an error signaling response in Rabbitt's task requires leaving the current task set to recode the responses and to establish a new response tendency. In contrast, intentional corrections in the present study merely require that the existing correct response tendency is enhanced to exceed response threshold. It seems conceivable that this enhancement is less time consuming than the generation of a new response.

As mentioned above, error correction rate was modulated by experimental instructions. Moreover, response strategy seems to be affected by the possibility to correct errors. Participants who were unaware that error corrections were recorded showed fewer errors, more late responses as well as a reaction time slowing after an error suggesting a more cautious response behavior. Ridderinkhof (2002) suggested that the degree of cautiousness or impulsivity in task performance depends on the circumstances. It seems that when participants are explicitly told to correct their errors they view errors as expected and more acceptable than participants in the noninstructed group, who presumably believe that errors are unacceptable. Consequently, participants in the noninstructed group make sure that the response is completely appropriate before its execution, resulting in lower error rates and increased late responses. In line with the findings by Rabbitt and Rodgers (1977), responses following erroneous responses on the preceding trial in the noninstructed group were not only slow, but also less accurate, a finding not observed for participants in the correction-instructed group.

The Correction-Related Negativity

Exclusively for corrected errors, the ERN was followed by a negative waveform that was associated with the behavioral corrective response. We referred to it as correction-related negativity. Both ERP waveforms, the ERN and the correction-related negativity, are distributed over frontal sites. The topography of the correction-related negativity is slightly broader than the scalp

distribution for the ERN. It extends to electrode sites covering premotor cortices.³ The correction-related negativity peaks in the time window from 200 to 240 ms after the onset of an incorrect response and has a peak-to-peak amplitude of about 5 μ V at FCz. Despite the fact that the correction-related negativity was also visible in previous experiments revealing high correction rates (Dikman & Allen, 2000; Falkenstein et al., 1994, 1996), this is the first study explicitly reporting a negative waveform related to error correction. In previous studies of Falkenstein et al. (1994, 1996), a small correction-related negativity is visible after visual and auditory stimuli, suggesting that the correction-related negativity is not affected by stimulus modality.

It is unlikely that the correction-related negativity is elicited by the additional motor response reflecting a movement-related potential (MRP; Shibasaki, Barrett, Halliday, & Halliday, 1980; Vaughan, Costa, & Ritter, 1968) of the correcting key press rather than a cognitive process. Recently published data by Rodriguez-Fornells and Münte (2004) compared one-hand responses and two-hand responses in a two-choice reaction time task. The result revealed no additional negative deflection for the second motor response. In an experiment by Falkenstein et al. (1994), participants were asked to press the response key twice. The time delay between the successive key presses approximated the delay of the correction key press. The data showed that MRPs only affected later ERPs effects, which occur around 300 ms (the Pe range).

The presence of the correction-related negativity does not seem to be related to the intention to correct errors as it was found in incidental corrections in the noninstructed group as well as in fast and slow corrections in the correction-instructed group, but its topography and amplitude may be modulated by intention. The ERP image plot indicates that the correction-related negativity is time-locked to the second corrective response rather than to the initial error. This offers the interpretation that the correction-related negativity is just a correct response negativity (CRN), an ERN-like wave observed after correct responses in some studies (Ford, 1999; Vidal, Hasbroucq, Grapperon, & Bonnet, 2000). However, if the second corrective response elicits a CRN, this component should also occur after the response on correct trials. As depicted in Figure 3B no negative deflection follows the first correct response. This is statistically supported by a significant main effect of the factor Condition (incompatible correct trials vs. incompatible corrected error trials) in the time window from 0 to 120 ms in the correct-response-locked and corrective-response-locked ERP averages, respectively, $F(1,13) = 13.7$, $p < .01$. To rule out the differential influence of the stimulus-related P300 that might have masked the CRN on correct first responses, a high-pass filter with a cutoff frequency of 3.5 Hz was applied. As can be seen in Figure 3C, no CRN is visible on correct trials, whereas the correction-related negativity remained present for corrective responses, $F(1,13) = 12.8$, $p < .01$. This finding makes it unlikely that the CRN and the correction-related negativity are the same component.

Recently, it has been suggested that the ERN reflects a burst of theta activity synchronized to the erroneous response (Luu & Tucker, 2001; Yordanova & Kolev, 2004). One could speculate that the correction-related negativity reflects a prolongation of

³The correction-related negativity also showed a slight lateralization to the right. Analyses of error and correction rates revealed no differences for right- and left-handed responses, so that the reason for the slight lateralization remains unclear.

this synchronized oscillatory activity of the (pre)motor system. The ERP image plot is inconsistent with this view: If the correction-related negativity results from the same theta oscillation as the ERN, the two waveforms should show a parallel distribution in the ERP image plot. However, with increasing correction time, the two waveforms diverge, that is, the correction-related negativity is delayed relative to the ERN. This was confirmed by a time-frequency analysis.⁴

In sum, we conclude that the correction-related negativity is most likely associated with corrective behavior. We speculate that the correction-related negativity reflects an evaluative function of the (pre)motor system that is active in the time range of the corrective response. Studies on motor responses sustained in time (in the range of seconds) reported a movement monitoring potential (MMP; Slobounov, Johnston, Chiang, & Ray, 2002), a negativity showing a frontocentral topography similar to the correction-related negativity but a different time course. Although the conditions under which the MMP and the correction-related negativity occur differ to an extent precluding direct comparisons, it could be speculated that both components are involved in monitoring processes of the premotor system. This assumption is consistent with the latest findings using functional magnetic resonance imaging (fMRI). The data showed a larger activation for corrected than uncorrected errors in the RCZ as well as in motor-related brain areas comprising the supplementary motor area (SMA) and the pre-SMA (Fiehler et al., 2004). The correction-related negativity could be associated with ongoing stimulus-response mapping based on continued stimulus processing and/or an enhancement of the evolving corrective response; however, the timing pattern makes it unlikely that the correction-related negativity is directly related to response selection. It is hence an important task for future experiments to reveal its precise functional role.

The ERN Latency and Error Correction

As expected, an ERN was observed after erroneous responses and occurred in the theta frequency range time-locked to the initial error. Taking the different theories of the ERN into account, the result pattern for ERN latencies can be explained in terms of the response conflict model (Botvinick et al., 2001; Carter et al., 1998; Yeung et al., 2004). Using computational models, Yeung et al. suggest that the ERN amplitude is related to the amount of post-response conflict, that is, a multiplicative measure of the activities of the executed and the still evolving competing response tendencies. According to this model, the ERN should peak at the time of maximal post-response conflict. The authors further assume that an error detection system could work on the

basis of post-response conflict monitoring by integrating the information about conflict with the information that a response has been already issued. In the present study, the latency of the ERN was delayed by about 15 to 20 ms for uncorrected and slowly corrected errors as compared to incidental and fast corrections, respectively. This is in line with the notion that the maximal post-response conflict is postponed when the second response tendency is delayed (Yeung et al., 2004).

The present findings seem rather inconsistent with the mismatch hypothesis (Falkenstein et al., 1990; Gehring et al., 1993). This model interpreted the ERN as an error detection signal resulting from a mismatch between the representation of the intended action and the actually performed action. In an early paper, Falkenstein et al. (1991, p. 453) assumed that the ERN was "elicited at the moment of the completion of the response selection process," that is, after completion of stimulus processing, when both response representations are fully available. This should result in an ERN latency in the time range of the corrective response. Particularly in slow corrections this should have led to an ERN latency increase of more than 150 ms, in contrast to 15 to 20 ms as observed in the present study. A later version of the mismatch hypothesis suggests that the comparison process takes place when the efference copy of the performed response arrives and is not waiting "until all possible information about the appropriate response is available" (Coles, Scheffers, & Holroyd, 2001, p. 175). Following this view, no latency differences should have been predicted.

Latency findings similar to the present results were reported by Falkenstein et al. (1996). Surprisingly, the ERN latencies between fast and slow corrected errors did not differ in the study by Rodriguez-Fornells et al. (2002). This difference might be explained by the medians of the reaction time for fast and slow corrected errors in the study by Rodriguez-Fornells et al., which are temporally closer than in the present results (104 ms vs. 141 ms). Assuming that the latency difference of the ERN depends on correction speed, a decreasing temporal distance between fast and slow corrected errors should diminish the ERN latency difference. Furthermore, in the comparison of uncorrected and corrected errors performed by Rodriguez-Fornells et al. one could argue that the interdiction to correct an error may have led to inhibition stopping all further stimulus evaluation and response selection processes immediately after delivery of the response. This may explain why only short ERN latencies were found in the uncorrected condition in that study.

ERN Amplitude

Our results for ERN amplitudes showed no significant difference between corrected and noncorrected errors in the correction-instructed group and between fast and slow corrections in the noninstructed group. This is inconsistent with any of the current theories of the ERN. Whereas a study by Falkenstein et al. (1994) also revealed no difference in the amplitude of the ERN between corrected and uncorrected errors after visual stimuli, other previous studies (Falkenstein et al., 1996; Gehring et al., 1993; Rodriguez-Fornells et al., 2002) have reported amplitude differences as predicted by the conflict monitoring model (Botvinick et al., 2001; Yeung et al., 2004) and the mismatch theory put forward by Coles et al. (2001). It remains unclear why the relationship of ERN amplitude and error corrections shows this inconsistent pattern of results in the literature and in the present study.

⁴We conducted a wavelet analysis of a time window ranging from -400 to +600 ms in relation to the erroneous responses based on the single-trial epochs in the continuous EEG data of each subject (cf. Tallon-Baudry, Bertrand, Delpuech, & Pernier, 1997). The analysis was carried out at FCz using a Morlet wavelet transform (wave number 5.03). Frequencies were sampled at 71 intervals between 1 and 60 Hz, that is, at 12 intervals per octave. An increase of synchronized as well as total theta power was found in the latency range of the ERN. The maxima were in uncorrected errors (noninstructed group) at a frequency of 5.6 Hz ($SEM = 0.26$) and latency of 66 ms ($SEM = 7$) for total and at 4.87 Hz ($SEM = 0.31$) and 57 ms ($SEM = 10$) for synchronized activity, and in corrected errors (correction-instructed group) at 6.4 Hz ($SEM = 0.25$) and 81 ms ($SEM = 11$) for total and at 5.5 Hz ($SEM = 0.33$) and 80 ms ($SEM = 10$) for synchronized activity. There was no significant difference in latencies of the theta activities between corrected and uncorrected errors either for total or for synchronized activity.

Inspection of the waveforms suggests a larger ERN in the noninstructed group independent of whether the error was corrected or not. This group difference reached significance when all errors were collapsed in each group, $F(2,76) = 6.0$, $p < .05$. As pointed out above, the groups seemed to differ with respect to the motivational significance of the errors, as the correction-instructed group appeared to believe that errors are to some degree acceptable. We therefore argue that this difference can explain ERN amplitude differences between groups (cf. Falkenstein et al., 1994; Gehring et al., 1993; Ullsperger & Szymanowski, 2004).

The Pe

The Pe did not differ significantly between corrected and uncorrected errors in the noninstructed group, suggesting that it is not modulated by incidental corrections. There was a difference between incidental and fast corrections as well as fast and slow corrections, however, mostly due to a larger positivity on fast error corrections at midfrontal electrodes. The functional significance of these findings is rather unclear, because the Pe is usually maximal at centro-parietal electrodes (Falkenstein, 2004; Falkenstein et al., 2000). Falkenstein et al. (1994) suggested that the Pe in corrected errors could be influenced by a late MRP. However, the fact that no Pe difference was observed between corrected and uncorrected errors within the noninstructed group renders this account unlikely. Furthermore, our Pe findings are not consistent with the notion that this component is associated with post-error slowing (Nieuwenhuis et al., 2001), as we found a smaller Pe for the noninstructed group showing post-error slowing as compared to the correction-instructed group, in which post-error slowing was absent. It is important to note that the Pe has a large variability across different individuals and different tasks such that the exact nature of this component still remains to be determined (Falkenstein, 2004; Falkenstein et al., 2000).

Conclusion

In the present study, we reported the characteristics of a previously unnoticed ERP waveform related to immediate error correction, which we call the correction-related negativity. The correction-related negativity was present on both intentional and incidental error corrections, and seems to be more closely time-locked to the corrective response than to the initial error. One could speculate that the correction-related negativity reflects evaluative functions of the (pre)motor system necessary for error corrections.

We observed a modulation of the ERN latency by the occurrence and temporal characteristics of immediate error correction, which is consistent with the response conflict model. The data suggest that quickly and incidentally corrected errors are delayed correct responses, which arise from further stimulus processing to be reflected by an early peak of the ERN. In contrast, slow error correction seems to be based on a delayed correct response tendency resulting in a later peak of the ERN.

The behavioral data showed that the intention to correct errors significantly increases the correction rate resulting mostly in slow error corrections. This gain in error correction is due to an additional intentional process. The present data, however, do not allow us to assess whether the intention to correct errors results in a prolongation of stimulus processing exceeding the first response or in a change in the response mode or in a phasic implementation of intentional corrections after an error has been detected.

The notion that error detection is not necessary for incidental correction bears one important implication for clinical studies of error processing. Spontaneous (incidental) error correction rate has been used as an additional measure for error detection abilities in patient groups (e.g., Gehring & Knight, 2000). To assess error detection, it seems to be better to investigate intentional error corrections by instructing patients prior to the experiment or by introducing an error-signaling response (cf. Rabbitt, 2002).

REFERENCES

- Badgaiyan, R., & Posner, M. (1998). Mapping the cingulate cortex in response selection and monitoring. *NeuroImage*, 7, 255–260.
- Bernstein, P., Scheffers, M., & Coles, M. (1995). "Where did I go wrong?" A psychophysiological analysis of error detection. *Journal of Experimental Psychology: Human Perception and Performance*, 21, 1312–1322.
- Botvinick, M. M., Braver, T. S., Barch, D. M., Carter, C. S., & Cohen, J. D. (2001). Conflict monitoring and cognitive control. *Psychological Review*, 108, 624–652.
- Carter, C., Braver, T., Barch, D., Botvinick, M., Noll, D., & Cohen, J. (1998). Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science*, 280, 747–749.
- Coles, M. G. H., Scheffers, M. K., & Holroyd, C. B. (2001). Why is there an ERN on correct trials? Response representation, stimulus-related components, and the theory of error-processing. *Biological Psychology*, 56, 173–189.
- Cooke, J. D., & Diggles, V. A. (1984). Rapid error correction during human arm movements: Evidence for central monitoring. *Journal of Motor Behavior*, 16, 348–363.
- Dehaene, S., Posner, M. I., & Tucker, D. M. (1994). Localization of a neural system for error detection and compensation. *Psychological Science*, 5, 303–305.
- Delorme, A., & Makeig, S. (2004). EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods*, 134, 9–21.
- Dikman, Z., & Allen, J. (2000). Error monitoring during reward and avoidance learning in high- and low-socialized individuals. *Psychophysiology*, 37, 43–54.
- Falkenstein, M. (2004). ERP correlates of erroneous performance. In M. Ullsperger & M. Falkenstein (Eds.), *Errors, conflicts, and the brain. Current opinions on performance monitoring* (pp. 5–14). Leipzig: Max Planck Institute for Human Cognitive and Brain Sciences.
- Falkenstein, M., Hohnsbein, J., & Hoormann, J. (1994). Event-related potential correlates of errors in reaction tasks. In G. Karmos, M. Molnar, V. Csepe, I. Czigler, & J. E. Desmedt (Eds.), *Perspectives of event-related potentials research* (pp. 287–296. (EEG Suppl. 441)). Amsterdam: Elsevier Science.
- Falkenstein, M., Hohnsbein, J., & Hoormann, J. (1996). Differential processing of motor errors. In C. Ogura, Y. Koga, & M. Shimokochi (Eds.), *Recent advances in event-related brain potential research* (pp. 579–585). Amsterdam: Elsevier Science.
- Falkenstein, M., Hohnsbein, J., Hoormann, J., & Blanke, L. (1990). Effects of errors in choice reaction time tasks on the ERP under focused and divided attention. In C. H. M. Brunia, A. W. K. Gaillard, & A. Kok (Eds.), *Psychophysiological brain research* (pp. 192–195). Tilburg, Germany: Tilburg University Press.
- Falkenstein, M., Hohnsbein, J., Hoormann, J., & Blanke, L. (1991). Effects of crossmodal divided attention on late ERP components. II. Error processing in choice reaction tasks. *Electroencephalography and Clinical Neurophysiology*, 78, 447–455.
- Falkenstein, M., Hoormann, J., Christ, S., & Hohnsbein, J. (2000). ERP components on reaction errors and their functional significance: A tutorial. *Biological Psychology*, 51, 87–107.
- Fiehler, K., Ullsperger, M., & von Cramon, D. Y. (2004). Neural correlates of error detection and error correction: Is there a common

- neuroanatomical substrate? *European Journal of Neuroscience*, 19, 3081–3087.
- Ford, J. M. (1999). Schizophrenia: The broken P300 and beyond. *Psychophysiology*, 36, 667–682.
- Gehring, W., & Fencsik, D. (2001). Functions of the medial frontal cortex in the processing of conflict and errors. *Journal of Neuroscience*, 21, 9430–9437.
- Gehring, W. J., Goss, B., Coles, M. G. H., Meyer, D. E., & Donchin, E. (1993). A neural system for error detection and compensation. *Psychological Science*, 4, 385–390.
- Gehring, W. J., Himle, J., & Nisenson, L. (2000). Action-monitoring dysfunction in obsessive-compulsive disorder. *Psychological Science*, 11, 1–6.
- Gehring, W. J., & Knight, R. T. (2000). Prefrontal-cingulate interactions in performance monitoring. *Nature Neuroscience*, 3, 516–520.
- Gevens, A., Smith, M. E., Le, J., Leong, H., Bennett, J., & Martin, M., et al. (1996). High resolution evoked potential imaging of the cortical dynamics of human working memory. *Electroencephalography and Clinical Neurophysiology*, 98, 327–348.
- Gratton, G., Coles, M. G. H., & Donchin, E. (1983). A new method for off-line removal of ocular artifact. *Electroencephalography and Clinical Neurophysiology*, 55, 468–484.
- Gratton, G., Coles, M. G. H., & Donchin, E. (1992). Optimizing the use of information: Strategic control of activation of responses. *Journal of Experimental Psychology: General*, 121, 480–506.
- Greenhouse, S., & Geisser, S. (1959). On methods in the analysis of profile data. *Psychometrika*, 25, 95–112.
- Higgins, J. R., & Angel, R. W. (1970). Correction of tracking errors without sensory feedback. *Journal of Experimental Psychology*, 84, 412–416.
- Holroyd, C., & Coles, M. (2002). The neural basis of human error processing: Reinforcement learning, dopamine, and the error-related negativity. *Psychological Review*, 109, 679–709.
- Holroyd, C., Dien, J., & Coles, M. (1998). Error-related scalp potentials elicited by hand and foot movements: Evidence for an output-independent error-processing system in humans. *Neuroscience Letters*, 242, 65–68.
- Huberty, C. J., & Morris, J. D. (1989). Multivariate analysis versus multiple univariate analyses. *Psychological Bulletin*, 114, 145–161.
- Kopp, B., Rist, F., & Mattler, U. (1996). N200 in the flanker task as a neurobehavioral tool for investigating executive control. *Psychophysiology*, 33, 282–294.
- Leuthold, H., & Sommer, W. (1999). ERP correlates of error processing in spatial S-R compatibility tasks. *Clinical Neurophysiology*, 110, 342–357.
- Luu, P., Collins, P., & Tucker, D. (2000). Mood, personality, and self-monitoring: Negative affect and emotionality in relation to frontal lobe mechanisms of error monitoring. *Journal of Experimental Psychology: General*, 129, 43–60.
- Luu, P., & Tucker, D. (2001). Regulating action: Alternating activation of midline frontal and motor cortical networks. *Clinical Neurophysiology*, 112, 1295–1306.
- Miltner, W., Braun, C., & Coles, M. (1997). Event-related brain potentials following incorrect feedback in a time-estimation task: Evidence for a “generic” neural system for error detection. *Journal of Cognitive Neuroscience*, 9, 788–798.
- Nieuwenhuis, S., Ridderinkhof, K. R., Blom, J., Band, G. P. H., & Kok, A. (2001). Error-related brain potentials are differentially related to awareness of response errors: Evidence from antisaccade task. *Psychophysiology*, 38, 752–760.
- Oken, B. S., & Chiappa, K. H. (1986). Statistical issues concerning computerized analysis of brainwave topography. *Annals of Neurology*, 19, 493–494.
- Pailing, P., Segalowitz, S., Dywan, J., & Davies, P. (2002). Error negativity and response control. *Psychophysiology*, 39, 198–206.
- Perrin, F., Pernier, J., Bertrand, O., & Echallier, J. F. (1989). Spherical splines for scalp potential and current density mapping. *Electroencephalography and Clinical Neurophysiology*, 72, 184–187.
- Pfeifer, E. (1993). IPCM—Iterative PCA correction method. A new method for the correction of ocular artifacts in the ERP-data. *Psychophysiology*, 30, 51.
- Picard, N., & Strick, P. L. (1996). Motor areas of the medial wall: A review of their location and functional activation. *Cerebral Cortex*, 6, 342–353.
- Rabbitt, P. M. A. (1966a). Error correction time without external error signals. *Nature*, 22, 438.
- Rabbitt, P. (1966b). Errors and error correction in choice-response tasks. *Journal of Experimental Psychology*, 71, 264–272.
- Rabbitt, P. M. A. (1967). Time to detect errors as a function affecting choice-response time. *Acta Psychologica*, 27, 131–142.
- Rabbitt, P. (2002). Consciousness is slower than you think. *The Quarterly Journal of Experimental Psychology*, 55A, 1081–1092.
- Rabbitt, P., & Rodgers, B. (1977). What does a man do after he makes an error? An analysis of response programming. *Quarterly Journal of Experimental Psychology*, 29, 727–743.
- Ridderinkhof, K. (2002). Micro- and macro-adjustments of task set: Activation and suppression in conflict tasks. *Psychological Research*, 66, 312–323.
- Rodriguez-Fornells, A., Kurzbuch, A. R., & Münte, T. F. (2002). Time course of error detection and correction in humans: Neurophysiological evidence. *Journal of Neuroscience*, 22, 9990–9996.
- Rodriguez-Fornells, A., & Münte, T. F. (2004). Is the error-related negativity driven by simultaneously active motor programs? In M. Ullsperger & M. Falkenstein (Eds.), *Errors, conflicts, and the brain. Current opinions on performance monitoring* (pp. 159–163). Leipzig: Max Planck Institute for Human Cognitive and Brain Sciences.
- Shibasaki, H., Barrett, G., Halliday, E., & Halliday, A. M. (1980). Components of the movement-related cortical potential and their scalp topography. *Electroencephalography and Clinical Neurophysiology*, 49, 213–226.
- Slobounov, S., Johnston, J., Chiang, H., & Ray, W. (2002). Movement-related EEG potentials are force or end-effector dependent: Evidence from a multi-finger experiment. *Clinical Neurophysiology*, 113, 1125–1135.
- Tallon-Baudry, C., Bertrand, O., Delpuech, C., & Pernier, J. (1997). Oscillatory gamma-band (30–70 Hz) activity induced by a visual search task in humans. *Journal of Neuroscience*, 17, 722–734.
- Ullsperger, M., & Szymanowski, F. (2004). ERP correlates of error relevance. In M. Ullsperger & M. Falkenstein (Eds.), *Errors, conflicts, and the brain. Current opinions on performance monitoring* (pp. 171–177). Leipzig: Max Planck Institute for Human Cognitive and Brain Sciences.
- Ullsperger, M., & von Cramon, D. Y. (2001). Subprocesses of performance monitoring: A dissociation of error processing and response competition revealed by event-related fMRI and ERPs. *NeuroImage*, 14, 1387–1401.
- Ullsperger, M., & von Cramon, D. Y. (2004). Neuroimaging of performance monitoring: Error detection and beyond. *Cortex*, 40, 593–604.
- Van Veen, V., & Carter, C. S. (2002). The timing of action-monitoring processes in the anterior cingulate cortex. *Journal of Cognitive Neuroscience*, 14, 593–602.
- Vaughan, H., Costa, L., & Ritter, W. (1968). Topography of the human motor potential. *Electroencephalography and Clinical Neurophysiology*, 25, 1–10.
- Vidal, F., Hasbroucq, T., Grapperon, J., & Bonnet, M. (2000). Is the ‘error negativity’ specific to errors? *Biological Psychology*, 51, 109–128.
- Yeung, N., Botvinick, M. M., & Cohen, J. D. (2004). The neural basis of error detection: Conflict monitoring and the error-related negativity. *Psychological Review*, 111, 939–959.
- Yordanova, J., & Kolev, V. (2004). Error-specific signals in the brain: Evidence from a time-frequency decomposition of event-related potentials. In M. Ullsperger & M. Falkenstein (Eds.), *Errors, conflicts, and the brain. Current opinions on performance monitoring* (pp. 41–47). Leipzig: Max Planck Institute for Human Cognitive and Brain Sciences.

(RECEIVED March 8, 2004; ACCEPTED October 28, 2004)

Chapter 12

How does error correction differ from error signaling? An event-related potential study.

In a number of patient studies, immediate error corrections have been used as an additional measure interpreted as reflecting the functional integrity of the performance monitoring system (Gehring and Knight, 2000; Swick and Turken, 2002; Chapter 8 [Ullsperger and von Cramon, 2006]). As mentioned in the previous Chapter, it has been doubted whether incidental (spontaneous, non-instructed) error corrections require performance monitoring at all. It has been suggested that, like in a horserace, the evolving incorrect and correct response tendencies could be executed sequentially without the necessity to detect the error (Rabbitt, 2002). In contrast, slow intentional corrections have been suggested to result from error processing (see Chapter 11). However, the proportion of those error corrections resulting from error processing and those that are in fact delayed correct responses is unknown. Therefore, the sensitivity of the error correction rate to dysfunctions of the performance monitoring system may be low.

This Chapter addresses the question whether an error signaling procedure may be better suited to test the functional integrity of the performance monitoring system at the behavioral level. To this end participants were instructed to press a signaling button that is unrelated to the primary task whenever they encountered an error. In a within-subjects design using ERPs, similarities and differences of immediate error corrections and error signaling responses are investigated. The findings are consistent with the response-conflict monitoring theory and suggest that the instruction to correct errors leads to a lowering of the motor threshold.

The major conclusion is that error signaling rate is a better measure of performance monitoring. Thus, future studies addressing pathological and pharmacological changes of the performance monitoring system should make use of the error signaling procedure.

ARTICLE IN PRESS

BRES-35071; No. of pages: 8; 4C:

BRAIN RESEARCH XX (2006) XXX–XXX



available at www.sciencedirect.com



www.elsevier.com/locate/brainres

**BRAIN
RESEARCH**

Research Report

How does error correction differ from error signaling? An event-related potential study

Markus Ullsperger*, D. Yves von Cramon

Max Planck Institute for Human Cognitive and Brain Sciences, Stephanstr. 1a, D-04103 Leipzig, Germany

ARTICLE INFO

Article history:
Accepted 5 January 2006

Keywords:
Performance monitoring
ERN
Error correction
ERP
Cognitive control
LRP

ABSTRACT

It has been a question of debate whether immediate error corrections in speeded forced-choice reaction time tasks require an error detection signal from the performance monitoring system or whether they reflect delayed correct responses that are executed after the premature error like in a horserace. In contrast, signaling the error by pressing a response button that is unrelated to the primary task is based on error detection. The present study investigates the similarities and differences between immediate error corrections and signaling responses by means of behavioral and event-related potential data. In a within-subject design, participants performed two sessions of the flanker task. In one session, errors had to be corrected by immediately pressing the correct response, in the other session, errors had to be signaled by pressing an error signaling button. Compared to the signaling session, in the correction session, more errors and error corrections were made, reaction times were shorter, and the amplitude of the error-related negativity (ERN) was reduced. Whereas the error significance did not seem to differ across session, participants have most likely reduced the motor threshold in the correction session to enable efficient immediate corrections. This interpretation is supported by the lateralized readiness potentials and is consistent with the response conflict monitoring hypothesis of the ERN. The present study demonstrates that differences in error corrections may be attributable to differences in motor threshold. We conclude that the error signaling procedure is a more direct and reliable way to behaviorally test the functional integrity of the performance monitoring system than the instruction to correct errors. The consequences for studies in patients and with pharmacological challenges are discussed.

© 2006 Elsevier B.V. All rights reserved.

1. Introduction

"A man who has committed a mistake and does not correct it is committing another mistake." (Confucius, 551–479 B.C., Chapter 15, Verse 29).

The ability to monitor for errors and to implement compensatory actions is a prerequisite of goal-directed and flexible behavior. Making use of event-related potentials (ERPs) and neuroimaging, performance monitoring research

has made substantial progress over the last two decades. The error-related negativity (ERN; also called error negativity, Ne) is a negative deflection observed after errors resulting from premature responses in forced-choice reaction time tasks (Falkenstein et al., 1990, 2000; Gehring et al., 1993). It peaks within 50 to 100 ms after the erroneous response and has a frontocentral distribution over the scalp. Source localization and functional magnetic resonance imaging (fMRI) studies have suggested the rostral cingulate zone (RCZ) to be its main

* Corresponding author. Fax: +49 341 9940 221.
E-mail address: ullspg@cbs.mpg.de (M. Ullsperger).

ARTICLE IN PRESS

2

BRAIN RESEARCH XX (2006) XXX-XXX

generator (Ridderinkhof et al., 2004; Ullsperger and von Cramon, 2001). A recent study using concurrent EEG and fMRI recordings not only provided evidence for a trial-by-trial coupling of the ERN and the fMRI signal in the RCZ but also showed that the dynamic fluctuations in ERN amplitude predict compensatory post-error slowing on trials subsequent to errors (Debener et al., 2005). Thus, the ERN seems to reflect a signal from the performance monitoring system indicating the need for adjustments (Ridderinkhof et al., 2004; Ullsperger et al., 2004). In forced-choice reaction time tasks, this signal may be operationalized as the amount of post-response conflict. The response conflict monitoring theory (Botvinick et al., 2004; Yeung et al., 2004) suggests that the performance monitoring system monitors for the conflict between simultaneously activated response tendencies. According to the theory, the amount of conflict determines subsequent modulations in cognitive control (Ullsperger et al., 2005). Simulations in connectionist models suggested that the ERN reflects the amount of post-response conflict, i.e., the conflict between the executed erroneous response and the still-evolving correct response tendency (Yeung et al., 2004).

The relationship between ERN amplitude and corrective behavior is less clear, however. A number of ERP studies revealed a modulation of the ERN by error correction (Falkenstein et al., 1994, 1996; Gehring et al., 1993; Rodriguez-Fornells et al., 2002). Larger ERN amplitudes were found for corrected compared to uncorrected errors. In contrast, a recent study investigating incidental (spontaneous) and intentional (instructed) error corrections failed to replicate this amplitude modulation (Fiehler et al., 2005). Interestingly, this study found larger ERN amplitudes in a group of participants that was not instructed to correct errors as compared to a group that was instructed to correct each encountered error by immediately pressing the correct response button, while no amplitude difference was found between corrected and uncorrected errors within the groups. Behavioral findings showing fewer errors, more late responses as well as a reaction time slowing subsequent to an error only in the group not instructed to correct errors suggested a more cautious response behavior in this group. One possible interpretation of these findings was the following: "It seems that when participants are explicitly told to correct their errors they view errors as expected and more acceptable than participants in the non-instructed group, who presumably believe that errors are unacceptable" (p. 8, Fiehler et al., 2005). This view was supported by concurrent recordings of phasic cardiac responses showing stronger error-related heart rate decelerations in the group unaware of the opportunity to correct errors (Fiehler et al., 2004).

It has been a matter of debate whether immediate error corrections in forced choice reaction time tasks can be interpreted as compensatory actions that result from error processing. Based on the observation that error correction time, i.e., the latency of the corrective response relative to the error, can be very short, it has been suggested that at least incidental error corrections may rather be a delayed correct response (Rabbitt, 2002). In other words, like in a horserace, the evolving incorrect and correct response tendencies could be executed sequentially without the necessity to detect the error. Fiehler et al. (2005) showed that the instruction to

correct errors yields a gain in slow error corrections and suggested that these slow, intentional error corrections require the detection of the preceding error. However, they could not rule out the alternative explanation that the intention to correct errors leads to a general reduction of the motor threshold. The motor threshold concept, implemented in the response conflict monitoring models, suggests that activation of a response channel needs to exceed a certain threshold to result in an overt response. A general reduction of the motor threshold would enable even the execution of weak correct response tendencies after the error, thereby increasing the number of error corrections. As weak response tendencies need longer to reach the threshold, a selective increase of slow corrections would be expected. Thus, the motor threshold account would suggest that even instructed error corrections do not necessarily reflect activity of the performance monitoring system. This is an important issue, as many patient studies showed pathological changes of the ERN but often failed to show clear impairments of error corrections (Gehring and Knight, 2000; Ullsperger, 2006; Ullsperger and von Cramon, in press). This discrepancy has been difficult to reconcile with the notion that the ERN is a correlate of performance monitoring. The major question that needs to be answered is whether error corrections are a reliable measure of the functional integrity of the performance monitoring system.

A way to test error detection is to instruct participants to press a signaling button that is unrelated to the primary task whenever they encounter an error (Rabbitt, 2002). The horse race model is unlikely to explain the signaling response, as it is not induced by the stimuli of the primary task. When an error has been detected by the performance monitoring system, the signaling response is initiated.

The present study investigates whether intentional error corrections differ from error signaling. ERPs and lateralized readiness potentials (LRP) are used with the aim to test the motor threshold account for intentional error corrections. To this end, participants performed two sessions of a modified flanker task in a within-subjects design. In one session, they were instructed to immediately correct errors; in the other session, they were asked to signal the error by pressing a specific response button. If an increase in error corrections is reached by a general decrease of the motor threshold, a number of predictions could be made. First, reaction times should be shortened as the response tendencies exceed the motor threshold earlier after stimulus presentation. Second, error rates are expected to be increased, because even weak incorrect response tendencies would be executed. Third, whereas with high motor threshold these weak tendencies are not executed and thus do not contribute to post-response conflict, the assumed reduction in motor threshold should result in lower post-response conflict caused by a contribution of strong and weak erroneous response tendencies. It follows that a reduced ERN should be associated with intentional error correction as compared to error signaling. Fourth, a reduced motor threshold is expected to result in reduced lateralizations of the readiness potential, indicating the differential engagement of the left and right (pre)motor cortices in the preparation and initiation of unimanual motor responses (Gratton et al., 1988; Kutas and Donchin, 1980). This motor-

related asymmetrical brain activity can be isolated by a double subtraction-averaging procedure resulting in the lateralized readiness potential (LRP) (De Jong et al., 1988; Rugg and Coles, 1995). Concerning the present study, the following prediction can be made: with a reduced motor threshold, only very weak erroneous response tendencies are not executed. Therefore, the lateralization to the incorrect side, typically observed in incompatible correct trials (Gratton et al., 1988), should be reduced in the correction session.

The aforementioned predictions are consistent with the results of a simulation based on a connectionist computational model of response conflict monitoring in a flanker task (Yeung et al., 2004). In Simulation 3 (p. 938), speed-accuracy shifts were modeled by varying the motor threshold and an additional parameter. While predictions for the LRP were not made explicit, the simulation predicts (1) shorter reaction times, (2) more errors, and (3) a smaller ERN for the speed condition, modeled by lowering the motor threshold.

2. Results

2.1. Behavioral findings

Reaction time and accuracy data are shown in Table 1. As usual in flanker tasks, reaction times were longer in incompatible than in compatible trials. Importantly, reaction times were shorter during the correction session than during the signaling session. These observations were confirmed by subjecting the data for correct responses to a repeated measures ANOVA with the factors Compatibility (compatible, incompatible) and Session (correction, signaling), revealing main effects of Compatibility ($F(1,14) = 413.78, P < 0.0001$) and Session ($F(1,14) = 5.34, P < 0.05$). An ANOVA conducted on incompatible trials with the factors Response (correct, incorrect) and Session gave rise to main effects of Response ($F(1,14) = 2137.6, P < 0.0001$) and Session ($F(1,14) = 6.52, P < 0.05$), reflecting that errors were associated with shorter reaction times than hits and, again, that reaction times were shorter in the correction session as compared to the signaling session. Error rates were higher for incompatible than for compatible

trials. Furthermore, participants made more errors in the correction session than in the signaling session. This was confirmed by an ANOVA revealing main effects for the factors Compatibility ($F(1,14) = 170.49, P < 0.0001$) and Session ($F(1,14) = 24.81, P < 0.001$). Moreover, an interaction Compatibility \times Session was found ($F(1,14) = 32.37, P < 0.0001$), reflecting a stronger interference effect in the signaling session.

In the correction session, participants corrected 97.2 (± 0.9)% of the incompatible errors. In the signaling session, they signaled 95.4 (± 0.8)% of the incompatible errors. Furthermore, they spontaneously corrected 24.6 (± 3.4)% (20.9 ± 3.4 were corrected and signaled; 3.7 ± 0.8 were corrected only). The difference in correction rate between the two sessions was significant ($t(14) = 20.19, P < 0.0001$), whereas correction rate in the correction session did not differ from the signaling rate in the signaling session ($t(14) = 1.45, P = 0.17$). Consistent with previous findings (Rabbitt, 2002; Rabbitt and Phillips, 1967), correction times (correction session, 264.0 ± 23.4 ms; incidental corrections in the signaling session 184.7 ± 14.4 ms) were significantly shorter than signaling times (530.6 ± 31.2 ms; $t(14) = 8.11, P < 0.0001$).

2.2. Post-test survey

After the experiments, participants rated the attention they paid to the task on a scale from 1 (very little) to 5 (very much) separately for both sessions. The mean rating amounted to 3.53 (± 0.29) in the correction session and 3.60 (± 0.19) in the signaling session. A Wilcoxon Signed Ranks test did not reveal a statistical difference ($P = 0.791$). Furthermore, participants responded to the question “Did you get upset when you encountered an error?” by rating between 1 (not at all) and 5 (very much). There was no difference in the ratings between sessions (correction, 2.87 ± 0.27 ; signaling, 2.87 ± 0.31). Finally, participants had to rate the number of errors they made on a scale between 1 (very few) and 5 (very many), revealing no significant difference between sessions (correction, 3.0 ± 0.07 ; signaling 2.8 ± 0.06 ; Wilcoxon Signed Ranks test, $P = 0.53$).

2.3. ERP findings

Fig. 1 depicts the response-locked grand mean average waveforms for incompatible errors in the correction and signaling sessions. Both waveforms show a clear negativity, the ERN followed by a distinct positive peak, both with highly similar scalp topographies and a maximum at FCz. At Pz, the positive wave has a more sustained time course, reflecting the ‘late’ error positivity (Falkenstein et al., 2000; van Veen and Carter, 2002). The ERN as well as the subsequent frontal positivity is larger in amplitude for the signaling session compared with the correction session. These findings are confirmed by repeated measures ANOVAs, revealing main effects of Session (ERN, $F(1,14) = 10.07, P < 0.01$; subsequent positivity, $F(1,14) = 21.63, P < 0.0005$). No significant interaction with Order was found ($P > 0.17$). The latency of the ERN was nominally longer in the correction session (51.6 ± 3.3 ms) than in the signaling session (48.2 ± 2.7 ms), but this difference did not reach significance ($P > 0.33$) as it was below the temporal resolution given a sampling rate of 250 Hz.

Table 1 – Mean proportions of correct, erroneous, and late responses in the two sessions broken down by compatibility

| | Compatible trials | | | | Incompatible trials | | | |
|--------------------------|--------------------|--------|---------------------|-------|---------------------|-------|---------------------|-------|
| | Response rates (%) | | Response times (ms) | | Response rates (%) | | Response times (ms) | |
| Error correction session | | | | | | | | |
| Correct | 99.2 | (0.17) | 306.1 | (5.5) | 74.8 | (1.9) | 385.0 | (6.3) |
| Error | 0.8 | (0.17) | – | – | 25.2 | (1.9) | 269.0 | (5.8) |
| Error signaling session | | | | | | | | |
| Correct | 99.1 | (0.2) | 313.7 | (5.5) | 81.8 | (1.6) | 393.6 | (8.0) |
| Error | 0.9 | (0.2) | – | – | 17.9 | (1.6) | 274.5 | (5.2) |

Note. In most participants, the number of compatible errors was insufficient to obtain reliable response times for this condition. Standard errors of the means are shown in parentheses.

ARTICLE IN PRESS

4

BRAIN RESEARCH XX (2006) XXX-XXX

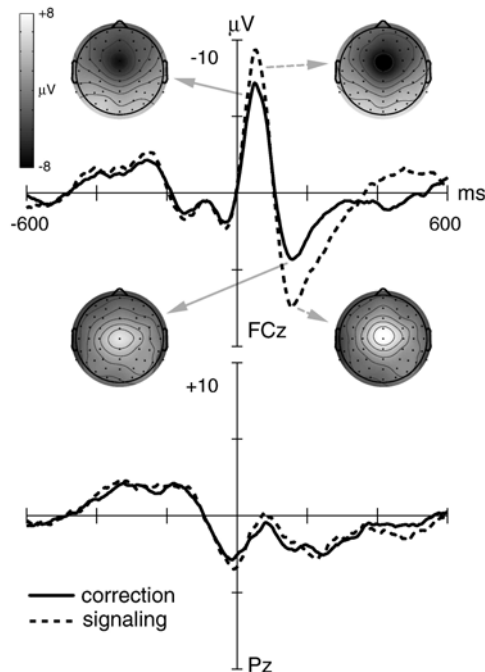


Fig. 1 – Response-locked grand mean average ERP waveforms for incompatible errors in the correction session (solid line) and the signaling session (dotted lines) at two midline electrodes. The insets show the scalp topographies for the ERN at 56 ms (upper plots) and the subsequent positivity at 156 ms (lower plots) for the correction session (left plots) and the signaling session (right plots). For the correction session, corrected errors are shown, for the signaling session, signaled ones.

The relationship between error rate and ERN amplitude is still rather unclear. While many studies have found no such relationship at the group level (Falkenstein et al., 2000), other studies reported a reduction of ERN amplitude with increasing error rate (Ruchow et al., 2005). In the present study, there was no significant correlation of ERN amplitude and error rate (correction session, $r = -0.01$, $P = 0.97$; signaling session, $r = -0.14$, $P = 0.933$). Note that investigations at the group level are not necessarily informative, as other between-subjects factors (e.g., variations in skull and brain anatomy) may influence ERN amplitudes to a large degree. To rule out a within-subjects effect of error rate, we matched trials from both sessions according to the number of errors in a window of 50 trials preceding the current trial. To this end, using a gliding window for each trial, the error rate over the preceding 50 trials was calculated. Then, for each subject, error trials from the two sessions were selected when the difference in preceding error rates was minimal. The success of matching was confirmed by subject-wise paired t tests comparing the preceding of error rates of the selected error trials revealing no significant differences at an alpha level of 0.05. At the group

level, this matching procedure resulted in a mean of 43 ± 2.0 selected trials per subject and session. For these trials, the mean error rate over all preceding 50 trials across subjects was $9.0 \pm 0.3\%$ for the signaling session and 9.3 ± 0.3 for the correction session ($T(28) = 0.20$, $P = 0.84$). The ERP results for the matched error trials are shown in Fig. 2. Inspection and statistical analyses confirmed that the ERN and frontal positivity were significantly larger in the signaling session. For the ERN and the subsequent frontal positivity, a main effect of Session (ERN, $F(1,14) = 4.67$, $P < 0.05$; subsequent positivity, $F(1,14) = 11.46$, $P < 0.005$) was found. The relationship between preceding error frequency and ERN is unknown; and if such relationship exists, it is unknown over how many preceding trials the performance monitoring system integrates. Therefore, we repeated the matching procedure with a window length of 10 preceding trials. Again, the ERP results indicated a larger ERN and frontal positivity in the signaling session (main effect of session for ERN, $F(1,14) = 3.48$, $P = 0.085$; subsequent positivity, $F(1,14) = 14.96$, $P < 0.005$). Taken together, the results of the matching procedure suggest that the difference in error rate does not account for the between-session difference in ERN amplitude.

As can be seen in Fig. 1, the Pe did not differ across sessions. This is supported by the fact that no significant main effects or

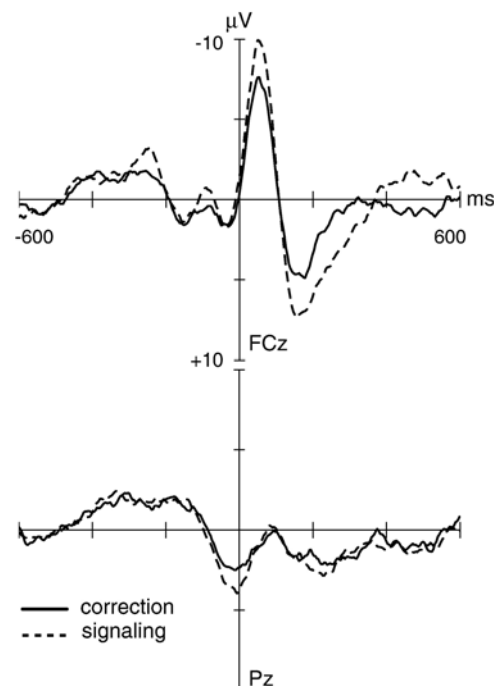


Fig. 2 – Response-locked grand mean average ERP waveforms for incompatible errors in the correction session (solid line) and the signaling session (dotted lines) at two midline electrodes after trials have been matched for occurrence of errors in a preceding window of 50 trials.

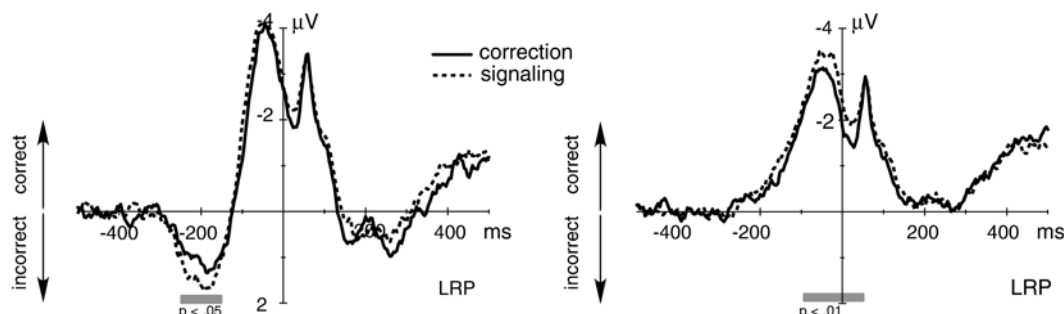


Fig. 3 – Response-locked grand mean LRP waveforms for incompatible correct trials (left panel) and compatible correct trials (right panel) in the correction session (solid line) and the signaling session (dotted lines). Time windows in which the waveforms were significantly different are indicated by a grey bar in the lower part of the panels.

interactions of the factors Session and Order were found ($P_s > 0.21$).

2.4. LRP findings

To test for differences of the motor threshold, LRPs were calculated for incompatible and compatible correct trials (Fig. 3). The LRP for the incompatible correct trials in the signaling session showed a stronger lateralization contralateral to the incorrect response, as confirmed by a t test in for the time window -250 to -150 ms ($t(14) = 3.01$, $P < 0.01$). This suggests that in the signaling session erroneous response tendencies were stronger in order to elicit overt errors. Similarly, the LRP for the compatible correct trials in the signaling session was more lateralized to the side contralateral to the correct response in a time window centered around the response (-100 to $+50$ ms; $t(14) = 2.14$, $P = 0.05$).

2.5. Stimulus-locked P300

Fig. 4 shows that the time course of the stimulus-locked waveforms for correct incompatible trials does not differ

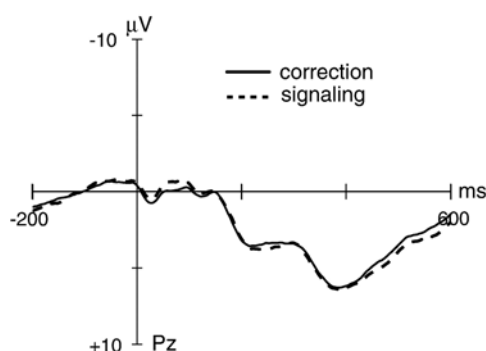


Fig. 4 – Stimulus-locked grand mean average ERP waveforms for incompatible correct trials in the correction session (solid line) and the signaling session (dotted lines) at Pz. No difference in the P300 is found.

across sessions. This is supported by the statistical analysis revealing no significant main effects or interactions of the factor Session ($P_s > 0.20$).

3. Discussion

The present study addressed the question whether intentional error correction can be interpreted as a behavioral indicator of performance monitoring. Alternatively, it was suggested to result from a reduction of the motor response threshold. Behavioral and electrophysiological findings for intentional error corrections were compared to error signaling using a signaling button to which no task-relevant stimulus was mapped. This error signaling procedure is assumed to require error detection (Rabbitt, 2002; Rabbitt and Phillips, 1967).

The behavioral data showed that error corrections were much faster than error signaling responses, as reported previously (Rabbitt, 2002; Rabbitt and Phillips, 1967). Several factors may account for this difference. In contrast to error corrections, error signaling requires interrupting the ongoing task routine and initiation of the signaling response. Moreover, while response fingers rested on the buttons assigned to the target stimuli, an additional movement was necessary to press the error signaling button. Based on this behavioral difference, it had been suggested that most immediate error corrections make use of the evolving, stimulus-driven correct response tendency (Rabbitt, 2002; Yeung et al., 2004), whereas error signaling requires error detection and additional response recoding.

The major ERP finding is that the error signaling session revealed higher amplitudes of the ERN and the subsequent frontal positive peak than in the error correction session. Based on findings from a simultaneous EEG/fMRI study using independent component analysis, it may be assumed that ERN and subsequent frontal positivity are closely related and both originate in the RCZ (Debener et al., 2005), thus supporting the findings of a source localization study (van Veen and Carter, 2002). Results of reanalyses of error trials from both sessions matched with respect to the prior occurrence of errors strongly suggest that the difference in error rates between the two sessions cannot explain the

ARTICLE IN PRESS

6

BRAIN RESEARCH XX (2006) XXX–XXX

results. It should be noted, however, that research is needed to elucidate whether and how the ERN is modulated by prior error frequency.

In a previous study, ERN amplitude differences between two groups differing with respect to their opportunity to correct errors were suggested to result from a difference in subjective error significance (Fiehler et al., 2005). It was assumed that errors which can be corrected immediately are perceived as being more admissible. A similar explanation could account for the present findings. However, the results of an introspective post-test survey indicate no difference in attention paid to the task and in the affective perception of errors between the two sessions. More importantly, the stimulus-locked P300 and the response-locked Pe did not differ across sessions. This suggests that task engagement in the two sessions did not differ. As the Pe has been implicated with conscious awareness of errors (Overbeek et al., 2005), it is likely that conscious processing of errors did not vary between sessions. Thus, a difference in error significance between error signaling and error correction seems unlikely. Finally, this motivational account does not suffice to explain the LRP findings.

Behavioral analyses revealed that participants followed the instruction and corrected more errors in the correction session. This increase in error corrections was reached at the cost of higher error rates. In addition, reaction times were decreased. These behavioral findings for the correction session are equivalent to what has been called increased “response impulsivity”, shown to be associated with reduced ERN amplitudes (Pailing et al., 2002; Ruchow et al., 2005). Why should participants become more impulsive when they are instructed to correct errors instead of signaling them? As the post-test survey suggests, it is unlikely that this shift in response impulsivity was based on motivational grounds. Increased response impulsivity can be reached by lowering the motor threshold. It is conceivable that participants have lowered their response threshold in the correction session thereby increasing the error correction rate. A lowered motor threshold may be an efficient way to enable the execution of even weak correct response tendencies without increasing the demands for the performance monitoring system. All behavioral predictions based on a motor threshold shift are met (see introduction): in the correction session, reaction times are decreased; error rates and correction rates are increased. Furthermore, a lowered motor threshold in the correction session should be associated with reduced post-response conflict on errors. Thus, the ERN, assumed to reflect the amount of post-response conflict (Yeung et al., 2004), would be expected to be smaller in the correction block. This prediction is also met by the empirical results. Finally, with a reduced motor threshold, the LRPs should show a reduced lateralization to the incorrect side in incompatible trials. Again, the empirical findings reveal a significantly reduced lateralization to the incorrect side in the correction session. An alternative explanation suggesting that the reduced lateralization to the incorrect side might result from preparation of the error correction response is unlikely, given the findings of a study investigating error corrections within the same experimental session (Falkenstein et al., 1994). Under these circumstances, when motor

threshold is unlikely to vary systematically across corrected and uncorrected errors, no difference in the LRP deviation to the incorrect side was found. With lower motor thresholds, also reduced lateralization to the correct side should be expected on compatible correct trials, which is also found in the data. Why did the lateralization of the LRPs to the correct side not differ significantly between sessions on incompatible correct trials? We suggest that this reflects a ceiling effect arising from the deadline procedure. Only responses prior to the deadline were included in the analysis, which leaves little room for variations in the strength and slope of the correct response tendencies of the included incompatible trials.

Thus, the most likely explanation for the present findings is that participants have lowered their motor threshold when they were instructed to correct errors in contrast to the signaling session in which error corrections were not required. It is likely that this shift in motor threshold is made in a block-wise manner: when investigating errors that were corrected and signaled in the signaling block, no difference of the ERN amplitude compared to signaled-only errors was found ($F_s < 1.1$; $P_s > 0.31$). This may explain the apparent inconsistencies in amplitude findings of previous studies on error corrections. While Fiehler et al. (2005) had used a between-subjects manipulation, most other studies (e.g., Falkenstein et al., 1994, 1996) have investigated the difference between uncorrected and corrected errors within the same experimental session, in which motor threshold may be expected to be more stable than at between subjects and sessions levels. Thus, we suggest that the previously reported ERN amplitude difference between the group instructed to correct errors and the group not instructed to correct errors (Fiehler et al., 2005) could result from a between-group difference in motor threshold.

While the motor threshold account fits the current data best and can explain previous findings, it is unknown how this shift in motor threshold is implemented by the participants. It does not seem to be a conscious change in strategy, however. One might speculate that basing immediate corrections on already evolving correct response tendencies is a more economic and faster way of correcting errors than initiating the corrective response as a result of performance monitoring. The costs of this motor threshold reduction (increased error rates) may remain unnoticed, as suggested by the post-test survey.

In summary, the present data show that differences in immediate error corrections may be attributable to modulations of motor threshold, which do not need to be directly related to performance monitoring. At a qualitative level, this is consistent with the response conflict monitoring hypothesis, but computational modeling of the present study by exclusively varying motor threshold has not been done, yet. Nevertheless, we can conclude that the error signaling procedure is a more direct and reliable way to behaviorally test the functional integrity of the performance monitoring system than the mere instruction to correct errors. This is of particular importance for performance monitoring studies in patients and after pharmacological challenges. Error signaling provides an additional behavioral measure which may serve to functionally interpret modulations of the ERN.

4. Experimental procedures

4.1. Participants

Fifteen young, healthy participants (eight female; mean age 26.6 ± 2.04 years) participated in this study after giving informed consent. They had no history of neurological or psychiatric disease and normal or corrected-to-normal vision. The study was performed in agreement with the Declaration of Helsinki. Participants were paid for their participation.

4.2. Task

An arrow version of the flanker task known to yield a sufficient number of errors was applied (Fiehler et al., 2005). Participants were instructed to press with the left or right index fingers according to the direction of a target arrow that was presented in the center of the screen for 30 ms. Distracting flanker arrows were presented above and below the target; their onset preceded the target onset by 80 ms. In 50% of the trials, the direction of the flanker arrows was incompatible with the required response. Participants were instructed to respond within a response deadline, which was dynamically adjusted to their response speed with the aim to obtain about 20% of errors on incompatible trials. After each response, a symbolic feedback indicated whether the deadline was met or whether participants should speed up on subsequent trials. Stimuli were presented using presentation™ (Neurobehavioral Systems). Further details on stimulus presentation can be obtained in Fiehler et al. (2005).

Participants performed two sessions of the task (960 trials each) in counterbalanced order. Every 10 min, participants were allowed to rest for about 3 min. Between sessions, there was a break of at least 10 min. In the correction session, participants were instructed to correct every encountered error by immediately pressing the correct response button. In the signaling session, they were asked to press a third button, on which no response to the primary task was mapped, whenever they realized they had made an erroneous response. Error correction was not encouraged but also not forbidden in the signaling session, i.e., no instruction regarding error corrections was given, thus avoiding attempts to inhibit spontaneous corrections. In both sessions, response speed and accuracy were emphasized equally.

4.3. EEG recordings

The participants were seated comfortably in a dimly lit, electrically shielded chamber. The electroencephalogram (EEG) was recorded with Ag/AgCl electrodes from 53 electrode sites (the extended 10–20 system, including the right mastoid) referenced to left mastoid. Electrode impedance was kept below 5 k Ω . The vertical electrooculogram (EOG) was recorded from electrodes placed above and below the right eye. To monitor horizontal eye movements, the EOG was collected from electrodes placed on the outer canthus of the left and right eye. EEG and EOG were recorded continuously with a low-pass filter of 70 Hz and AD converted with a 22-bit resolution at a sampling rate of 250 Hz.

4.4. Data analysis

Reaction times were defined as the latency of the response button relative to the onset of the target arrow. The latency of corrective responses relative to the preceding erroneous response will be called correction time. Similarly, the latency of signaling responses relative to the preceding error will be called signaling time. Results are listed as mean (\pm standard error of the mean), unless specified differently.

EEG analysis was performed using Matlab 7.01 (The Mathworks) and EEGLAB 4.51 (Delorme and Makeig, 2004). Continuous

EEG data were off-line re-referenced to common average reference and subjected to a 0.75–25 Hz band-pass filter. Visual inspection was used to reject data epochs contaminated with muscular artifacts. Thereafter, data were subjected to extended infomax independent component analysis (ICA, Bell and Sejnowski, 1995; Lee et al., 1999) for further artifact control. ICA finds an unmixing square matrix of the size of the number of channels, which, when matrix-multiplied with the raw data, reveals maximally temporally independent activations. A weight change of 10^{-7} as stop criterion resulted in stable decompositions after less than 800 iterations. Each independent component (IC) can be characterized by a time course (IC activation) and a spatial filter (IC map), the latter being given by the inverse weights. IC reflecting eye motion and residual muscular artifacts were discarded and activations of the remaining components backprojected to the voltage time series (Makeig et al., 2004). The response-locked epochs (–600 to +600 ms relative to the button press) of the resulting artifact-free EEG data were averaged. Here, we report ERPs for incompatible errors that were signaled in the signaling session and corrected in the correction session, respectively. Only trials in which the deadline was met were included. The average voltage of the time window between 600 and 400 ms prior to the response was used as a baseline. Response-locked LRP (–500 to +500 ms relative to the button press) were calculated for incompatible and compatible correct trials using the in-house EEProbe software. The LRP was assessed by using the ERP waveforms recorded at C3 and C4 using the double subtraction-averaging method (De Jong et al., 1988).

Analysis of the ERN was performed at the midline electrode FCz, using a peak-to-peak quantification providing baseline-independent measures (Falkenstein et al., 2000). The ERN amplitude was measured as the difference of the negative peak in a time window 0 to 120 ms relative to the button press and the preceding positive peak found in the time window –80 to 20 ms. Moreover, the frontal positivity immediately following the ERN, sometimes called ‘early error positivity’ (van Veen and Carter, 2002), was quantified in an analogous way as the difference of the positive peak in the time window +50 to +250 ms and the positive peak preceding the ERN. Furthermore, the classical error positivity (Pe) was quantified at Pz as the mean amplitude in the time window +200 to +500 ms relative to the positive peak preceding the ERN. Finally, in order to address the question whether engagement in the task differed between sessions and whether the session had a general effect on ERPs, the stimulus-locked P300 was analyzed for incompatible correct trials. Quantification was performed at Pz using the mean amplitude in the time window +200 to +500 ms after the target onset relative to a 200 ms pre-stimulus baseline. To address potential influences of session order, data were subjected to a repeated measures ANOVA with the factors Session (correction, signaling) and Order (signaling–correction, correction–signaling). In order to avoid reporting a large amount of data not speaking to the issues of interest, only main effects of Session and interactions with the factors Session and Order will be reported.

Acknowledgments

The authors wish to thank K. Fiehler, C. Klinge, and K. Wermann for their help in data collection and artifact control.

REFERENCES

- Bell, A.J., Sejnowski, T.J., 1995. An information-maximization approach to blind separation and blind deconvolution. *Neural Comput.* 7, 1129–1159.

ARTICLE IN PRESS

8

BRAIN RESEARCH XX (2006) XXX–XXX

- Botvinick, M.M., Cohen, J.D., Carter, C.S., 2004. Conflict monitoring and anterior cingulate cortex: an update. *Trends Cogn. Sci.* 8, 539–546.
- Debener, S., Ullsperger, M., Siegel, M., Fiehler, K., von Cramon, D.Y., Engel, A.K., 2005. Trial-by-trial coupling of concurrent electroencephalogram and functional magnetic resonance imaging identifies the dynamics of performance monitoring. *J. Neurosci.* 25, 11730–11737.
- De Jong, R., Wierda, M., Mulder, G., Mulder, L., 1988. Use of partial stimulus information in response processing. *J. Exp. Psychol. Hum. Percept. Perform.* 14, 682–692.
- Delorme, A., Makeig, S., 2004. EEGLAB: an open source toolbox for analysis of single trial EEG dynamics including independent component analysis. *J. Neurosci. Methods* 134, 9–21.
- Falkenstein, M., Hohnsbein, J., Hoormann, J., Blanke, L., 1990. Effects of errors in choice reaction tasks on the ERP under focused and divided attention. In: Brunia, C.H.M., Gaillard, A.W.K., Kok, A. (Eds.), *Psychophysiological Brain Research*, vol. 1. Tilburg Univ. Press, pp. 192–195.
- Falkenstein, M., Hohnsbein, J., Hoormann, J., 1994. Event-related potential correlates of errors in reaction tasks. In: Karmos, G., Molnar, M., Csepe, V., Czizler, I., Desmedt, J.E. (Eds.), *Perspectives of Event-Related Potentials Research (EEG Suppl. 44)*, vol. Suppl. 44. Elsevier Science, pp. 287–296.
- Falkenstein, M., Hohnsbein, J., Hoormann, J., 1996. Differential processing of motor errors. In: Ogura, C., Koga, Y., Shimokochi, M. (Eds.), *Recent Advances in Event-Related Brain Potential Research*. Elsevier Science, pp. 579–585.
- Falkenstein, M., Hoormann, J., Christ, S., Hohnsbein, J., 2000. ERP components on reaction errors and their functional significance: a tutorial. *Biol. Psychol.* 51, 87–107.
- Fiehler, K., Ullsperger, M., Grigutsch, M., von Cramon, D., 2004. Cardiac responses to error processing and response conflict. In: Ullsperger, M., Falkenstein, M. (Eds.), *Errors, Conflicts, and The Brain. Current Opinions on Performance Monitoring*. MPI for Human Cognitive and Brain Sciences, Leipzig, pp. 135–140.
- Fiehler, K., Ullsperger, M., Von Cramon, D.Y., 2005. Electrophysiological correlates of error correction. *Psychophysiology* 42, 72–82.
- Gehring, W.J., Knight, R.T., 2000. Prefrontal–cingulate interactions in action monitoring. *Nat. Neurosci.* 3, 516–520.
- Gehring, W.J., Goss, B., Coles, M.G., Meyer, D.E., et al., 1993. A neural system for error detection and compensation. *Psychol. Sci.* 4, 385–390.
- Gratton, G., Coles, M.G., Sirevaag, E.J., Eriksen, C.W., Donchin, E., 1988. Pre- and poststimulus activation of response channels: a psychophysiological analysis. *J. Exp. Psychol. Hum. Percept. Perform.* 14, 331–344.
- Kutas, M., Donchin, E., 1980. Preparation to respond as manifested by movement-related brain potentials. *Brain Res.* 202, 95–115.
- Lee, T.W., Girolami, M., Sejnowski, T.J., 1999. Independent component analysis using an extended infomax algorithm for mixed subgaussian and supergaussian sources. *Neural Comput.* 11, 417–441.
- Makeig, S., Debener, S., Onton, J., Delorme, A., 2004. Mining event-related brain dynamics. *Trends Cogn. Sci.* 8, 204–210.
- Overbeek, T.J.M., Nieuwenhuis, S., Ridderinkhof, K.R., 2005. Dissociable components of error processing: on the functional significance of the Pe Vis-à-vis the ERN/Ne. *J. Psychophysiol.* 19, 319–329.
- Pailing, P.E., Segalowitz, S.J., Dywan, J., Davies, P.L., 2002. Error negativity and response control. *Psychophysiology* 39, 198–206.
- Rabbitt, P., 2002. Consciousness is slower than you think. *Q. J. Exp. Psychol.* A 55, 1081–1092.
- Rabbitt, P.M.A., Phillips, S., 1967. Error detection and correction latencies as a function of S–R compatibility. *Q. J. Exp. Psychol.* 19, 37–42.
- Ridderinkhof, K.R., Ullsperger, M., Crone, E.A., Nieuwenhuis, S., 2004. The role of the medial frontal cortex in cognitive control. *Science* 306, 443–447.
- Rodriguez-Fornells, A., Kurzbuch, A.R., Munte, T.F., 2002. Time course of error detection and correction in humans: neurophysiological evidence. *J. Neurosci.* 22, 9990–9996.
- Ruchow, M., Spitzer, M., Grön, G., Grothe, J., Kiefer, M., 2005. Error processing and impulsiveness in normals: evidence from event-related potentials. *Cogn. Brain Res.* 24, 317–325.
- Rugg, M.D.C., Coles, M.G.H., 1995. *Electrophysiology of Mind. Event-Related Brain Potentials and Cognition*. Oxford Univ. Press, New York.
- Ullsperger, M., 2006. Performance monitoring in neurological and psychiatric patients. *Int. J. Psychophysiol.* 59 (1), 59–69.
- Ullsperger, M., von Cramon, D.Y., 2001. Subprocesses of performance monitoring: a dissociation of error processing and response competition revealed by event-related fMRI and ERPs. *NeuroImage* 14, 1387–1401.
- Ullsperger, M., von Cramon, D.Y., in press. The role of intact frontostriatal circuits in error processing. *J. Cogn. Neurosci.* 18 (4).
- Ullsperger, M., Volz, K.G., von Cramon, D.Y., 2004. A common neural system signaling the need for behavioral changes. *Trends Cogn. Sci.* 8, 445–446.
- Ullsperger, M., Bylsma, L.M., Botvinick, M.M., 2005. The conflict adaptation effect: it's not just priming. *Cogn. Affect Behav. Neurosci.* 5 (4), 467–471.
- van Veen, V., Carter, C.S., 2002. The timing of action-monitoring processes in the anterior cingulate cortex. *J. Cogn. Neurosci.* 14, 593–602.
- Yeung, N., Cohen, J.D., Botvinick, M.M., 2004. The neural basis of error detection: conflict monitoring and the error-related negativity. *Psychol. Rev.* 111, 931–959.

Chapter 13

The conflict-adaptation effect: it's not just priming.

In addition to the immediate motor action compensating errors, a number of adjustments concern trials subsequent to the situation involving an error or high error likelihood. The study presented in Chapter 5 demonstrates that the error monitoring signal predicts post-error slowing. In addition to this rather global shift in the tradeoff between speed and accuracy of responding that place the cognitive system in a more cautious (as opposed to impulsive) response mode, such adjustments can also lead to increases in control that improve the efficiency of information processing (Ridderinkhof, 2002; Ridderinkhof et al., 2002).

For example, in the flanker task trial-by-trial modulations of reaction times and error rates have been observed. Gratton and colleagues (Gratton et al., 1992) investigated the effects of trial-type transitions (compatible – compatible [C-C], compatible – incompatible [C-I], incompatible – compatible [I-C], and incompatible – incompatible [I-I]) and showed that the interference effect (reaction time for incompatible minus compatible trials) was reduced following incompatible trials. The occurrence of an incompatible trial thus seemed to enhance target processing and/or suppress flanker processing on the following trial. This finding appears to provide an example of the reactive adjustments in control posited by the conflict monitoring hypothesis: Incompatible trials involve response conflict, and it is this, according to the theory, that causes them to be associated with a subsequent intensification of top-down control (Botvinick et al., 1999; Botvinick et al., 2001; Botvinick et al., 2004). Similar findings have been reported for the Stroop color-naming task and for the Simon spatial-congruency task (Sturmer et al., 2002; Kerns et al., 2004).

However, a recent study has challenged the view that the observed sequential effects reflect conflict adaptation and cognitive adjustments (Mayr et al., 2003). The authors suggest that the sequential effects are a result of perceptual priming due to stimulus repetitions. The present Chapter addresses this debate and shows in two behavioral experiments that the perceptual priming account is not sufficient to explain the data. Thus, the present findings support the view that response conflict monitoring may play a role in the modulation of ongoing task performance.

Cognitive, Affective, & Behavioral Neuroscience
2005, 5 (4), 467-472

The conflict adaptation effect: It's not just priming

MARKUS ULLSPERGER

Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany

and

LAUREN M. BYLSMA and MATTHEW M. BOTVINICK

University of Pennsylvania, Philadelphia, Pennsylvania

Analyses of trial sequences in flanker tasks have revealed cognitive adaptation, reflected in a reduced interference effect following incompatible trials (Gratton, Coles, & Donchin, 1992). These effects have been explained on the basis of the response conflict monitoring model of Botvinick, Braver, Barch, Carter, and Cohen (2001), who proposed that preceding response conflict triggers stronger top-down control, leading to performance improvements on subsequent trials of similar context. A recent study (Mayr, Awh, & Laurey, 2003) has challenged this account, suggesting that the behavioral adaptations are confined to trial sequences of exact trial repetitions and can therefore be explained by repetition priming. Here, we present two experiments in which the sequential dependency effect was present even on trial sequences that did not involve stimulus repeats. We discuss the data with respect to the conflict-monitoring and repetition-priming accounts.

In a recent work, Botvinick, Braver, Barch, Carter, and Cohen (2001) proposed that cognitive control is modulated, in part, on the basis of a process referred to as *response conflict monitoring*. According to this account, increased top-down control over information processing is triggered by the occurrence of response competition. In addition to certain neuroscientific data, the conflict monitoring theory is based on a set of behavioral phenomena that appear to reflect online reactive adjustments in control. A prominent example is provided by Gratton, Coles, and Donchin (1992), who reported evidence of a sequential dependency effect in the Eriksen flanker task (Eriksen & Eriksen, 1974). The flanker task calls for a left or right response based on the identity of a centrally presented target symbol. This target is surrounded by distractor flanker symbols, which themselves map to responses that are either compatible or incompatible with the required response. Gratton et al. investigated the effects of trial-type transitions (compatible-compatible [C-C], compatible-incompatible [C-I], incompatible-compatible [I-C], and incompatible-incompatible [I-I]) and showed that the interference effect (reaction time [RT] for incompatible trials minus RT for compatible trials) was reduced following incompatible trials. The occurrence of an incompatible trial thus appeared to enhance target processing and/or suppress flanker processing on the following trial. As Botvinick and colleagues ar-

gued (Botvinick et al., 2001; Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999), this finding appears to provide an example of the reactive adjustments in control posited by the conflict monitoring hypothesis: Incompatible trials involve response conflict, and it is this that causes them to be associated with a subsequent intensification of top-down control.

A challenge to this account was recently put forth by Mayr, Awh, and Laurey (2003). They suggested that the effect reported by Gratton et al. (1992) might simply reflect repetition priming. Note that one way of describing that effect is as a shortening of RTs in trials in which the stimulus type (compatible vs. incompatible) is the same as it was on the preceding trial. Note further that in the usual version of the task, such trial type repeats also frequently involve a repetition of the entire stimulus (e.g., > > < > > → > > < > >). Taking both of these points into account, Mayr et al. suggested that stimulus repetition itself might be responsible for the faster RTs seen with trial type repeats, simply as a consequence of repetition priming.

Mayr et al. (2003) presented evidence for this account from two experiments. In the first, participants performed a version of the flanker task using left- and right-facing arrow heads. Although their performance displayed the effect originally described by Gratton et al. (1992), this effect was limited to trials in which the target item was the same as it was on the preceding trial. Trials in which there was no repeat showed no such effect. A second experiment, in which stimulus elements never repeated from one trial to the next, also failed to show the effect described by Gratton et al.

The findings reported by Mayr et al. (2003) are surprising for a number of reasons. First, they contrast with the results of Gratton et al. (1992), who addressed the

The work of M.M.B. was supported in part by National Institute of Mental Health Grant K01 MH 65241-2. We are indebted to D. Y. von Cramon for suggestions on an earlier version of the manuscript. Correspondence concerning this article should be addressed to M. Ullsperger, Max Planck Institute for Human Cognitive and Brain Sciences, Stephanstr. 1A, Leipzig D-04103, Germany (e-mail: ullsperg@cbs.mpg.de).

priming explanation for their findings by showing that there was no significant difference between target alternation and target repetition trials.¹ Moreover, in their Experiment 3 Gratton et al. showed that similar effects can be obtained by modulating expectancy for incompatible trials using an arbitrary precue, thus eliminating the relationship with previous stimuli and responses as a factor. Second, there is evidence that conflict adjustment effects can be observed, independent of priming, in other tasks (e.g., the Stroop task [Kerns et al., 2004] and the Simon task [Sohn & Carter, 2003]; see the Discussion section). Given these considerations, it seems important to determine the extent to which the findings of Mayr et al. are replicable and, in particular, the extent to which they generalize across task implementations.

We report here the results of two experiments that speak to this issue. In each, a conflict adaptation effect was observed in the flanker task, in a form not attributable to priming. The first experiment involved a reanalysis of previously collected data based on the conventional arrowhead flanker task. The second was a new experiment, in which an attempt was made to minimize repetitions of stimulus elements from one trial to the next by using a larger stimulus set.

EXPERIMENT 1

Method

Participants. Nineteen University of Leipzig undergraduates (9 female) took part in the study. Their ages ranged from 19 to 31 years. The participants provided informed consent prior to the beginning of the experiment and received an hourly base rate for their participation.

Procedure. The stimuli, which were presented using the ERTS software package (BeriSoft, Frankfurt), consisted of a central left- or right-facing arrow with two flanker arrows above and two below. The arrows were 0.46° tall and 1.08° wide, and the flankers were presented 0.52° and 1.04° above and below the screen center. Targets were presented for 30 msec together with the flankers, which first appeared 80 msec earlier than the targets. The left and right index fingers were used for buttonpress responses according to the direction indicated by the target arrow. Responses had to be given before a response deadline (377 msec). When the response was given after the deadline had elapsed, the participants received feedback indicating that they should speed up their responses. The participants performed two 264-trial blocks containing randomly sequenced 50% incompatible and 50% compatible trials. The intertrial interval (ITI) varied randomly between 5,000 and 6,000 msec in steps of 500 msec. The blocks differed with respect to instructions, which were reinforced by financial incentives. In both blocks, correct responses were rewarded (€0.07). In one block, response accuracy was instructed and errors were penalized more (−€0.40) than late responses (−€0.20). In the other block, response speed was stressed in the instructions and, in consistency with this, late responses were penalized more (−€0.40) than errors (−€0.20). Block sequence was counterbalanced across participants. Between blocks, the participants had a short break, after which they received the instructions for the next block. Behavioral data were collected and event-related potentials were recorded during the experiments. The electrophysiological data, irrelevant to the issue discussed here, is reported elsewhere (Ullsperger & Szymanowski, 2004).

Results

Four-way analyses of variance (ANOVAs) were conducted for both error rates and hit RTs, with factors of current trial type (compatible vs. incompatible) and previous trial type (compatible vs. incompatible), a third factor (target type) coding for the relationship of the target item on the current trial to the target on the previous trial (target-repeat vs. target-alternation), and a fourth factor coding for instruction (speed vs. accuracy). Trials following errors were excluded from the analyses. Figure 1 depicts the mean RTs and error rates as a function of response conflict on the current trial and resolved conflict on the preceding trials, broken down by the target-type and the instruction factors. The results of the ANOVAs are shown in Table 1.

Both analyses yielded significant main effects of current trial type (the standard flanker effect) and target type. Moreover, the main effect of instruction for error rate confirms that fewer errors were made when accuracy was emphasized, whereas RTs tended to be longer. The main effect of previous trial type was significant for error rate but not for RT. More to the point, the conflict adaptation effect was evident in an interaction between current and previous trial types for both analyses. Critically, and in contrast with the findings of Mayr et al. (2003), the conflict adaptation effect was observed even on target alternation trials. Follow-up ANOVAs focusing only on these trials yielded a significant interaction between current and previous trial types [for RT, $F(1,18) = 10.89, p < .01$; for error rate, $F(1,18) = 9.92, p < .01$] as well as a main effect of previous trial type for error rate [$F(1,18) = 6.33, p < .05$]. No significant interactions between previous trial type and instruction or between previous trial type and target type were found. In follow-up comparisons, the interaction between current and previous trial types was addressed, revealing that error rates were lower in I–I trial sequences than in C–I trial sequences [main effect of previous trial type: $F(1,18) = 10.05, p < .01$]. For RT, an interaction between previous trial type and instruction was found [$F(1,18) = 8.88, p < .01$], reflecting the fact that RT was shorter in I–I trial sequences than in C–I trial sequences in the accuracy condition ($p < .0001$) but not in the speed condition ($p = .41$). In compatible trials, RTs showed a tendency to be shorter in C–C trial sequences than in I–C trial sequences [$F(1,18) = 3.58, p = .07$]. Due to floor effects, for error rates in compatible trials no significant sequence effect was found ($p = .74$).

EXPERIMENT 2

Method

Participants. The participants included 8 University of Pennsylvania undergraduates (4 female) who had responded to an electronic newsgroup posting. Their ages ranged from 18 to 21 years. The participants provided informed consent prior to the beginning of the experiment and received an hourly base rate for their participation.

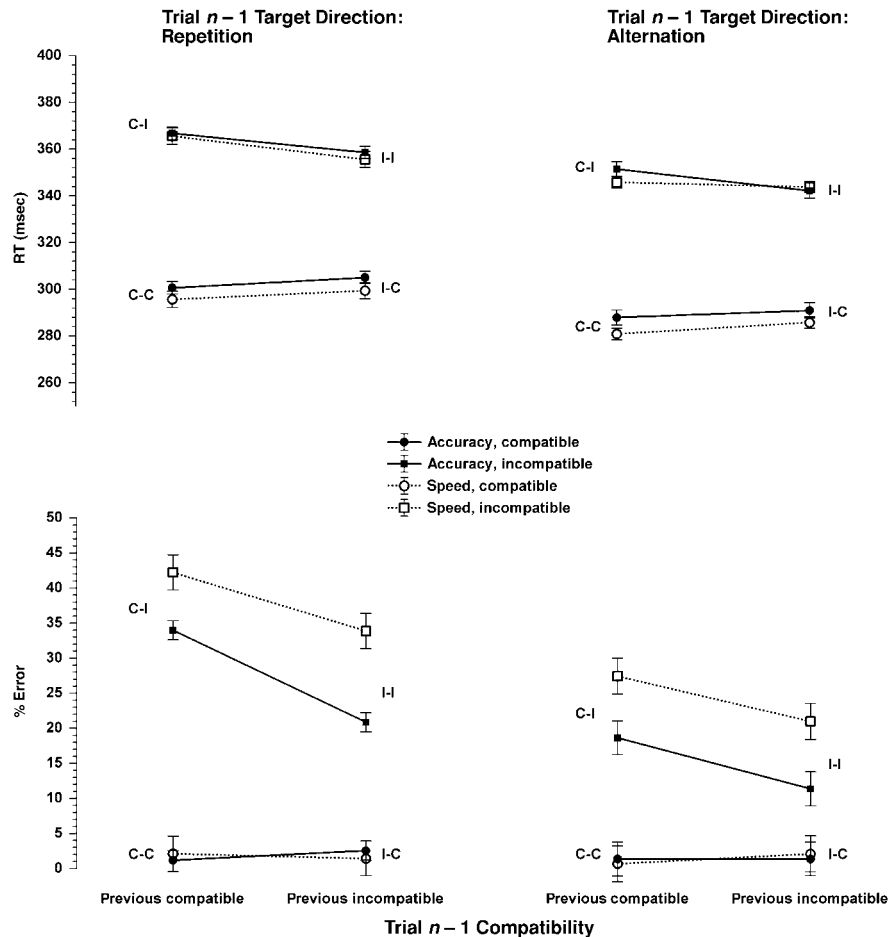


Figure 1. Mean reaction times (RTs, upper panel) and error rates (lower panel) as a function of response conflict on trial n and resolved conflict on the preceding trial $n-1$, broken down by the target transition factor (left, repetition; right, alternation) and by instruction (solid lines, accuracy instruction; dotted lines, speed instruction). Error bars show standard errors of the means, computed to partial out between-sessions variance (following Loftus & Masson, 1994).

Procedure. The experiment was conducted on a standard desktop computer using the E-Prime software package (Psychological Research Tools, Pittsburgh, PA). Each stimulus consisted of a six-digit array presented at the center of the computer monitor. Each array consisted of a central target digit (between 1 and 9, inclusive) and four identical flanker digits (also between 1 and 9, inclusive), two on either side of the target. The target item was underscored. Stimuli could be either compatible (flanker digits identical to target digit) or incompatible (flanker digits different from target). Beyond this constraint, component digits were selected randomly. In response to each stimulus, the participant was instructed to indicate the target digit by pressing the appropriate key on the computer's numeric keypad. Trials began with a 50-msec warning tone followed by a 1,000-msec preparatory period. Next, the target appeared and remained on the screen for 100 msec. The ITI, measured from the participant's response, varied randomly between 3,500 and

5,500 msec (in steps of 250 msec). Within each block, compatible and incompatible trials were intermixed randomly and in equal proportions. Each participant participated in one practice and three experimental sessions, each composed of 15 blocks of 80 trials. Each session lasted approximately 2 h, and the participants were given the opportunity to take a 10-min break at the halfway point. The participants participated in no more than one session per day and completed all sessions within 1 week.

Results

Data analysis focused on trials on which none of the stimulus elements had appeared on the preceding trial. Trials following errors were discarded, as were the first five trials in each block. Average RTs (for correct responses) and error rates are shown in Figure 2.

Table 1
Results of the Repeated Measures ANOVAs for
Error Rates and Hit Reaction Times (RTs)

| Factors and Interactions | df | Error Rate <i>F</i> | Hit RT <i>F</i> |
|--|------|---------------------|-----------------|
| Current trial type | 1,18 | 106.82* | 333.46* |
| Previous trial type | 1,18 | 15.22* | 1.61 |
| Target type | 1,18 | 15.63* | 10.99* |
| Instruction | 1,18 | 14.45* | 3.48† |
| Current trial type × instruction | 1,18 | 18.85* | 1.74 |
| Current trial type × target type | 1,18 | 20.11* | 0.60 |
| Current trial type × previous trial type | 1,18 | 21.06* | 33.89* |

† $p < .1$. * $p < .01$.

A repeated measures (within-blocks) ANOVA on RT was conducted, with current trial type and previous trial type as factors. A main effect of current trial type was present [$F(1,23) = 162.17, p < .001$], confirming the presence of the basic flanker effect. More important, a significant interaction was found between current and previous trial types [$F(1,23) = 6.36, p = .019$]. The details of this interaction were consistent with the conflict adaptation effect; the flanker effect (RT for incompatible trials minus RT for compatible trials) was 26% smaller following incompatible trials than following compatible ones (19 vs. 26 msec). The main effect of previous trial type did not reach significance [$F(1,23) = 2.68, p = .12$]. A comparable ANOVA on error rate yielded a main effect of current trial type [$F(1,23) = 21.31, p < .001$] and a main effect of previous trial type [$F(1,23) = 4.57, p < .05$], reflecting slightly lower error rates for both compatible and incompatible trials when these followed incompatible trials.

Two comments are merited concerning these results. The first pertains to the size of the RT effect. It is important to note, in this connection, that the basic interference effect was small—an anticipated consequence of increasing the response set from the usual two to nine. Because the sought adjustment effect would not have been expected to surpass the basic interference effect, the former effect was predicted to be well below 25 msec. It should not be surprising, therefore, that the absolute size of the adjustment effect was small, and this does nothing to undermine its theoretical implications. Indeed, as a proportion of the overall interference effect, the adjustment was similar in magnitude to that reported by Gratton et al. (1992).

A second comment pertains to error rates. The presence of a main effect of previous trial type suggests that two forms of conflict adaptation may have been occurring: (1) an increased focus on the central target item, evident in the interaction effect seen in the RT data, and (2) a speed–accuracy trade-off, reflected in overall lower error rates (and the trend toward slower responses²) following incompatible trials. This speed–accuracy trade-off can be seen as an adaptation to the specifics of the task, which, unlike the task used in Experiment 1, required the participants to select among nine response keys. Further analyses suggested that the majority of errors in this experiment were due to inaccurate aiming of manual responses rather than to stimulus-driven interference effects (specifically, 76% of the errors involved striking a key adjacent to the target; in only 3% of incompatible trials did the response match the flanker item). Given the frequency of such spatial inaccuracies,

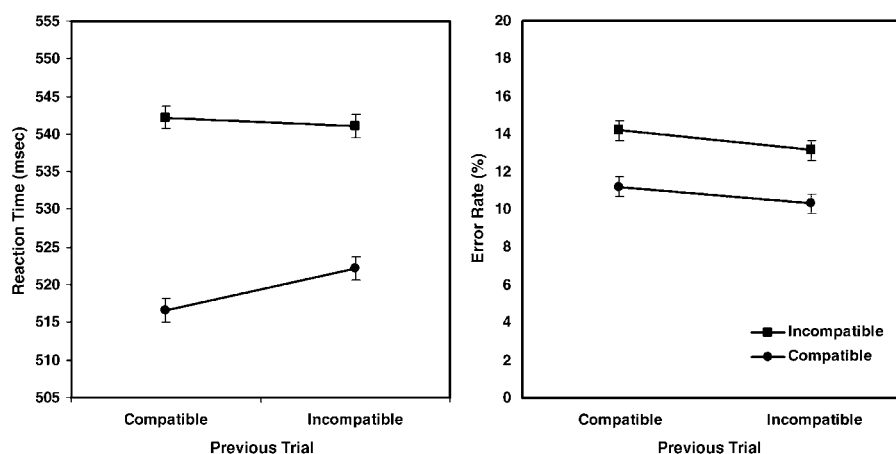


Figure 2. Left: Mean reaction times (RTs) for compatible and incompatible trials, reported separately for trials coming after compatible and incompatible trials. Error bars show standard errors of the means, computed to partial out between-sessions variance (following Loftus & Masson, 1994). Right: Mean error rates for the same trial types.

it may have been useful to trade speed for accuracy following high-conflict trials.

DISCUSSION

In both experiments, significant sequence dependency effects were found—that is, RTs and error rates were lowered on incompatible trials that were preceded by incompatible ones. Because in both cases target repetitions were excluded from analysis, the findings cannot be explained by response priming. Instead, in line with the account put forth by Botvinick et al. (2001), the observed fluctuations in behavior appear consistent with adjustments in control triggered by conflict.

Given all these results, an obvious question is why Mayr et al. (2003) failed to observe a conflict adjustment effect in their two experiments. One possible explanation, which applies to their first experiment, is that the adjustment effect may have been masked by negative priming. Stadler and Hogan (1996) have shown that RTs are unusually high for incompatible flanker stimuli when the locations of target and flanker items are reversed from those of the preceding trial (e.g., $< < > < < \rightarrow > > < > >$). In the analysis presented by Mayr et al., which took only target change trials into account, this negative priming effect would have the result of inflating RTs for I–I trials, possibly masking an underlying conflict adjustment effect. Our own experiments may have avoided this masking effect by minimizing the effect of negative priming. Such priming is unlikely to have played any role in our Experiment 2, in which stimulus elements rarely repeated from one trial to the next. Although such repetitions did occur in Experiment 1, the associated priming effect may have been minimized by the use of relatively long ITIs and brief stimulus presentation times (in contrast with Mayr et al., 2003, in which stimuli remained on the screen until the participant responded, and the response–stimulus interval was 1,000 msec; U. Mayr, personal communication, May 28, 2003). It seems plausible that these parameters minimized negative priming effects, allowing us to avoid the hypothesized masking effect. A further difference with the Mayr et al. study may be important: Gratton et al. (1992) and the present authors used speeded tasks, whereas Mayr et al. applied unspeeded versions, which may have resulted in a decreased need to utilize conflict-based strategy adjustments.

The findings from the second experiment of Mayr et al. (2003) are somewhat harder to explain. In that experiment, trials alternated between stimuli consisting of left- and right-facing arrows and stimuli consisting of upward- and downward-facing arrows. One possibility is that this alternation was treated by participants as a switch between two independent tasks. Such switching has been shown to involve complex effects on cognitive control (Rogers & Monsell, 1995). In view of this, it is not clear that the conflict monitoring model would predict the top-down control modulations across the two

tasks embedded in the Mayr et al. experiment. Recently, Corballis and Gratton (2003) showed that sequence dependence effects in a flanker task do not generalize from stimulus locations in one hemifield to locations in the other hemifield. Similarly, it may be hypothesized that response-conflict-triggered attentional modulations would not generalize from one stimulus orientation to the other.

Our present findings fit well with observations from other tasks. For example, in a study of the Stroop task, Kerns et al. (2004) found less influence of word identity on color naming following incompatible trials than following compatible trials, in consistency with the idea that participants focused more exclusively on the task-relevant color dimension following high-conflict incongruent trials. Sohn and Carter (2003) obtained parallel results in the Simon task—that is, interference effects on trials following incongruent trials were attenuated, again in accordance with the idea that participants focused more on the task-relevant stimulus dimension following high-conflict responses.

The idea that conflict triggers adjustments in control is also supported by data from cognitive neuroscience. Several neuroimaging studies have supported the idea that posterodorsal mesial frontal cortex (pmFC), in the vicinity of the anterior cingulate cortex, responds to the occurrence of response conflicts (e.g., Botvinick et al., 1999; Carter et al., 1998; MacDonald, Cohen, Stenger, & Carter, 2000; Ullsperger & von Cramon, 2001). Recent neuroimaging evidence supports the view that this conflict-related activity is linked to subsequent adjustments in control; Kerns et al. (2004) showed, in the Stroop task, that the strength of trial-specific pmFC activation predicts the degree of Stroop interference (and, by inference, the state of top-down control) on the subsequent trial.

Experiment 3 of the original work by Gratton et al. (1992) suggests that, like response conflict, arbitrary cues also may trigger the implementation of top-down control.

Whatever the explanation for the findings of Mayr et al. (2003), the present data indicate that those findings may not widely generalize a consideration that limits their theoretical implications. Instead, taken together with converging evidence from other domains, the present findings support the view that conflict monitoring may play a role in the modulation of ongoing task performance.

A final consideration is necessary to address some differences in the adjustments subsequent to response conflict between the two experiments. The data from Experiment 2 can be understood in terms of a twofold response to conflict involving (1) an increased focus on the target item and (2) a raising of response threshold. Experiment 2 further suggests that the latter adjustment can effectively mask the effect of focusing on incompatible trials. Interestingly, data from the accuracy block in Experiment 1 do not reflect the adjustment of response threshold (which would result in between-trials speed–

accuracy changes). This may be explained by the response deadline, which limits the range in which response threshold can be varied. Thus, the present study suggests that task context may influence the form of adjustments resulting from response conflict.

REFERENCES

- BOTVINICK, M. M., BRAVER, T. S., BARCH, D. M., CARTER, C. S., & COHEN, J. D. (2001). Conflict monitoring and cognitive control. *Psychological Review*, **108**, 624-652.
- BOTVINICK, M. [M.], NYSTROM, L. E., FISSELL, K., CARTER, C. S., & COHEN, J. D. (1999). Conflict monitoring versus selection-for-action in anterior cingulate cortex. *Nature*, **402**, 179-181.
- CARTER, C. S., BRAVER, T. S., BARCH, D. M., BOTVINICK, M. M., NOLL, D., & COHEN, J. D. (1998). Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science*, **280**, 747-749.
- CORBALLIS, P. M., & GRATTON, G. (2003). Independent control of processing strategies for different locations in the visual field. *Biological Psychology*, **64**, 191-209.
- ERIKSEN, B. A., & ERIKSEN, C. W. (1974). Effects of noise letters upon the identification of a target letter in a nonsearch task. *Perception & Psychophysics*, **16**, 143-149.
- GRATTON, G., COLES, M. G. H., & DONCHIN, E. (1992). Optimizing the use of information: Strategic control of activation of responses. *Journal of Experimental Psychology: General*, **121**, 480-506.
- KERNS, J. G., COHEN, J. D., MACDONALD, A. W., III, CHO, R. Y., STENGER, V. A., & CARTER, C. S. (2004). Anterior cingulate conflict monitoring and adjustments in control. *Science*, **303**, 1023-1026.
- LOFTUS, G. R., & MASSON, M. E. J. (1994). Using confidence intervals in within-subject designs. *Psychonomic Bulletin & Review*, **1**, 476-490.
- MACDONALD, A. W., III, COHEN, J. D., STENGER, V. A., & CARTER, C. S. (2000). Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science*, **288**, 1835-1838.
- MAYR, U., AWH, E., & LAUREY, P. (2003). Conflict adaptation effects in the absence of executive control. *Nature Neuroscience*, **6**, 450-452.
- ROGERS, R. D., & MONSELL, S. (1995). Costs of a predictable switch between simple cognitive tasks. *Journal of Experimental Psychology: General*, **124**, 207-231.
- SOHN, M. H., & CARTER, C. S. (2003). *Conflict adaptation is independent of stimulus repetition: Evidence for the conflict monitoring model*. Manuscript submitted for publication.
- STADLER, M. A., & HOGAN, M. E. (1996). Varieties of positive and negative priming. *Psychonomic Bulletin & Review*, **3**, 87-90.
- ULLSPERGER, M., & SZYMANOWSKI, F. (2004). ERP correlates of error relevance. In M. Ullsperger & M. Falkenstein (Eds.), *Errors, conflicts, and the brain: Current opinions on performance monitoring* (pp. 171-177). Leipzig: MPI for Human Cognitive and Brain Sciences.
- ULLSPERGER, M., & VON CRAMON, D. Y. (2001). Subprocesses of performance monitoring: A dissociation of error processing and response competition revealed by event-related fMRI and ERPs. *NeuroImage*, **14**, 1387-1401.

NOTES

1. Gratton et al. (1992) did not report separate statistical analyses for target alternation trials alone, however.
2. The trend toward overall slower responses following incompatible trials may account for the fact that RTs for incompatible trials did not differ on the basis of preceding trial type [$t(23) = 0.58, p > .05$]. The difference for compatible trials was found to be statistically significant [$t(23) = 3.05, p < .01$].

(Manuscript received February 4, 2004;
revision accepted for publication November 11, 2004.)

Part V

Factors Modulating Performance Monitoring

Chapter 14

ERP correlates of error relevance

In Chapter 2.4 evidence is reviewed that shows the influence of affective and motivational factors on ERP correlates of performance monitoring. It is very plausible to assume a bidirectional relationship between emotional and motivational processes on one hand and performance monitoring on the other. The exact nature of these interactions is still rather unclear. It seems conceivable that, for example, the experienced frequency of errors influences the motivation to pursue a certain task. Conversely, variations in the relevance of an action goal can be assumed to influence the engagement of the performance monitoring system. Two studies investigating the latter relationship are reported in this and the following Chapters (EEG study, Chapter 14; fMRI study, Chapter 15).

As outlined in Chapter 2.4, based on the evidence that affective factors interact with the ERN some researchers have reasoned that the ERN reflects the activity of a general evaluative system concerned with the motivational significance of errors and emotional reactions to errors. Neuroimaging findings showing correlations between the activity in the pFMC and autonomic responses have been interpreted as supporting these evaluative monitoring accounts (Critchley et al., 2000; Critchley et al., 2003; Luu and Posner, 2003; Critchley et al., 2005). It should be noted, however, that the reported interactions of emotional factors with correlates of performance monitoring do not contradict other models of performance monitoring like the mismatch, reinforcement learning, and response conflict monitoring theories. In agreement with a recent discussion paper I believe that the cognitive and affective theories of performance monitoring are rather complementary than contradictory (Yeung, 2004). This is also reflected in the unified view on the role of the pFMC in performance monitoring (Chapter 6), which suggests that this region is engaged in signaling the need for adjustments whenever the action outcome is at risk or worse than expected. As we have clarified in a commentary paper (Ullsperger et al., 2004), the adjustments may affect motor, cognitive, affective, autonomic, and even social levels of human information processing. Moreover, the evaluation whether an action outcome is *worse* than expected or *at risk* implicitly contains an affective aspect. Thus, a strict dichotomy between cognitive and emotional functions of the performance monitoring system seems to be neither appropriate nor plausible. Thus, functional considerations and the neuroanatomical position of the performance monitoring system involving limbic, paralimbic, neocortical and subcortical structures suggest that it has an intermediate position bridging cognition and emotion, motivation and drive in order to allow goal-directed behavior in the service of action outcome optimization.

These considerations notwithstanding, it is important to disentangle the different factors influencing the engagement of the performance monitoring system. The following two Chapters address the subjective significance of errors. It will be shown that higher error significance is associated with larger ERN amplitudes and increased fMRI signals in the RCZ.

ERP Correlates of Error Relevance

Markus Ullsperger and Friedemann Szymanowski

Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany

Motivational aspects have repeatedly been proposed to modulate the involvement of the error processing system. The present study addresses the influence of error relevance on remedial actions and electrophysiological correlates of error processing. We recorded event-related potentials (ERPs) from 32 electrodes, while healthy volunteers performed two blocks of a speeded flanker task in counterbalanced order. Blocks differed with regard to instruction (accuracy vs. speed) which was reinforced by monetary reward. Behavioral data suggest that error relevance influenced only prolonged adjustments, such as post-error slowing, but not immediate corrections. The ERP study revealed a larger amplitude for the error-related negativity (ERN/ N_E), when accuracy was reinforced, thus replicating the findings by Gehring et al. (1993). In addition, in contrast to the speed condition the error positivity (P_E) was lateralized to the left when accuracy was emphasized. The findings are discussed with respect to recent neuroimaging findings.

Introduction

Action slips due to premature responses are commonly detected by the acting individual and followed by remedial actions such as immediate corrections and post-error adjustments (Rabbitt, 1966). Error detection is a prerequisite for the implementation of these remedial actions in order to finally reach a certain goal. If, however, a goal becomes less relevant to the individual, detection of errors which would disturb the achievement of this currently irrelevant goal is less important. Therefore, it is conceivable that for economical reasons the error detection system is less active during currently irrelevant errors. Already in 1993, Gehring and colleagues showed that the error-related negativity (ERN or N_E ; Falkenstein et al., 1990; Gehring et al., 1993) amplitude was larger when accuracy was instructed as compared to speed. Consistent with this finding, we recently showed that the hemodynamic activity of the likely generator of the ERN was modulated by error relevance (Ullsperger and von Cramon, in press): The human homologue of the monkey rostral cingulate motor area, the rostral cingulate zone (RCZ, Picard and Strick, 1996) was more active when accuracy was emphasized over speed.

In the present study we aimed at replicating and extending the findings originally reported by Gehring et al. (1993). In addition to the ERN, we investigated how the error positivity (P_E) and remedial actions were modulated by speed-accuracy shifts. We expected that higher error relevance should lead to more activation of the error processing system, reflected in a larger ERN. Furthermore, the P_E should also be increased, given that it reflects emotional processes and a re-evaluation of the error situation as suggested by Falkenstein and colleagues (2000). Moreover, more pronounced remedial actions could also be expected when errors were more relevant.

Methods

Nineteen healthy, right-handed volunteers (9 female, mean age 24.1 years, ranging from 19-31) with normal or corrected-to-normal vision participated in the study after giving written informed consent. The experiment complied with German legal requirements. Participation was paid.

They performed two successive blocks of a modified flanker task known to yield a sufficient number of errors (Ullsperger and von Cramon, 2001, in press). Participants had to respond with a left or right response button according to the direction of a target arrow briefly (30 ms) presented in the center of the screen. Above and below the target arrow four irrelevant flanker arrows were presented, which were in 50 % compatible (same direction as target) and in 50 % incompatible with the required response (opposite direction). The onset of the flankers preceded the target onset by about 100 ms. The arrows were 0.46° tall and 1.08° wide, and the flankers were presented 0.52°

and 1.04° above and below the screen center. After stimulus presentation, a blank screen was shown and responses were registered. When participants did not respond within a certain response time (mean: 377.1 ms; SEM: 4.7), which was individually adjusted in a training block prior to the main experiment (by a stepwise procedure aiming at error rates of 20% of incompatible trials), a feedback ("respond faster") appeared on the screen for 900 ms, otherwise a blank screen; followed by a fixation cross. The total inter-trial interval amounted to 5000 ms (varying in steps of 500 ms between 5500 and 6000 ms).

Each volunteer performed two successive blocks of the flanker task with different instructions. The instructions were reinforced by a financial incentive system: in both blocks correct responses were rewarded (0.07 EUR). In one block, response accuracy was instructed, and errors were punished more (-0.40 EUR) than late responses (-0.20 EUR). In the other block, response speed was stressed in the instruction, and consistent with this, late responses were punished more (-0.40 EUR) than errors (-0.20 EUR). Block sequence was counterbalanced across subjects. Each block contained 264 trials (50% compatible and 50% incompatible) in randomized order (block duration 25 min). Between blocks, participants had a short break after which they received the instruction for the next block.

Participants were seated in a dimly lit, electrically shielded chamber. The electroencephalogram (EEG) activity was recorded with Ag/AgCl electrodes mounted in an elastic cap (Electrocap International, Eaton, OH) from Nz, FPz, Fz, FCz, Cz, CPz, Pz, Oz, F3, F4, FC3, FC4, C3, C4, CP5, CP6, P3, P4, O1, O2, F7, F8, FT7, FT8, T7, T8, P7, and P8 according to the 10-20 system (American Electroencephalographic Society, 1991). The right mastoid was recorded as an additional channel. All scalp electrodes were referenced to the left mastoid and were re-referenced off-line to linked mastoids. The vertical electrooculogram (EOG) was recorded from electrodes located above and below the right eye. The horizontal EOG was collected from electrodes positioned at the outer canthus of each eye. Electrode impedance was kept below 5 kOhm. The EEG and EOG were recorded continuously with a band pass from DC to 30 Hz and were A-D converted with 16-bit resolution at a sampling rate of 250 Hz and stored on hard disc and CD-ROM for off-line-analysis.

In a first step, the EEG epochs were scanned for muscular and large EOG artifacts. Whenever the standard deviation in a 200-ms interval exceeded $50 \mu\text{V}$, the epoch was rejected. In a second step, small horizontal and vertical EOG artifacts that were still present in the EEG signal were corrected by an eye movement correction procedure (Pfeifer, 1993) based on a linear regression method described by Gratton et al. (1983). Finally, ERPs were separately averaged for correct and erroneous responses on incompatible trials. Late responses (followed by the feedback "respond faster") were excluded from averaging. The epochs were response-locked and lasted from 100 ms before to 500 ms after the button press. The average voltages in the 100 ms preceding the response onset served as a baseline. Mean amplitude measures in given time windows (centered around the peaks of the ERN; for the P_E , two time windows covering the early and the late parts of this deflection were chosen; cf. e.g., Van Veen et al., 2001) at the electrodes that spanned the region where the ERN and P_E are largest (F3, Fz, F4, FC3, FCz, FC4, C3, Cz, C4, P3, Pz, P4) were used for statistical analysis. All effects with more than one degree of freedom in the numerator were adjusted for violations of sphericity according the formula of Huynh and Feldt (1970). To avoid reporting large amounts of statistical results not relevant for the issues under investigation, only main effects or interactions, including the factors Response Type (correct, incorrect) and Instruction (accuracy, speed), are reported here. Topographical scalp potential maps were generated using a two-dimensional spherical spline interpolation (Perrinet al., 1989) and a radial projection from Cz, which respects the length of the median arcs.

Results

Behavioral Data

Table 1 shows error rates and response times for hits broken down by instruction and compatibility.

To test for effects of compatibility and instruction, the error rate data was submitted to repeated measures ANOVAs, revealing significant main effects of compatibility ($F_{1,18} = 112.61, p < .0001$) and of instruction ($F_{1,18} = 29.26, p < .0001$) as well as a significant interaction of these factors ($F_{1,18} = 24.29, p < .0001$), confirming that less errors were made during the accuracy condition. The same ANOVA performed for the reaction times revealed significant main effects of compatibility ($F_{1,18} = 858.94, p < .0001$) and instruction ($F_{1,18} = 8.04, p < .05$). These results suggest that reaction times were shorter in the speed condition.

The rate of immediate corrections as well as the correction times did not differ significantly between speed and accuracy conditions (correction rate, speed, 44.81%, SEM 6.81; accuracy, 44.69%, SEM 6.08; correction time, speed, 98.1 ms, SEM 5.88; accuracy, 102.0 ms, SEM 5.29; $p > .4$).

Table 1. Error rates and response times for correct responses broken down by instruction and compatibility.

| condition | error rates in % | | response times in ms | |
|-----------|------------------|--------------|----------------------|---------------|
| | compatible | incompatible | compatible | incompatible |
| speed | 1.75 (.49) | 27.99 (2.62) | 288.62 (4.25) | 338.50 (3.97) |
| accuracy | 1.04 (.34) | 18.94 (1.92) | 296.26 (3.88) | 342.11 (4.15) |

As can be seen in Figure 1, only in the accuracy condition a post-error effect was present. This was confirmed by an ANOVA with the factors Instruction (speed, accuracy), Compatibility (compatible, incompatible) and Preceding Response (correct, error). To control for a potential confound with sequential effects of compatibility (Gratton et al., 1992) trials preceded by compatible ones were excluded from analysis. The analysis revealed main effects of all three factors (Instruction, $F_{1,18} = 6.32, p < .05$; Compatibility, $F_{1,18} = 205.88, p < .0001$; Preceding Response, $F_{1,18} = 6.02, p < .05$) and a significant Instruction \times Preceding Response interaction ($F_{1,18} = 5.81, p < .05$).

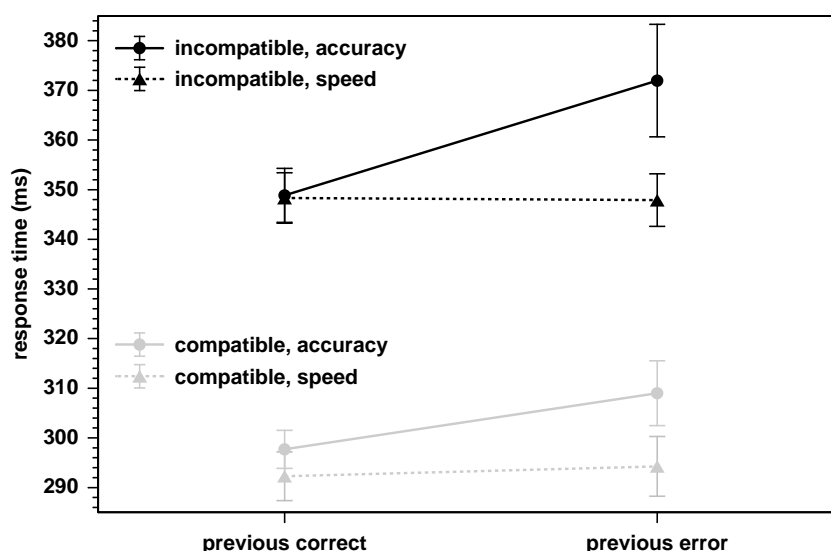


Figure1.

Response times broken down by compatibility, instruction, and preceding response type. Note that post-error slowing occurred only for the accuracy condition.

ERP data

The response-locked ERPs are shown for two electrodes in Figure 2. In both instruction conditions, on erroneous trials a clear frontocentral ERN could be identified, which was followed by a parietal P_E . The ERN was larger in amplitude for the accuracy condition. Inspection of the waveforms suggests that the early P_E was modulated by a small second negative deflection recently described

as the correction-related negativity (CoRN, Fiehler et al., submitted) in both conditions. The mean amplitudes for three time windows (50-110, 200-270, 380-500 ms) capturing the ERN, the early and the late PE were submitted to ANOVAs with the factors Instruction (INST), Response Type (RESP), Lateral Dimension (LAT) and Anterior-Posterior Dimension (AP). The results are shown in Table 2.

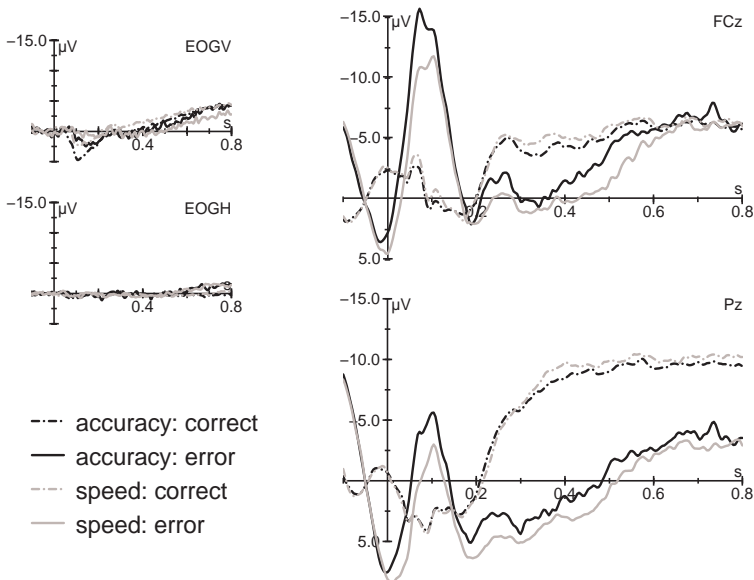


Figure 2.

Response-locked grand mean waveforms for correct (dashed) and erroneous (solid) incompatible trials at FCz and Pz for accuracy (black) and speed (gray) instruction.

ERN. The significant main effect of RESP reveals that in both conditions the ERN was significantly different from the waveforms for correct responses. The observation that the ERN amplitude was larger when accuracy was emphasized as compared to the speed condition is confirmed by the main effect of INST. In order to test whether the interaction of INST with the topographical factor LAT reflects a topographical difference, amplitude-normalized data were submitted to the same ANOVA (McCarthy and Woods, 1985), revealing no significant interaction of INST with a topographical factor ($p > .16$). This suggests no topographical difference between conditions, and that the observed amplitude difference was largest at midline electrodes (this was

Table 2. Results of the repeated measures ANOVAs for ERP amplitudes in three time windows.

| | df | 50 – 110 ms <i>F</i> | 200 – 270 ms <i>F</i> | 380 – 500 ms <i>F</i> |
|-------------------|--------|-------------------------|--------------------------|--------------------------|
| INST | 1, 18 | 5.41* | - | - |
| RESP | 1, 18 | 33.93 [†] | 9.68** | - |
| INST × RESP | 1, 18 | 12.20 [†] | - | 4.91* |
| INST × LAT | 2, 36 | 4.75* | 3.88* | 4.49* |
| RESP × LAT | 2, 36 | 14.67 [†] | - | - |
| RESP × AP | 3, 54 | 13.32** | 25.19 [†] | 67.18 [†] |
| RESP × AP × LAT | 6, 108 | 4.89** | - | 4.10** |
| INST × RESP × LAT | 2, 36 | 3.93* | - | - |

Note: INST = Instruction, RESP = Response Type, LAT = Lateral Dimension, AP = Anterior-Posterior Dimension; * $p < .05$, ** $p < .01$, [†] $p < .001$; [‡] $p < .0001$.

confirmed by subordinate ANOVAs).

P_E. In the middle and late time window the main effect of RESP confirms that the P_E was significantly different from the waveform for correct responses (cf. Table 2). The RESP × AP interaction suggests that the P_E was maximal at central and parietal electrodes (as confirmed by follow-up ANOVAs). In both time windows a significant interaction INST × LAT was found,

which was also significant when the same ANOVA was performed on amplitude-normalized data in the late time window (middle time window, $F_{2,36} = 3.11$, $p < .057$; late time window, $F_{2,36} = 3.51$, $p < .05$). Follow-up ANOVAs confirmed that this reflects a lateralization of the P_E to the left in the accuracy condition, while it was not lateralized in the speed condition. This effect is visualized in Figure 3 showing the topographical distributions of the early and late P_E .

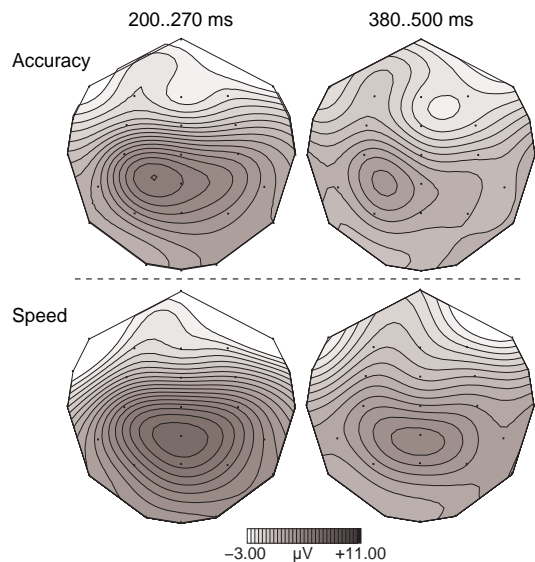


Figure 3.

Topographical scalp distribution of the P_E for incompatible erroneous trials in an early (left) and late (right) time window during the accuracy (upper panel) and speed (lower panel) blocks. Note that the P_E is slightly lateralized to the left in the accuracy condition.

Discussion

The behavioral data provide evidence that participants followed the instructions: error rates were lower when response accuracy was reinforced, and RTs were shorter when response speed was emphasized. Interestingly, there was no difference in the rate of immediate error corrections and the correction time between the two conditions. This can be explained by the fact that participants were not instructed that error corrections would be recorded. Hence, for them an immediate correction would not have helped in reaching the task goals. Based on our recent findings we would argue that immediate corrections in the present study were incidental, i.e., based on the stimulus-driven second response tendency and not requiring error detection (cf. Fiehler et al., submitted). Post-error slowing, however, was observed in the present study. It was only present when accuracy was instructed, suggesting that errors had larger relevance to the individual in this condition.

As expected, the ERN was larger when accuracy was emphasized. This finding is consistent with Gehring et al. (1993). It is furthermore consistent with the result of a recent fMRI study showing that the error-related hemodynamic activity of the rostral cingulate zone (RCZ) is increased when accuracy is emphasized as compared to speed instruction (Ullsperger and von Cramon, in press). These results suggest that the system involved in error detection is dynamically modulated by motivational factors. An alternative explanation of the decreased ERN amplitude in the speed condition could result from the higher error rate. A higher error rate could lead to habituation and/or change in motivational relevance of errors. However, we did not find correlations of error rate and ERN amplitude nor of the error rate difference and the ERN amplitude difference between blocks ($ps > .14$) making this explanation unlikely. This is also consistent with the finding by Falkenstein and colleagues (2000) that differential time pressure rather than the error rate per se modulates the ERN amplitude.

Surprisingly, the P_E was slightly smaller and lateralized to the left in the accuracy condition. Based on earlier studies (e.g., Falkenstein et al., 2000; Nieuwenhuis et al., 2001) we expected the P_E to be larger when accuracy was emphasized. To our knowledge, no lateralization of the P_E has been reported before. We can only speculate that the larger error relevance during the accuracy condition

has led to additional, perhaps verbal, processes involved in a reevaluation of the error situation (Falkenstein et al., 2000).

In sum, we replicated and extended the findings reported by Gehring and colleagues (1993) as well as Falkenstein et al. (1995). The error processing system can be dynamically adapted to the current needs according to the subjective goals. This is reflected in behavioral measures, such as post-error slowing, a modulation of the ERN amplitude and a change of error-related hemodynamic activity of the putative ERN generator (Ullsperger and von Cramon, in press). These findings need to be considered when ERN amplitude differences between groups (e.g., in patient studies) are discussed.

Author Note

Correspondence should be addressed to Markus Ullsperger (ullspERG@cns.mpg.de).

References

- Falkenstein M, Hohnsbein J, Hoormann J, Blanke L (1990). Effects of errors in choice reaction tasks on the ERP under focused and divided attention. In: Psychophysiological Brain Research (Brunia CHM, Gaillard AWK, Kok A, eds) pp 192-195 Tilburg, The Netherlands: Tilburg Univ. Press.
- Falkenstein M, Hohnsbein J, Hoormann J (1995). Event-related potential correlates of errors in reaction tasks. *Electroencephalogr Clin Neurophysiol Suppl.* 44:287-96.
- Falkenstein M, Hoormann J, Christ S, Hohnsbein J (2000). ERP components on reaction errors and their functional significance: a tutorial. *Biol Psychol* 51:87-107.
- Fiehler K, Ullsperger M, von Cramon DY (submitted). Electrophysiological correlates of error correction.
- Gehring WJ, Goss B, Coles MGH, Meyer DE, Donchin E (1993). A neural system for error detection and compensation. *Psychol Sci* 4:385-390.
- Gratton G, Coles MGH, Donchin E (1983). A new method for off-line removal of ocular artifact. *Electroencephalogr Clin Neurophysiol* 55:468-484.
- Gratton G, Coles MGH, Donchin E (1992). Optimizing the use of information: Strategic control of activation of responses. *J Exp Psychol Gen* 121:480-506.
- Nieuwenhuis S, Ridderinkhof KR, Blom J, Band GPH, Kok A (2001). Error-related brain potentials are differentially related to awareness of response errors: Evidence from an antisaccade task. *Psychophysiology* 38:752-760.
- Perrin F, Pernier J, Bertrand O, Echallier JF (1989). Spherical splines for scalp potential and current density mapping. *Electroencephalogr Clin Neurophysiol* 72:184-187.
- Pfeifer E (1993). IPCM-Iterative PCA correction method. A new method for the correction of ocular artifacts in the ERP-data. *Psychophysiology* 30:51.
- Picard N, Strick PL (1996) Motor areas of the medial wall: a review of their location and functional activation. *Cereb Cortex* 6:342-353.
- Rabbitt PMA (1966) Errors and error correction in choice-response tasks. *J Exp Psychol* 71:264-272.
- Ullsperger M, von Cramon DY (2001). Subprocesses of performance monitoring: a dissociation of error processing and response competition revealed by event-related fMRI and ERPs. *NeuroImage* 14:1387-1401.
- Ullsperger M, von Cramon DY (in press). Neuroimaging of performance monitoring: Error detection and beyond. *Cortex*, special issue Neuroimaging of Higher Cognitive Function.
- Van Veen V, Cohen JD, Botvinick MM, Stenger VA, and Carter CS. Anterior cingulate cortex, conflict monitoring, and levels of processing. *NeuroImage*, 14:1302-1308, 2001.

Bibliographic Information:

This article appeared in

M. Ullsperger and M. Falkenstein (Eds.)

Errors, Conflicts, and the Brain: Current Opinion on Performance Monitoring

ISBN: 3-936816-16-6

Series Title: MPI Special Issue in Human Cognitive and Brain Sciences

Volume: 1

Year: 2004

Publisher: Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig

Print: Sächsisches Digitaldruckzentrum GmbH, Dresden

Chapter 15

Neuroimaging of performance monitoring: Error detection and beyond

The current Chapter addresses the influence of subjective error significance on performance-monitoring-related activity in the pFMC. Consistent with the findings reported in Chapter 14, activity in the RCZ is shown to be increased when error significance is larger as compared to situations with low error significance. The current Chapter additionally contains a selective review of the performance monitoring literature which was available in early 2003.

SPECIAL SECTION

NEUROIMAGING OF PERFORMANCE MONITORING: ERROR DETECTION AND BEYOND

Markus Ullsperger and D. Yves von Cramon

(Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany)

ABSTRACT

The ability to monitor performance and behavior is crucial for goal-directed, adaptive behavior in a changing environment. Performance monitoring has been extensively investigated using behavioral, electrophysiological and hemodynamic measures, and is still in the focus of many research projects. This paper gives an overview on neuroimaging of performance monitoring and the models which arose from several research approaches, taking into account the knowledge stemming from electrophysiological and lesion studies. Particular emphasis is put on error detection and response conflict monitoring, but also at motivational factors. Furthermore, the paper presents and discusses data from an fMRI study investigating the influence of error relevance on the hemodynamic correlates of error processing. By instruction and financial reward manipulation, the relevance of errors were block-wise modulated in a flanker paradigm. The results suggest that the engagement of the posterior frontomedian wall (pFMC) previously shown to be involved in performance monitoring is dependent on error relevance.

Key words: error processing, response conflict, ACC, RCZ, fMRI, ERP

INTRODUCTION

Erroneous actions lead to several negative and positive outcomes. In the first place errors result in effects deviating from the originally intended ones, that means they at least hinder the achievement of the goals, sometimes even cause harm to the individual. On a longer perspective, errors may lead to adaptation of behavior, learning and skill acquisition.

An important prerequisite for positive effects of errors is that the cognitive system is able to detect them. Based on behavioral findings an error detection system was postulated which online monitors actions by comparing them with the respective intentions (e.g., Rabbitt, 1966; Higgins and Angel, 1970; Angel, 1976; Rabbitt and Rodgers, 1977). The interest in performance monitoring processes and their implementation in the human brain grew significantly when error-related event-related potentials (ERPs) were discovered (Falkenstein et al., 1990; Gehring et al., 1993). The error-related negativity (ERN) – also referred to as error negativity (N_E) – is best identified in response-locked ERPs, in which it onsets at about the response and peaks around 50-100 msec after the button press. It has a frontocentral maximum, and frontomedian cortical structures such as the anterior cingulate cortex (ACC) have been suggested to be its main generator. While the ERN has been extensively investigated during the last decade, the second error-related ERP component, the P_E , has received much less attention. Hence, its role is still far from clear. It has a centroparietal maximum and peaks around 200-500 msec after the erroneous response.

The use of hemodynamic neuroimaging

methods such as fMRI advanced the knowledge about the neuroanatomical substrate of performance monitoring. Several theories of performance monitoring and the implementation of its sub-processes in humans have been suggested. Recently, several fMRI studies on error processing have been published, and the debate on the underlying mechanisms continues.

In the first part of the present paper we selectively review recent neuroimaging findings on error processing in the light of electrophysiological and lesion studies. Sections 1-3 review studies addressing the main theories of how performance monitoring is implemented in the brain, particularly the error detection (mismatch) and the conflict monitoring models.

The differential involvement of frontomedian cortices in the sub-processes of performance monitoring is highlighted in section 3. Section 4 addresses the role of the lateral frontal cortex in performance monitoring. An important role of emotional and motivational processes in error monitoring is often assumed. However, up to now mostly ERP studies have addressed this aspect. Section 5 reviews the relevant electrophysiological findings on the relationship between the ERN and emotional processing. In the last part of the paper (section 6) we present original data from an fMRI study addressing the role of error relevance for the engagement of the error processing network.

THE ERROR DETECTION HYPOTHESIS

The ability to correct action slips within less than 100 msec and the finding that errors can result

in slower but sometimes more accurate responses in subsequent trials has led to the idea of an error-detection system (e.g., Rabbitt and Rodgers, 1977; Angel, 1976; but see also Rabbitt, 2002). The electrophysiological studies investigating the ERN provided a great body of evidence for the existence of an error detection system. It has been shown that the ERN is present in tasks in which errors (action slips) can easily be detected by the individual, but not in experimental settings in which the participant has too little information for detecting errors without external feedback (Scheffers and Coles, 2000; Coles et al., 2001, Holroyd and Coles, 2002). If, however, in such underdetermined response situations external feedback indicates an error, a negative ERP component comparable to the ERN is elicited (Miltner et al., 1997; Badgaiyan and Posner, 1998; Luu et al., 2003). Bernstein and colleagues (1995) as well as Falkenstein et al. (1997) showed that the amplitude of the ERN is larger when errors are easy to detect (but see Gehring and Fencsik, 2001, for a differing view). Furthermore, the ERN seems to be independent of response modality: it has been demonstrated for hand, foot, and eye movements (Holroyd et al., 1997; Van't Ent and Apkarian, 1999; Nieuwenhuis et al., 2001, Gehring and Fencsik, 2001) as well as for vocal errors (Masaki et al., 2001).

Cumulating evidence has resulted in a refinement of the error detection model. It assumes, that the ERN is a correlate of a mismatch detected by comparing the representations of the intended and the actually performed action (Falkenstein et al., 1990, 2000; Gehring et al., 1993, Coles et al., 2001). Behavioral observations (Higgins and Angel, 1970; Angel, 1976) and particularly the early onset of the ERN suggest that the representation of the correct response results from an 'efference copy' rather than from proprioceptive feedback (Gehring et al., 1993; Falkenstein et al., 2000; Coles et al., 2001). The representation of the intended action is assumed to directly result from full stimulus evaluation and application of the task set. It is noteworthy that the ERN is usually found on action slips due to premature responding (i.e., the response was made before stimulus evaluation and task-set-related functions were completed). Therefore, the representation of the intended response is still being built up when the erroneous response program is issued. It has been shown that compromising these representations reduces the amplitude difference between the ERN and the negativity occasionally observed on correct responses, reflecting disturbance of the comparison process (Coles et al., 2001).

Several source localization studies have suggested that the frontomedian wall is involved in error detection, particularly the anterior cingulate cortex (ACC). This was corroborated by fMRI studies (e.g., Carter et al., 1998; Kiehl et al., 2000,

Braver et al., 2001; Ullsperger and von Cramon, 2001; Garavan et al., 2002) indicating error-related increases in hemodynamic activity in the vicinity of the ACC, most often in the human homologue of the monkey rostral cingulate motor area (rCMA). In a metaanalysis of PET activations in motor areas of the frontomedian wall, Picard and Strick (1996) named this region the rostral cingulate zone (RCZ).

Computational modeling further refined the error detection hypothesis and integrated it with findings on reward processing in primates and reinforcement learning theories (Holroyd and Coles, 2002). Errors result in the non-achievement of the goals, hence, the detection of an error indicates a worse outcome than the desired one. In other words, an error is associated with the non-occurrence of an anticipated reward. The reward can be concrete (e.g., financial incentive) or more abstract (e.g., the knowledge to have performed well). The reward prediction and the value of reward varies from trial to trial based on the integrated previous performance of the participant. In brief, the Holroyd-Coles model proposes the ERN to arise from disinhibition of pyramidal cells in the ventral bank of the anterior cingulate sulcus (i.e., in the RCZ) by a phasic decrease of dopaminergic input originating in the ventral tegmental area (VTA) of the midbrain. The detection of an error is an event predicting the non-occurrence of a reward, i.e., it indicates a negative error in reward prediction which – according to findings in non-human primates – transiently reduces dopaminergic activity (e.g., Schultz, 2002; Schultz and Dickinson, 2000). The dopaminergic disinhibition could enable large proportions of apical dendrites of Layer V neurons in the RCZ (which are aligned perpendicular to the scalp surface) to become depolarized. These postsynaptic potentials could sum up to generate the ERN (Holroyd and Coles, 2002).

The functional significance of the P_E is much less clear. It seems to vary independently of the ERN and shows a high variance across subjects and tasks (Falkenstein et al., 2000). In their review, Falkenstein and colleagues considered several hypotheses regarding the P_E . According to their results it seems that the P_E could be a delayed stimulus-related P300 or a correlate of immediate error correction. The P_E may rather represent a P300-like wave elicited by the error event and reflecting additional processing becoming necessary when an error was encountered. This view is supported by Davies et al. (2001). Nieuwenhuis et al. (2001) reported that the P_E was present only on errors of which individuals became aware, while the ERN was also elicited on unaware errors. Van Veen and Carter (2002) tried to localize the generators of the P_E by dipole modeling suggesting a three dipole solution. While the early portion of the P_E seemed to coincide with main generator of the ERN (located in the caudal ACC),

for the later portion of the P_E two more generators were suggested – one in the rostral ACC and one in the left parietal cortex. Because that there is no unique dipole solution and the modeling was performed on grand average data, the results can only provide a model which needs to be tested in future studies.

THE CONFLICT MONITORING HYPOTHESIS

In an attempt to characterize the evaluative aspect of cognitive control, which is a prerequisite for adaptive behavior, the response conflict monitoring model was developed.

This model, its theoretical implications and supporting evidence from computational modeling are comprehensively described by Botvinick et al. (2001). A series of neuroimaging studies suggests that a region involving Brodmann Area (BA) 6 (the pre-supplementary motor area [pre-SMA]), mesial BA 8, and BA 32 is engaged when pre-response conflict occurs (e.g., Carter et al., 1998; Botvinick et al., 1999; Hazeltine et al., 2000; Barch et al., 2001; Milham et al., 2001; Zysset et al., 2001). Due to a rather large interindividual variance and the inaccuracy in determining the borders of cytoarchitectonic regions in anatomical MR images, we would prefer to call the region of interest *posterior frontomedian cortex* (pFMC). Pre-response conflict arises when more than one response tendencies induced by the same goal are activated simultaneously, and when these response tendencies are in conflict. Milham et al. (2001) reported that activation of the pFMC is primarily limited to situations of response conflict and does not occur on the occurrence of conflict at non-response levels. Similarly, van Veen and colleagues (2001) showed that the conflict-related activity varies with the amount of conflict at the response level but not with conflicts at the level of stimulus identification.

Braver et al. (2001) investigated the conditions under which pre-response conflict is most likely to occur. By employing three different cognitive tasks (Go/NoGo, oddball, forced choice) and varying the frequency of relevant task events they showed that the same pFMC region was equally responsive to low-frequency events. They reasoned that low-frequency responding might provide a minimal condition for eliciting response conflict. Moreover, the findings from this study suggest that the conflict between the tendency to respond and the tendency to withhold a response activated the same regions as response conflict in a two alternative forced choice task. A companion paper by Barch and colleagues (2001) reported that the pFMC activity was elicited by pre-response conflict irrespective of response modality (vocal and manual responses) and of processing domain (verbal and spatial processing).

Several recent studies suggest that uncertainty in decision making is very similar to (if not the same as) 'traditional' response conflict investigated in interference tasks. E.g., a study examining uncertainty in decision making (Volz et al., 2003) reported that the pFMC activation increased with rising uncertainty in a prediction task based on a natural sampling approach. Other studies on decision making during response uncertainty such as hypothesis testing (Elliot and Dolan, 1998), rule application (Goel and Dolan, 2000), serial event prediction in increasingly complex stimulus trains (Schubotz and von Cramon, 2002) found activations of the pFMC, particularly in the mesial BA 8 and in the most anterior part of the pre-SMA. In a recent study (Ullsperger and von Cramon, 2003) we disentangled feedback-related activity from activations related to uncertainty which arose from pre-response conflict (participants were uncertain what response to choose) and continued after the response (they were uncertain as to whether the chosen response was correct). Again, uncertainty was accompanied by activations of the pFMC, while feedback itself did not activate this region (in contrast, negative feedback indicating errors activated the RCZ – see below). All in all, these studies suggest, that the pFMC is involved, when the individual needs to act but is uncertain about which action to choose. Botvinick and colleagues (2001) also pointed out the similarities between pre-response conflict in interference tasks and underdetermined responding, i.e. with uncertainty.

As noted by Botvinick et al. (2001), activations in the pFMC and ACC were often tied to the regulative component of control, which led to the term *attention or selection for action*.

Two studies directly addressed this issue examining tasks where the strength of control varied from trial to trial (Botvinick et al., 1999; Carter et al., 2000). Both studies found greater pFMC activation on trials where control was weakest (and resulting from this pre-response conflict was highest). This contradicts regulative accounts of the pFMC function and suggests that it rather signals the need for current and future control.

While the electrophysiological correlate of error detection – the ERN – was found more than a decade ago, it is under debate which ERP component might reflect pre-response conflict. Several studies reported the presence of a similar response-locked negativity on correct responses (the 'correct-related negativity', CRN; Ford 1999; Vidal et al., 2000).

However, it seems implausible that pre-response conflict is reflected in a post-response component. As elaborated by Coles et al. (2001), the CRN might rather be a correlate of a compromised comparison process when one of the response representations is disturbed. In terms of the

response conflict model, the presence of a CRN (and a diminished difference between ERN and CRN) may indicate ongoing response conflict after the response was issued. In other words the individual remains uncertain about whether the response was correct or not (post-response conflict). This may be the case in pathological conditions such as lesions of the lateral frontal cortex (Gehring and Knight, 2000; Ullsperger et al., 2002) and schizophrenia (Ford, 1999; Mathalon et al., 2002; Alain et al., 2002), particularly with time pressure. Hence, an ERP-correlate of conflict monitoring should be searched in stimulus-locked ERPs, i.e., before the response. Already in 1996, Kopp et al. suggested that the N2c – a pre-response component – might be a correlate of response inhibition and conflict, and recent studies seem to confirm this view (van Veen and Carter, 2002; Nieuwenhuis et al., 2003). Following the same logic as Braver and colleagues (2001), Nieuwenhuis and colleagues varied the frequency of the stimuli in a Go/NoGo task. Conflict on correct Go trials should be higher when Go signals are rare as compared to frequent NoGo stimuli, and this was reflected in a higher amplitude of the N2 preceding the response. This study provides evidence that the N2 preceding the response is modulated by response conflict, and the investigation of Go trials prevented the confound with response inhibition (a traditional account of the increase of the N2 amplitude in Go/NoGo tasks).

CONFLICT VS. ERROR MONITORING

Considering both models of performance monitoring the question arises whether the activations found in the pFMC during conflicts and errors reflect the same or different processes. Only few studies have investigated error processing and response conflict at the same time. Carter et al. (1998) found that the same region of the pFMC was active during errors as well as during response conflict on correct trials. The authors reasoned that the pFMC region monitors for response conflict rather than for errors *per se*, and that erroneous response involve high conflict. However, in order to induce more errors, Carter and colleagues degraded the stimuli which again must have led to a high level of uncertainty. It is conceivable that error detection was rather difficult in this case and that the FMC activation could also be attributed to high uncertainty about what response to choose and about the correctness of the response.

In order to address the current debate on the models of performance monitoring several studies aimed at disentangling error-processing- from response-conflict-related activations. Kiehl and colleagues (2000) reported activations related to errors of commission in a Go/NoGo task in the

rostral and caudal ACC, while response conflict and inhibition activated more dorsal regions of the frontomedian wall. We found a similar neuroanatomical dissociation in a speeded modified flanker task (Ullsperger and von Cramon, 2001). The main focus of response-conflict-related activation was in the mesial BA 8. In contrast, error processing but not response conflict engaged the RCZ. The posteriorly adjacent pre-SMA (BA 6) was activated by both processes. Using a different analysis approach in a Go/NoGo paradigm, Garavan and colleagues (2002) obtained similar results. Corroborating this finding, Braver et al. (2001) reported that the error-related focus of activity was more inferior than the response-conflict-associated activation. Further evidence supporting a subareal dissociation of error processing and response conflict comes from a single-case ERP study in a patient with a lesion of the ACC (Swick and Turken, 2002). As compared to controls the ERN was attenuated, accompanied by lower error correction rates. In contrast, a stimulus-locked conflict-related component resembling the N2c (cf. Kopp et al., 1996) was enhanced. Finally, we found a dissociation between activations due to error detection based on feedback and uncertainty (Ullsperger and von Cramon, 2003). While processing of negative feedback on errors due to lack of knowledge activated the RCZ (as self-detection of errors does, too), uncertainty led to activations in the pFMC.

The main activation coordinates related to response conflict and error processing, respectively, from 14 studies are depicted in Figure 1¹. Hemodynamic responses to response conflict seem to cluster in a region consisting of the mesial BA 8, mesial BA 6 (pre-SMA) and the caudal paracingulate cortex (BA 32), while five out of six error-related activations fall into the RCZ. This subregional dissociation in the superior-inferior direction becomes obvious when the mean coordinates of the activations are considered: the mean z coordinates for response conflict (44.2, SEM: 1.2) and for error processing (34.8, SEM: 2.6) are significantly different [$T(14), p < .005$]. Mean x (response conflict: 4.7, SEM: .7; error processing: 3.8; SEM: 1.1) and y (response conflict: 16.0, SEM: 3.0; error processing: 16.5; SEM: 2.5) coordinates do not differ significantly ($ps > .5$). It is important to note, however, that a

¹ Fourteen studies published between 1998 and 2002 have been included in the analysis. Inclusion criteria were the investigation of response conflict and/or error processing and the publication of tables of the activations in the contrasts of interest. In addition, studies with contrasts based on low trial numbers in relevant conditions (e.g., error numbers below 15 in each participant) were excluded. The coordinates of the statistically most reliable activation (as reflected in z- or p-values) on the frontomedian wall ($-10 < x\text{-coordinate} < 10$) in the relevant contrasts of each study were used for the metaanalysis. For studies in which coordinates referred to the Montréal Neurological Institute (MNI) standard brains, a conversion of the y- and z-coordinates to the Talairach space was performed according to the method suggested by Brett (2002). The x-coordinate was uniformly set to 4 to allow visualization on one sagittal plane.

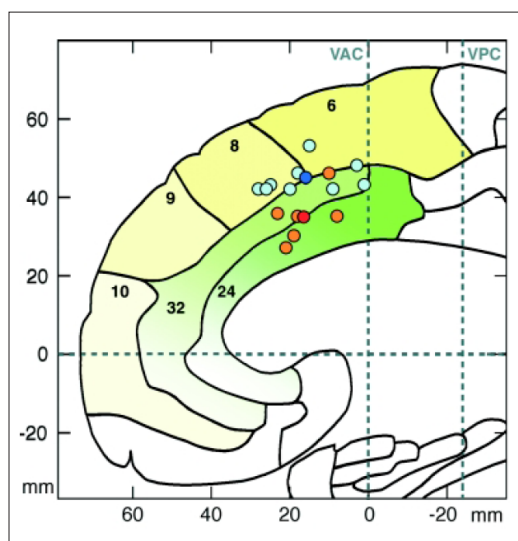


Fig. 1 – Comparison of frontomedian activations associated with response conflict (light blue) and error processing (orange) in previous and the present studies. The mean localization of conflict-related activations is depicted in dark blue and the mean localization of error-related activity is depicted in red. The crosshairs are located in the anterior and posterior commissures, respectively. The coordinates were taken from Barch et al. (2001; response conflict), Braver et al. (2001; response conflict and error processing), Carter et al. (1998, 2000; both response conflict), Garavan et al. (2002; error processing), Kiehl et al. (2000; error processing), Mac Donald et al. (2000; response conflict), Milham et al. (2001; response conflict), Ullsperger and von Cramon (2001, 2003; both response conflict and error processing), Volz et al. (2003; response conflict), Zysset et al. (2001; response conflict), and the present study (error processing). When necessary, coordinates were transformed to the Talairach space according to the method suggested by Brett (2002). The x coordinates were uniformly set to 4 to allow visualization on one sagittal slice. VAC = vertical plane on the anterior commissure; VPC = vertical plane on the posterior commissure.

mean difference of 9 mm is at the lower limit of what can be measured with fMRI and reliably compared across laboratories. Moreover, only maximal activation foci were considered. The extent of the activations makes some overlap between conditions likely.

Taken together, there seems to be growing evidence for a subregional dissociation which suggests that the two processes of performance monitoring – error processing (post-response conflict and subsequent error-related processes) and pre-response conflict – are located differently. It might be speculated that the computational demands are similar in both processes (detection of conflict or difference between two response tendencies or between representations of the performed response and an actually intended response), but the consequences are different. While detection of conflict between response tendencies can prevent an impending error by online implementation of control processes, detected errors call for correction, i.e., the alternation of behavior, and/or adjustments in similar situations in the future.

THE LATERAL PREFRONTAL CORTEX

Activations of the lateral prefrontal cortex (LPFC) repeatedly have been shown during pre-response conflict (e.g., Carter et al., 1998; Konishi et al., 1999; Hazeltine et al., 2000; Braver et al., 2001; Ullsperger and von Cramon, 2001; Zysset et al., 2001) as well as during error detection (Kiehl et al., 2000; Garavan et al., 2002).

In a study using a task-switching version of the Stroop task, MacDonald III et al. (2000) found a double dissociation of the pFMC and LPFC activations with respect to the implementation of control and performance monitoring which signals the need of cognitive adjustments. During task preparation, the LPFC was more active when the task which needed more control was cued, while the pFMC was not differentially active during the preparation of both tasks. In contrast, during the response only the pFMC showed differential activation according to conflict size. Thus, the authors suggested that the LPFC is involved in task preparation (implementation of control) and the pFMC in performance monitoring. A similar argument regarding the relationship of LPFC and pFMC was put forward by several other groups (e.g., Zysset et al., 2001; Milham et al., 2001). In a recent task-switching study, Brass and von Cramon (2002) suggested that the LPFC in the vicinity of the junction of the inferior frontal and the inferior precentral sulcus is involved in updating task representations, task preparation and implementation of the current action rule contained in the task set. Thus, the LPFC plays a major role in preparation and adaptation of task sets suggesting that it is needed for error detection and compensation.

In addition to fMRI studies occasionally showing error-related activations of the LPFC, two patient studies using ERPs demonstrated the importance of the LPFC and premotor cortex (PMC) in error detection. Gehring and Knight (2000) and Ullsperger et al. (2002) showed that in the time range of the ERN the difference between the response-locked ERPs on errors and correct responses vanishes when the lateral (pre-)frontal cortex is damaged. It was suggested that in these patients the application of the task set and the adjustment of cognitive control was compromised, resulting in an incomplete representation of the intended response at the time when the comparison is being made (Ullsperger et al., 2002). In the view of the conflict model for the patients the response selection is underdetermined such that there was high uncertainty (response conflict) during and after the response, hindering the patients to properly detect their errors.

In summary, the findings suggest that the LPFC – although most likely not directly involved in performance monitoring but rather in task preparation and control adjustments – has a close relationship to the structures engaged in evaluative functions. The control system cannot properly work

without a functioning monitoring counterpart and vice versa.

EMOTIONAL PROCESSING AND INDIVIDUAL DIFFERENCES

It is conceivable that error detection, emotional, and motivational processes interact reciprocally. While detection of many errors may well influence emotions and further motivation, also a specific motivational state may influence the subjective relevance of errors and thus the effort put into error detection. Furthermore, the ACC as part of the limbic lobe and particularly its rostral portion is related to affect (Bush et al., 2000; Devinsky et al., 1995; Paus et al., 1998). Several lines of evidence suggest that the RCZ is anatomically and functionally located at an interface position between cognition, affect and motor control (Picard and Strick, 1996; Paus, 2001).

While to our knowledge this topic has not been addressed with neuroimaging methods, yet, a number of electrophysiological studies demonstrated an influence of emotional factors on the ERN. Luu and colleagues (2000a) examined the relationship between the ERN and personality and affective dimensions of distress. In the initial stages of the experiment, high negative-emotionality and affect participants had larger ERN amplitudes than low negative-emotionality and affect participants. In later stages of the experiment, however, the ERN amplitudes of the high negative-emotionality and affect participants decreased while they became less involved in the task. In a different study of this research group, a frontomedial negativity similar to the ERN and the feedback-related negativity was also observed in response to good and bad targets in a video game (Tucker et al., 1999). Dikman and Allen (2000) reported that participants who scored low on a socialization scale showed smaller ERN amplitudes in a punishment task than in a reward task, whereas high-socialized participants produced similar ERNs in both conditions. Pailing and Segalowitz (2004) described interactions between motivation, neuroticism and conscientiousness in their influence on the ERN amplitude: highly conscientious participants as well as those higher on neuroticism showed a larger motivation effect (larger ERNs on errors in conditions with monetary incentives). These findings resulted in the notion that the ERN and similar medial frontal negativities reflect affective and motivational evaluation processes in error detection (Bush et al., 2000; Luu et al., 2000b; Gehring and Willoughby, 2002). Alternatively, it seems conceivable, that the effort put into performance monitoring (and thus the involvement of the performance monitoring system) is influenced by emotional and affective factors and viceversa.

ERROR RELEVANCE – THE PRESENT STUDY

As already pointed out, error detection is required for the implementation of remedial actions in order to finally reach a certain goal. If, however, a goal becomes less relevant to the individual, detection of errors which would hinder the achievement of this currently irrelevant goal is less important. Therefore, it is conceivable that for economical reasons the error detection system is less active during irrelevant errors. Already in 1993, Gehring and colleagues showed that the ERN was larger when accuracy was instructed as compared to speed. Recently, this finding was replicated (Ullsperger and Szymanowski, 2004). To our knowledge, so far no neuroimaging data addressing this questions have been published. Therefore, we will present a study testing as to whether the relevance effect is also reflected in the hemodynamic response. We performed an fMRI study in which we varied error relevance by instructing participants to either focus on accuracy (high error relevance) or speed (low error relevance) of the responses. We hypothesized that the RCZ activity should be higher during the accuracy condition. Higher error relevance should not only lead to more activation of the error processing system, but it may be reflected in more pronounced remedial actions, e.g., more immediate corrections, too.

METHODS

Participants

Sixteen young healthy volunteers (8 female) participated in the study (mean age: 25.7, SEM: .6) after their informed consent was obtained. The measurements were approved by the Ethics committee of the University of Leipzig and carried out according to the Declaration of Helsinki.

Stimuli and Procedure

A speeded modified flanker task known to produce response conflict and to yield high error rates was employed (Kopp et al., 1996; Ullsperger and von Cramon, 2001). Participants had to respond with a left or right response button according to the direction of a target arrow briefly (30 msec) presented in the center of the screen. Above and below the target arrow four irrelevant flanker arrows were presented, which were in 50 % compatible (same direction as target) and in 50 % incompatible with the required response (opposite direction). The onset of the flankers preceded the target onset by about 100 msec. The arrows were 0.46° tall and 1.08° wide, and the flankers were presented 0.52° and 1.04° above and below the screen center. After stimulus presentation, a blank screen was shown and responses were registered.

When participants did not respond within a certain response time (mean: 460.0 msec; SEM: 3.5), which was individually adjusted in a training block prior to the functional scans, a feedback ("respond faster") appeared on the screen for 900 msec, otherwise a blank screen; thereafter a fixation cross. The total inter-trial interval amounted to 5000 msec.

Each volunteer performed two successive blocks of the flanker task with different instructions. The instructions were reinforced by a financial incentive system: in both blocks correct responses were rewarded (0.07 EUR). In one block, response accuracy was instructed, and errors were punished more (−0.40 EUR) than late responses (−0.20 EUR). In the other block, response speed was stressed in the instruction, and consistent with this, late responses were punished more (−0.40 EUR) than errors (−0.20 EUR). Block sequence was counterbalanced across subjects. Each block contained 264 trials (50% compatible and 50% incompatible) as well as 36 non-events in randomized order (block duration 25 min). Between blocks, participants had a short break after which they received the instruction for the next block.

Image acquisition and analysis

Imaging was performed at 3T on a Bruker Medspec 30/100 system equipped with the standard bird cage head coil. 16 functional slices were obtained parallel to the AC-PC line (thickness 5mm, spacing 1mm) using a single-shot gradient EPI sequence (TR = 1 sec, TE = 30 msec, 64×64 pixel matrix, flip angle 90° , field of view 192 mm; 1510 scans per block) sensitive to BOLD contrast. Trials occurred at multiple, systematically offset time points (range 0–0.5 sec) in relation to the image acquisition to improve temporal resolution (Josephs et al., 1997; Miezin et al., 2000). Prior to the functional runs, anatomical MDEFT and EPI-T1 slices in plane with the functional images were collected.

Data processing was performed using the software package LIPSIA (Lohmann et al., 2001). Functional data were corrected for motion artifacts and for slice-time acquisition differences using sinc-interpolation. Signal changes and baseline-drifts were removed by applying a temporal highpass filter with a cut-off frequency of 1/124 Hz. Spatial smoothing was applied using a Gaussian filter with

5.65 mm full width at half maximum (FWHM). The anatomical MDEFT and EPI-T1 slices were co-registered with high resolution whole brain images (which resided in the stereotactic coordinate system and was acquired in a separate session from each participant using a T1-weighted three-dimensional segmented MDEFT sequence) and then transformed by linear scaling to a standard size (Talairach and Tournoux, 1988). The obtained transformation parameters were subsequently applied to the functional slices and slice-gaps were scaled using a trilinear interpolation, generating output data with a spatial resolution of 3 mm³. The statistical analysis was based on a least squares estimation using the general linear model for serially autocorrelated observations (Friston et al., 1995; Worsley and Friston, 1995; Aguirre et al., 1997; Zarahn et al., 1997). The design matrix was generated with a synthetic hemodynamic response function (Friston et al., 1998). The model equation, including the observation data, the design matrix, and the error term, was convolved with a Gaussian kernel of dispersion of 4 s FWHM. The effective degrees of freedom were estimated as described by Worsley and Friston (1995). For each block, separate analyses of error-related brain activations were performed by contrasting erroneous incompatible with correct incompatible trials, thus extracting specific signal increases on errors and eliminating conflict-related activity. The resulting contrast images of all participants were subjected to a voxel-wise one-sample t-test that indicated whether observed differences between conditions were significantly distinct from zero (Holmes and Friston, 1998). Resulting z-maps were thresholded at $z > 3.09$, uncorrected. Finally, in order to determine the effect of error relevance operationalized by the instruction effect, we directly contrasted error-related activations between both sessions.

RESULTS

Behavioral Data

In both sessions we found the typical compatibility effects seen in flanker tasks, i.e., higher error rates and longer reaction times (RTs) on incompatible trials than on compatible ones (see Table I). This was confirmed by ANOVAs with the

TABLE I
Performance data during accuracy and speed instruction

| | Accuracy instruction | | Speed instruction | |
|----------------|----------------------|--------------|-------------------|--------------|
| | Compatible | Incompatible | Compatible | Incompatible |
| Error rate | 1.56 (.54) | 18.13 (3.09) | 2.51 (.76) | 25.19 (3.09) |
| Late responses | 8.10 (1.71) | 22.02 (4.21) | 6.58 (1.81) | 19.13 (3.98) |
| RT corrects | 372.2 (5.9) | 422.7 (5.2) | 366.4 (5.5) | 420.4 (5.3) |
| RT errors | n.a. | 346.7 (6.8) | n.a. | 339.6 (6.5) |

Note: The rate of errors and late responses is given in percent of the total number of the respective trial type, reaction times in msec. RT: reaction time; n.a.: not applicable due to low number of trials.

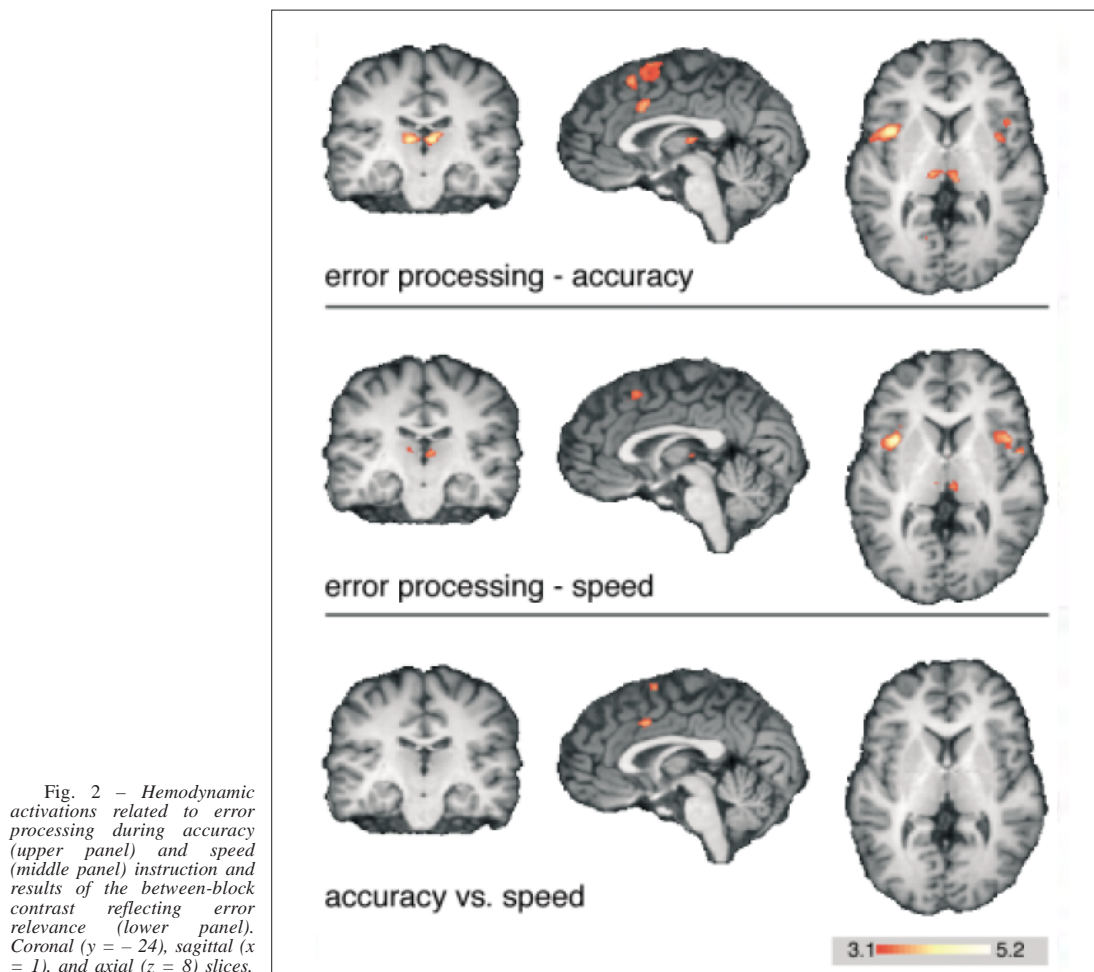


Fig. 2 – Hemodynamic activations related to error processing during accuracy (upper panel) and speed (middle panel) instruction and results of the between-block contrast reflecting error relevance (lower panel). Coronal ($y = -24$), sagittal ($x = 1$), and axial ($z = 8$) slices.

factors Instruction and Compatibility, which revealed a main effect of Compatibility [error rates: $F(1, 15) = 66.5$, $p < .0001$; RTs: $F(1, 15) = 298.82$, $p < .0001$]. In addition, there was a main effect of Instruction on error rates and RTs [error rates: $F(1, 15) = 9.01$, $p < .005$; RTs: $F(1, 15) = 4.71$, $p < .05$], reflecting that less errors were made in the accuracy block and that RTs were lower in the speed block.

Although more errors were immediately corrected when accuracy was instructed (32.3%, SEM: 5.3) than during speed instruction (24.7%, SEM: 4.8), this difference did not reach significance ($p = .10$). The correction time showed a tendency to be longer in the accuracy block (101.7 msec, SEM: 7.2) than during speed instruction (81.0 msec, SEM: 6.8; $p < .1$).

fMRI Data

As can be seen in Figure 2 (upper panel), the error processing contrast for the accuracy condition

revealed significant error-related signal increases in the RCZ and pFMC (specifically, in the superior pre-SMA and SMA) as well as in the inferior precentral sulcus, the superior and inferior anterior insula, and the parietal cortex (see Table II for a complete list of activations). In addition, we found bilateral error-related activations of the epithalamus including the habenular complex.

The error processing contrast for speed instruction revealed a similar pattern of hemodynamic activity. However, statistical power as indicated by z-values was lower (cf. Table III, upper part, and Figure 2, middle panel). The activity in the RCZ did not reach significance, while a region of the pFMC located in the mesial BA 6 (pre-SMA) was active.

As in the accuracy session, error-related activations of the anterior superior insula and the habenular complex were revealed.

The results of the between-session contrast of error-processing-related activity are depicted in Figure 2 (lower panel). The RCZ as well as a

TABLE II
Localization of error-related fMRI activations in the block emphasizing accuracy.

| Area | Hemisphere | Coordinates | | | Z-score |
|---|------------|-------------|-----|----|---------|
| | | x | y | z | |
| RCZ (BA 24c') | R | 4 | 8 | 35 | 3.82 |
| pFMC (pre-SMA, mesial BA 6) | R | 4 | 18 | 53 | 4.03 |
| pFMC (SMA, mesial BA 6) | R | 4 | -1 | 53 | 3.85 |
| inferior precentral sulcus / subcentral gyrus | L | -50 | 2 | 15 | 4.52 |
| superior precentral sulcus | R | 37 | -1 | 53 | 3.45 |
| Insula | | | | | |
| anterior superior | L | -35 | 5 | 12 | 5.04 |
| | R | 35 | 2 | 9 | 3.83 |
| anterior inferior | L | -29 | 17 | 0 | 3.78 |
| | R | 32 | 14 | 3 | 3.39 |
| epithalamus | R | 7 | -27 | 10 | 4.68 |
| | L | -10 | -22 | 9 | 4.28 |
| supramarginal gyrus | L | -56 | -47 | 32 | 3.86 |
| posterior STG (TPJ) | R | 58 | -55 | 15 | 3.45 |
| calcarine sulcus | L | -10 | -76 | 15 | 3.57 |

Note: x, y, and z are coordinates in the standard stereotactic space (Talairach and Tournoux, 1988) in which positive values refer to regions right of (x), anterior to (y), and superior to (z) the anterior commissure. Abbreviations as used in this and all following Tables: RCZ = rostral cingulate motor area, pFMC = posterior frontomedian cortex, STG = superior temporal gyrus, TPJ = temporoparietal junction area.

TABLE III
Localization of error-related fMRI activations in the block emphasizing speed and of the significant activation differences between both blocks

| Area | Hemisphere | Coordinates | | | Z-score |
|---|------------|--------------------|------|----|---------|
| | | x | y | z | |
| | | speed instruction | | | |
| pFMC (mesial BA 8/6) | R | 4 | 14 | 50 | 3.73 |
| inferior precentral sulcus / subcentral gyrus | R | 49 | − 1 | 12 | 4.43 |
| anterior middle frontal gyrus (BA 9) | R | 26 | 41 | 27 | 3.49 |
| Insula | | | | | |
| anterior superior | L | − 35 | 8 | 6 | 4.89 |
| | R | 34 | 11 | 12 | 3.73 |
| epithalamus | R | 4 | − 24 | 9 | 3.71 |
| | L | − 8 | − 22 | 9 | 3.81 |
| posterior STG (TPJ) | R | 55 | − 61 | 32 | 3.49 |
| | | accuracy vs. speed | | | |
| RCZ | R | 1 | 8 | 35 | 3.57 |
| | L | − 4 | 5 | 38 | 3.26 |
| pFMC (pre-SMA, mesial BA 6) | R | 1 | 2 | 59 | 3.69 |

region in the superior pre-SMA were significantly more activated by errors during the accuracy condition than during the speed condition (cf. Table III, lower part).

DISCUSSION

The behavioral data provide evidence that the instruction was followed by the participants: error rates were lower when response accuracy was reinforced, and RTs were shorter when response speed was emphasized. There was a tendency that immediate corrections occurred more often and needed more time in the accuracy block, suggesting that error relevance had an influence on remedial actions. In addition to a possible lack of statistical power, one reason which may explain why this trend did not reach significance could be that participants were not instructed that error corrections would be recorded. Hence, for them an immediate correction would not have helped in reaching the task goals. In contrast to a companion ERP study with 20

participants (Szymanowski, 2002; Ullsperger and Szymanowski, 2004) in which post-error slowing was observed when accuracy was instructed, no consistent post-error slowing effects were observed in the present study. This supports the notion that post-error slowing may reflect an effect of low robustness in tasks with high time pressure. More research is needed to examine the conditions under which this prolonged remedial action can be elicited.

The fMRI results of this study replicated the previous finding that the RCZ is involved in error processing (Ullsperger and von Cramon, 2001; Braver et al., 2001). An additional activation in the superior pre-SMA (located slightly more posterior and superior than activations usually associated with pre-response conflict) was found in the error processing contrast. A similar activation pattern (RCZ and superior pre-SMA) was recently reported by Braver et al. (2001) for response inhibition. At this stage, it can only be speculated that the pre-SMA activation could reflect an insufficient inhibition of the erroneous responses.

The between-session contrast revealed that the

error-related RCZ and pFMC activations are modulated by error relevance. This finding is consistent with the larger ERN amplitude under accuracy conditions (Gehring et al., 1993; Ullsperger and Szymanowski, 2004), and it supports the assumption that the RCZ is the main generator of the ERN. Thus, the present study provides evidence that the engagement of the performance-monitoring system is dynamically adjusted to the current requirements and goals. It could, however, be argued that the differential involvement of the performance-monitoring system reflects a habituation effect, because more errors were made during the speed condition. It seems to be difficult to disentangle error relevance, motivation, and error rate, without influencing other potentially confounding factors (e.g., task complexity). In addition, Falkenstein et al. (2000) found no amplitude differences of the ERN between two groups with high and low error rates respectively.

Particularly interesting was an activation of the epithalamus on errors in both speed and accuracy sessions. The involvement of the epithalamus including the habenular complex, in performance monitoring and reward processing was recently reported in a study investigating error processing based on external feedback (Ullsperger and von Cramon, 2003).

It is a critical modulatory relay between limbic forebrain structures and the midbrain (Scheibel, 1997). It might be speculated that the habenular complex could be involved in the modulation of the scalar dopaminergic error signal due to an error in reward prediction, which Holroyd and Coles (2002) suggested to underlie the generation of the ERN. Future studies in humans and non-human primates are needed to shed more light on the role of this structure.

As in previous studies (e.g., Braver et al., 2001; Ullsperger and von Cramon, 2001, 2003; Garavan et al., 2002), the anterior insula was activated during errors. A comparison of the insular activations in both sessions suggests more activation of the inferior anterior insula when accuracy was emphasized. However, in the direct contrast, this difference did not reach significance. Based on knowledge from functional neuroanatomy (Mesulam, 2000) one might speculate that activations of the inferior anterior insula may reflect co-activations of the autonomic system, which most likely responds to errors. Future studies investigating peripheral psychophysiological measures during error commission and correction are highly relevant for this issue.

7. Summary

The overview of the literature and the present study support the notion that the motor areas of the pFMC play an important role in performance

monitoring. Growing evidence suggests that performance monitoring comprises at least two sub-processes: one monitoring for pre-response conflict and uncertainty and one related to errors. It seems that the activation focus within the pFMC depends on the sub-process currently predominating. Pre-response conflict and uncertainty seems to involve more superior regions with a more differentiated cortex (i.e., the isocortical BAs 6 and 8 and the transitional cortex BA 32). Detection of errors based on internal comparison as well as external feedbacks shifts the focus of activity to the RCZ, a proisocortical region (BA 24c'). In a larger context, the pFMC seems to have a signaling function, monitoring for the demand for control (Botvinick et al., 2001). Similarly as detected conflict, errors, and external feedback pain is such a signal indicating that a reconfiguration of behavior is necessary to reach the goals and to prevent negative outcomes.

Interestingly, pain has repeatedly been shown to activate the ACC – often not far from RCZ activations during error detection (e.g., Porro et al., 2002; Bantick et al., 2002; Binkowski et al., 1998). Errors and pain require a change of behavior and foster learning in order to avoid similar situations in the future (see also Gabriel et al., 2002, for the role of the cingulate cortex in conditioning and learning). There is evidence that the neurons in rCMA in monkeys are specifically engaged when behavior is alternated subsequent to reward reduction (Shima and Tanji, 1998). In other words, remedial actions are implemented in order to reach the goal (reflecting the maximal reward). Bush et al. (2002) adapted the Shima and Tanji study for an fMRI experiment in humans and found a pFMC activation, suggesting the presence of homologous neurons in humans.

In contrast to errors, response conflicts and uncertainty might invoke somewhat different processes: the best way to handle pre-response conflict is to resolve it. All available information potentially helpful for conflict resolving should be sought by reinforcing the task set (according to the conflict model this could be accomplished by increasing gain using neuromodulatory input [Botvinick et al., 2002]), fully evaluating external stimuli, and by memory retrieval. When a decision was made and a response issued, immediate evaluation is required whether the action was goal-directed or not, i.e., the response monitoring system becomes active. If however the conflict could not be resolved and uncertainty persists, the performance monitoring system is dependent on external feedback. These considerations suggest that in adaptive behavior the sub-processes of performance monitoring are highly interactive and quickly alternating.

Furthermore, as elaborated in the introductory section, the frontomedian wall has intensive

reciprocal interactions with the LPFC, which is assumed to play a major role in regulative, task-set-related functions. In addition, a close interplay with emotional, motivational and autonomic functions can be assumed. Finally, the involvement of subcortical structures in performance monitoring has repeatedly been suggested (Holroyd and Coles, 2002; Falkenstein et al., 2001; Ullsperger and von Cramon, 2003) and needs to be addressed in neuroimaging, electrophysiological, pharmacological and patient studies in more detail.

REFERENCES

- AGUIRRE GK, ZARAHN E and D'ESPOSITO M. Empirical Analysis of BOLD fMRI statistics II. *NeuroImage*, 5: 199-212, 1997.
- ALAIN C, MCNEELY HE, HE Y, CHRISTENSEN BK and WEST R. Neurophysiological evidence of error-monitoring deficits in patients with schizophrenia. *Cerebral Cortex*, 12: 840-846, 2002.
- ANGEL RW. Efference copy in the control of movement. *Neurology*, 26: 1164-1168, 1976.
- BADGAIYAN RD and POSNER MI. Mapping the cingulate cortex in response selection and monitoring. *NeuroImage*, 7: 255-260, 1998.
- BANTICK SJ, WISE RG, PLOGHAUS A, CLARE S, SMITH SM and TRACEY I. Imaging how attention modulates pain in humans using functional MRI. *Brain*, 125: 310-319, 2002.
- BARCH DM, BRAVER TS, AKBUDAK E, CONTURO T, OLLINGER J and SNYDER A. Anterior cingulate cortex and response conflict: Effects of response modality and processing domain. *Cerebral Cortex*, 11: 837-848, 2001.
- BERNSTEIN PS, SCHEFFERS MK and COLES MGH. "Where did I go wrong?" A psychophysiological analysis of error detection. *Journal of Experimental Psychology: Human Perception and Performance*, 21: 1312-1322, 1995.
- BINKOFKI F, SCHNITZLER A, ENCK P, FRIELING T, POSSE S, SEITZ RJ and FREUND HJ. Somatic and limbic cortex activation in esophageal distention: A functional magnetic resonance imaging study. *Annals of Neurology*, 44: 811-815, 1998.
- BOTVINICK MM, BRAVER TS, BARCH DM, CARTER CS and COHEN JD. Conflict monitoring and cognitive control. *Psychological Review*, 108: 624-652, 2001.
- BOTVINICK MM, NYSTROM L, FISSELL K, CARTER CS and COHEN JD. Conflict monitoring versus selection-for-action in anterior cingulate cortex. *Nature*, 402: 179-181, 1999.
- BRASS M and VON CRAMON DY. The role of the frontal cortex in task preparation. *Cerebral Cortex*, 12: 908-914, 2002.
- BRAVER TS, BARCH DM, GRAY JR, MOLFESE DL and SNYDER A. Anterior cingulate cortex and response conflict: Effects of frequency, inhibition and errors. *Cerebral Cortex*, 11: 825-836, 2001.
- BRETT M. The MNI brain and the Talairach atlas. Posted at <http://www.mrcbu.cam.ac.uk/Imaging/mnispace.html>, 2002.
- BUSH G, LUU P and POSNER MI. Cognitive and emotional influences in anterior cingulate cortex. *Trends in Cognitive Sciences*, 4: 215-222, 2000.
- BUSH G, VOGT BA, HOLMES J, DALE AM, GREVE D, JENIKE MA and ROSEN BR. Dorsal anterior cingulate cortex: A role in reward-based decision making. *Proceedings of the National Academy of Sciences*, 99: 523-528, 2002.
- CARTER CS, BRAVER TS, BARCH DM, BOTVINICK MM, NOLL D and COHEN JD. Anterior cingulate cortex, error detection and the online monitoring of performance. *Science*, 280: 747-749, 1998.
- CARTER CS, MACDONALD III AM, BOTVINICK M, ROSS LL, STENGER VA, NOLL D and COHEN JD. Parsing executive processes: Strategic vs. evaluative functions of the anterior cingulate cortex. *Proceedings of the National Academy of Sciences*, 97: 1944-1948, 2000.
- COLES MGH, SCHEFFERS MK and HOLROYD CB. Why is there an ERN or Ne on correct trials? Response representations, stimulus-related components and the theory of error processing. *Biological Psychology*, 56: 173-189, 2001.
- DAVIES PL, SEGALOWITZ J, DYWAN J and PAILING PE. Error-negativity and positivity as they relate to other ERP indices of attentional control and stimulus processing. *Biological Psychology*, 56: 191-206, 2001.
- DEHAENE S, POSNER MI and TUCKER DM. Localization of a neural system for error detection and compensation. *Psychological Science*, 5: 303-305, 1994.
- DEVINSKY O, MORRELL MJ and VOGT BA. Contributions of anterior cingulate cortex to behavior. *Brain*, 118: 279-306, 1995.
- DIKMAN ZV and ALLEN JJB. Error monitoring during reward and avoidance learning in high- and low-socialized individuals. *Psychophysiology*, 37: 43-45, 2000.
- ELLIOTT R and DOLAN RJ. Activation of different anterior cingulate foci in association with hypothesis testing and response selection. *NeuroImage*, 8: 17-29, 1998.
- FALKENSTEIN M, HIELSCHER J, DZIOBEK I, SCHWARZENAU P, HOORMANN J, SUNDERMANN B and HOHNSBEIN J. Action monitoring, error detection and the basal ganglia: An ERP study. *NeuroReport*, 12: 157-161, 2001.
- FALKENSTEIN M, HOHNSBEIN J, HOORMANN J and BLANKE L. Effects of errors in choice reaction tasks on the ERP under focused and divided attention. In CHM Brunia, AWK Gaillard and A Kok (Eds), *Psychophysiological Brain Research*. Tilburg, The Netherlands: Tilburg University Press, 1990, pp. 192-195.
- FALKENSTEIN M, HOORMANN J, CHRIST S and HOHNSBEIN J. ERP components on reaction errors and their functional significance: tutorial. *Biological Psychology*, 51: 87-107, 2000.
- FALKENSTEIN M, HOORMANN J and HOHNSBEIN J. Fehlerbezogene Komponenten im ereigniskorrelierten Potential (EKP). *Zeitschrift für Experimentelle Psychologie*, 44: 117-138, 1997.
- FORD JM. Schizophrenia: the broken P300 and beyond. *Psychophysiology*, 36: 667-682, 1999.
- FRISTON KJ, FLETCHER P, JOSEPHS O, HOLMES A, RUGG MD and TURNER R. Event-related fMRI: Characterizing differential responses. *NeuroImage*, 7: 30-40, 1998.
- FRISTON KJ, HOLMES AP, WORSLEY KJ, POLINE JP, FRITH CD and FRACKOWIAK RSJ. Statistical parametric maps in functional imaging: A general linear approach. *Human Brain Mapping*, 2: 189-210, 1995.
- GABRIEL M, BURHANS L, TALK A and SCALF P. Cingulate cortex. In VS Ramachandran (Ed), *Encyclopedia of the Human Brain*. Amsterdam: Academic Press, 2002, pp. 775-791.
- GARAVAN H, ROSS TJ, KAUFMAN J and STEIN EA. A midline dissociation between error processing and response conflict monitoring. *NeuroImage*, in press.
- GARAVAN H, ROSS TJ, MURPHY K, ROCHE RAP and STEIN EA. Dissociable executive functions in the dynamic control of behavior: Inhibition, error detection, and correction. *NeuroImage*, 17: 1820-1829, 2002.
- GEHRING WJ and FENCSIK DE. Functions of the medial frontal cortex in the processing of conflict and errors. *The Journal of Neuroscience*, 21: 9430-9437, 2001.
- GEHRING WJ, GOSS B, COLES, MGH, MEYER DE and DONCHIN E. A neural system for error detection and compensation. *Psychological Science*, 4: 385-390, 1993.
- GEHRING WJ, HIMLE J and NISENSEN LG. Action monitoring dysfunction in obsessive-compulsive disorder. *Psychological Science*, 11: 1-6, 2000.
- GEHRING WJ and KNIGHT RT. Prefrontal-cingulate interactions in performance monitoring. *Nature Neuroscience*, 3: 516-520, 2000.
- GEHRING WJ and WILLOUGHBY AR. The medial frontal cortex and the rapid processing of monetary gains and losses. *Science*, 295: 2279-2282, 2002.
- GOEL V and DOLAN RJ. Anatomical segregation of component processes in an inductive inference task. *Journal of Cognitive Neuroscience*, 12: 110-119, 2000.
- GREENHOUSE S and GEISSER S. On methods in the analysis of profile data. *Psychometrika*, 24: 95-112, 1959.
- HAZELTINE E, POLDRACK R and GABRIELI JDE. Neural activation during response competition. *Journal of Cognitive Neuroscience*, 12(Suppl. 2): 118-129, 2000.
- HIGGINS JR and ANGEL RW. Corrections of errors without sensory feedback. *Journal of Experimental Psychology*, 84: 412-416, 1970.
- HOLMES AP and FRISTON KJ. Generalisability, random effects and population inference. *NeuroImage*, 7: S754, 1998.
- HOLROYD C and COLES MGH. The neural basis of human error processing: reinforcement learning, dopamine and the error-related negativity. *Psychological Review*, 109: 679-709, 2002.
- HOLROYD CB, DIEN J and COLES MGH. Error-related scalp potentials elicited by hand and foot movements: Evidence for an output-independent error-processing system in humans. *Neuroscience Letters*, 242: 65-68, 1998.
- JOSEPHS O, TURNER R and FRISTON K. Event-related fMRI. *Human Brain Mapping*, 5: 243-248, 1997.

- KIEHL KA, LIDDLE PF and HOPFINGER JB. Error processing and the rostral anterior cingulate: An event-related fMRI study. *Psychophysiology*, 37: 216-223, 2000.
- KONISHI S, NAKAJIMA K, UCHIDA I, KIKYO H, KAMEYAMA M and MIYASHITA Y. Common inhibitory mechanism in human inferior prefrontal cortex revealed by event-related functional MRI. *Brain*, 122: 981-991, 1999.
- KOPP B, RIST F and MATTLER U. N200 in the flanker task as a neurobehavioral tool for investigating executive control. *Psychophysiology*, 33: 282-294, 1996.
- LOHMANN G, MUELLER K, BOSCH V, MENTZEL H, HESSLER S, CHEN L, ZYSSET S and VON CRAMON DY. LIPSIA: A new software system for the evaluation of functional magnetic resonance images of the human brain. *Computerized Medical Imaging and Graphics*, 25: 449-457, 2001.
- LUU P, COLLINS P and TUCKER DM. Mood, personality, and self-monitoring: Negative affect and emotionality in relation to frontal lobe mechanisms of error monitoring. *Journal of Experimental Psychology: General*, 129: 43-60, 2000a.
- LUU P, FLAISCH T and TUCKER DM. Medial frontal cortex in action monitoring. *Journal of Neuroscience*, 20: 464-469, 2000b.
- LUU, P, TUCKER DM, DERRYBERRY D, REED M and POULSEN C. Electrophysiologic responses to errors and feedback in the process of action regulation. *Psychological Science*, 14: 47-53, 2003.
- MACDONALD III AW, COHEN JD, STENGER VA and CARTER CS. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science*, 288: 1835-1838, 2000.
- MASAKI H, TANAKA H, TAKASAWA N and YAMAZAKI K. Error-related brain potentials elicited by vocal errors. *NeuroReport*, 12: 1851-1855, 2001.
- MATHALON DH, FEDOR M, FAUSTMANN WO, GRAY M, ASKARI N and FORD J. Response monitoring dysfunction in schizophrenia: An event-related brain potential study. *Journal of Abnormal Psychology*, 111: 22-41, 2002.
- MESULAM MM. Paralimbic (mesocortical) areas. In Mesulam MM. *Principles of Behavioral and Cognitive Neurology*. 2nd Edition. Oxford: Oxford University Press, 2000, pp. 49-54.
- MIEZIN FM, MACCOTTA L, OLLINGER JM, PETERSEN SE and BUCKNER RL. Characterizing the hemodynamic response: effects of presentation rate, sampling procedure, and the possibility of ordering brain activity based on relative timing. *NeuroImage*, 11: 735-759, 2000.
- MILHAM MP, BANICH MT, WEBB A, BARAD J, COHEN NJ, WSZALEK T and KRAMER AF. The relative involvement of anterior cingulate and prefrontal cortex in attentional control depends on nature of conflict. *Cognitive Brain Research*, 12: 467-473, 2001.
- MILTNER WHR, BRAUN CH and COLES MGH. Event-related brain potentials following incorrect feedback in a time-estimation task: evidence for a 'generic' neural system for error detection. *Journal of Cognitive Neuroscience*, 9: 788-798, 1997.
- NIEUWENHUIS S, RIDDERINKHOF KR, BLOM J, BAND GPH and KOK A. Error-related brain potentials are differentially related to awareness of response errors: Evidence from an antisaccade task. *Psychophysiology*, 38: 752-760, 2001.
- NIEUWENHUIS S, YEUNG N, VAN DEN WILDENBERG W and RIDDERINKHOF KR. Electrophysiological correlates of anterior cingulate function in a go/no-go task: Effects of response conflict and trial-type frequency. *Cognitive, Affective, and Behavioral Neuroscience*, 3: 17-26, 2003.
- PAILING PE and SEGALOWITZ SS. The error-related negativity as a state and trait measure: Motivation, personality and lips in response to errors. *Psychophysiology*, 41: 84-95, 2004.
- PAUS T, KOSKI L, ZOGRAFOS C and WESTBURY C. Regional differences in the effects of task difficulty and motor output on blood flow response in the human anterior cingulate cortex: A review of 107 PET activation studies. *NeuroReport*, 9: R37-R47, 1998.
- PICARD N and STRICK PL. Motor areas of the medial wall: A review of their location and functional activation. *Cerebral Cortex*, 6: 342-353, 1996.
- PORRO CA, BARALDI P, PAGNONI G, SERAFINI M, FACCHIN P, MAIERON M and NICHELLI P. Does anticipation of pain affect cortical nociceptive systems? *Journal of Neuroscience*, 22: 3206-3214, 2002.
- RABBITT PMA. Errors and error correction in choice-response tasks. *Journal of Experimental Psychology*, 71: 264-272, 1966.
- RABBITT P. Consciousness is slower than you think. *Quarterly Journal of Experimental Psychology*, 55A: 1081-1092, 2002.
- RABBITT P and ROGERS B. What does a man do after he makes an error? An analysis of response programming. *Quarterly Journal of Experimental Psychology*, 30: 319-332, 1977.
- REASON J. The detection of errors. In: Reason J, *Human Error*. Cambridge, UK: Cambridge University Press, 1990, pp. 148-172.
- SCHEFFERS MK and COLES MGH. Performance monitoring in a confusing world: error-related brain activity, judgments of response accuracy, and types of errors. *Journal of Experimental Psychology: Human Perception and Performance*, 26: 141-151, 2000.
- SCHEIBEL AB. The thalamus and neuropsychiatric illness. In S Salloway, P Malloy and JL Cummings (Eds), *The Neuropsychiatry of Limbic and Subcortical Disorders*. Washington, DC: American Psychiatry Press, 1997, pp. 31-40.
- SCHUBOTZ RI and VON CRAMON DY. A blueprint for target motion: fMRI reveals perceptual complexity to modulate a premotor-parietal network. *NeuroImage*, 16: 920-935, 2002.
- SCHULTZ W. Getting formal with dopamine and reward. *Neuron*, 36: 241-263, 2002.
- SCHULTZ W and DICKINSON A. Neuronal coding of prediction errors. *Annual Review of Neuroscience*, 23: 473-500, 2000.
- SHIMA K and TANJI J. Role for cingulate motor area cells in voluntary movement selection based on reward. *Science*, 282: 1335-1338, 1998.
- SWICK D and TURKEN A. Dissociation between conflict detection and error monitoring in the human anterior cingulate cortex. *Proceedings of the National Academy of Sciences*, 99: 16354-16359, 2002.
- TALAIRACH P and TOURNOUX J. *A Stereotactic Coplanar Atlas of the Human Brain*. Stuttgart: Thieme, 1988.
- TUCKER DM, HARTRY-SPEISER A, MCDUGAL L, LUU P and DEGRANDPRE D. Mood and spatial memory: Emotion and right hemisphere contribution to spatial cognition. *Biological Psychology*, 50: 103-125, 1999.
- ULLSPERGER M and SZYMANOWSKI F. ERP Correlates of error relevance. In M Ullsperger and M Falkenstein (Eds), *Errors, conflict and the Brain. Current Opinions on Performance Monitoring*. Leipzig: MPI for Human Cognitive and Brain Sciences, 2004, pp. 171-177.
- ULLSPERGER M and VON CRAMON DY. Sub-processes of performance monitoring: A dissociation of error processing and response competition revealed by event-related fMRI and ERPs. *NeuroImage*, 14: 1387-1401, 2001.
- ULLSPERGER M and VON CRAMON DY. Error monitoring using external feedback: Specific roles of the habenular complex, the reward system and the cingulate motor area revealed by fMRI. *Journal of Neuroscience*, 23: 4308-4314, 2003.
- ULLSPERGER M, VON CRAMON DY and MÜLLER NG. Interactions of focal cortical lesions with error processing: Evidence from event-related brain potentials. *Neuropsychology*, 16: 548-561, 2002.
- VAN VEEN V and CARTER CS. The timing of action-monitoring processes in the anterior cingulate cortex. *Journal of Cognitive Neuroscience*, 14: 593-602, 2002.
- VAN VEEN V, COHEN JD, BOTVINICK MM, STENGER VA and CARTER CS. Anterior cingulate cortex, conflict monitoring, and levels of processing. *NeuroImage*, 14: 1302-1308, 2001.
- VAN'T ENT D and APKARIAN P. Motoric response inhibition in finger movement and saccadic eye movement: A comparative study. *Clinical Neurophysiology*, 110: 1058-1072, 1999.
- VIDAL F, HASBROUCQ T, GRAPPERON J and BONNET M. Is the 'error negativity' specific to errors? *Biological Psychology*, 51: 109-128, 2000.
- VOLZ KG, SCHUBOTZ RI and VON CRAMON DY. Predicting events of varying probability: Uncertainty investigated by fMRI. *NeuroImage*, 19: 271-280, 2003.
- WORSLEY KJ and FRISTON KJ. Analysis of fMRI time-series revisited - again. *NeuroImage*, 2: 173-181, 1995.
- ZARAHN E, AGUIRRE GK and D'ESPOSITO M. Empirical Analysis of BOLD fMRI statistics I. *NeuroImage*, 5: 179-197, 1997.
- ZYSSET S, MÜLLER K, LOHMANN G and VON CRAMON DY. Color-word matching Stroop task: Separating interference and response conflict. *NeuroImage*, 13: 29-36, 2001.

Markus Ullsperger, Max Planck Institute for Human Cognitive and Brain Sciences, Stephanstr. 1a, D-04103 Leipzig, Germany. E-mail: ullsp@cps.mpg.de

In sum, the findings reported in Chapters 14 and 15 suggest that changes in speed-accuracy tradeoff lead to modulations of error significance, which in turn are associated with modulations of the electrophysiological and hemodynamic correlates of performance monitoring. A potential limitation of both studies is that the error rates vary between the speed and accuracy blocks. In addition, the findings could be explained by a variation of the motor threshold (see Chapter 12 and simulation 3 in (Yeung et al., 2004)). While the studies on speed-accuracy shifts cannot counter these arguments, a follow-up study supports the view that subjective error relevance influences the ERN amplitude (Hämmerer, 2004; Hämmerer and Ullsperger, in preparation). After a modified flanker task participants were asked to judge how much they were concerned when they detected an error. Across participants a significant correlation between error significance and ERN amplitude was revealed ($r = .38$, $p = .03$; see Figure V-01). Importantly, no correlation of the ERN amplitude with error rate was found.

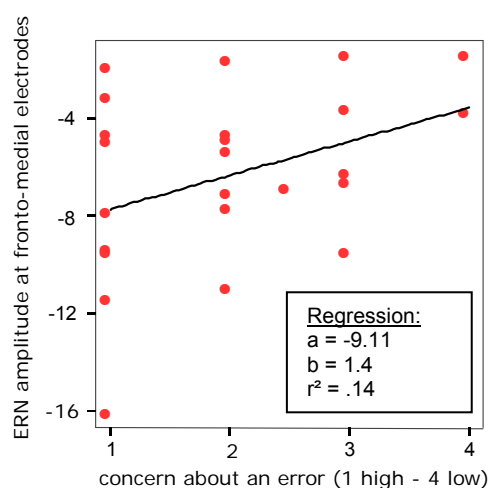


Figure V-01.

Correlation between ERN amplitude and subjective error significance (concern about an error). $N = 26$. Taken from Hämmerer, 2004.

Other factors which may influence the performance monitoring system are, for example, positive and negative emotions (Luu et al., 2000; Simon-Thomas and Knight, 2005), personality traits (Dikman and Allen, 2000; Allen et al., 2004; Pailing and Segalowitz, 2004), and also fatigue (Lorist et al., 2005) and sleep deprivation (Scheffers et al., 1999). With respect to studies on personality traits it should be noted that the investigated sample sizes are still rather low, such that additional research is needed. It would be particularly interesting to combine these studies with genotyping, i.e., the examination of relevant polymorphisms (see Chapter 16).

Part VI

Future Directions

Chapter 16

Outlook

The present volume has given an overview about the implementation of performance monitoring in the human brain. Particularly the role of the pFMC in signaling the need for adjustments necessary to optimize action outcome is now well-established. The network of brain regions interacting with the pFMC has been identified to a large extent. Moreover, the functional significance of EEG and fMRI correlates of performance monitoring has been elucidated, as have been their modulations by a broad range of neurological and psychiatric diseases. Finally, a number of factors modulating performance monitoring has been described.

However a number of questions remain open and need to be addressed in the future. Starting from present knowledge, several directions of research should be pursued:

16.1 Spatiotemporal dynamics of performance monitoring

While it seems clear that the lateral prefrontal cortex (LPFC), the basal ganglia and the midbrain interact with the pFMC during performance monitoring, the temporal dynamics of these interactions is still unknown. For example, resulting from its function in maintaining and updating task and contextual information the LPFC is assumed to play a role in performance monitoring at two stages. First, it has been suggested to provide the information on the task at hand thus allowing to predict the action outcome. Second, it is implicated in updating the task representation and regulating the amount of top-down influences on association and perceptual cortices in order to implement the adjustments whenever the outcome is worse than intended. FMRI alone can hardly disentangle the at least two time points at which the LPFC becomes active during performance monitoring and subsequent adjustments. Combining FMRI with EEG in a similar fashion as demonstrated in Chapter 5 can be expected to reveal the time course of the interactions within the performance monitoring network. Further on, the time course of adjustments can be investigated. If, for example, an error results in subsequent focusing of stimulus processing on its relevant rather than its distracting features, the performance monitoring signal must be followed by activity changes in perceptual brain areas. A recent study provided supporting evidence by demonstrating a modulation of activity in the fusiform face area by the amount of response conflict (Egner and Hirsch, 2005). It remains to be established, how the information is conveyed from the pFMC to the perceptual areas. Often, the LPFC, in particular the inferior frontal junction (cortex in the vicinity of the confluence of inferior precentral and inferior frontal sulci) seems to play an important role in the adjustments. Kerns et al. (2004) and Garavan et al. (2002) have shown that the activity in the LPFC is modulated by the preceding performance-monitoring-related activity of the pFMC. Using an fMRI-informed dipole analysis of an EEG study on task preparation, we found evidence for lateral frontal top-down modulation of the parietal cortex during the updating of task representations (Brass et al., 2005).

One brain area that has only recently received attention in the context of performance monitoring is the orbitofrontal cortex (OFC). This to a large degree results from the fact that fMRI signals are often lost and/or distorted in that region due to inhomogeneities in the magnetic field induced by the nearby located air-filled sinuses. These susceptibility artifacts make fMRI data collection and interpretation from the OFC very difficult. While the patient study presented in Chapter 7 revealed no direct effect of lesions in the anterior OFC on the generation of the ERN, several studies demonstrated that the OFC plays a major role in monitoring the outcomes of actions and external events (Bechara et al., 1998; O'Doherty et al., 2001; Kringelbach and Rolls, 2004; Walton et al., 2004). The study by Walton and colleagues (2004) showed that both the pFMC as well as the OFC are engaged in monitoring functions. One of their findings was that the pFMC is particularly involved when actions are selected by the individual him/herself, while the OFC seems to be more engaged when the individual had no choice but was guided by external necessities. Based on this we suggested a gradual difference in the respective monitoring functions of the pFMC and OFC (Ullsperger and von Cramon, 2004). Whereas the pFMC is involved in *performance monitoring*, i.e., the monitoring of ongoing actions potentially requiring immediate motor adjustments, the OFC is more active during *outcome monitoring*, i.e., the monitoring of sensory events that may require future adjustments at more abstract levels (memory, choice of strategies etc.). This hypothesis needs to be addressed in future experiments.

A great challenge for the future will be to address the specific time course and effects of midbrain, basal ganglia and thalamus activity. Neuronal activity in these regions is unlikely to yield direct EEG changes measurable at the scalp. Invasive recordings, for example in epilepsy patients undergoing presurgical diagnostics and patients with deep-brain stimulators, are one possible way to address the role of these structures in performance monitoring.

Moreover, neurobiologically plausible computational models are needed to better understand the function of the performance monitoring network as a whole. Temporal difference error learning models, as, for instance, the one implemented in the theory by Holroyd and Coles (Holroyd and Coles, 2002), can be a starting point for such models. A number of recent neuroimaging studies seems to be in line with these reinforcement learning models (Berns et al., 2001; Pagnoni et al., 2002; McClure et al., 2003; Montague et al., 2004; O'Doherty et al., 2004; O'Doherty, 2004). However, the rather simple temporal difference error learning model cannot account for higher-order contingencies in stimulus-action-reward associations. Moreover, an exploitation-exploration dilemma occurs, when several ways of achieving a goal are available. Is it better to exploit an action sequence that is often successful and leads to at least partial goal achievement or to explore other ways to test whether they are better suited? These more abstract, higher-level monitoring processes need to be understood better. A promising way is to implement Bayesian algorithms in the reinforcement learning model (O'Doherty, 2006).

16.2 Molecular bases of performance monitoring

Neurobiological theories of performance monitoring should – in addition to information about the underlying neuroanatomy and timing of the processes – involve knowledge on neurotransmitter actions. A large body of animal work suggests a prominent role of

monoamines, such as dopamine, in higher cognitive function. In recent years, an increasing number of EEG and neuroimaging studies has been combined with pharmacological challenges (Cools and Robbins, 2004). A number of studies have profiled several readily available drugs like caffeine and alcohol (Ridderinkhof et al., 2002; Tieges et al., 2004) and pharmaceuticals for clinical use (Johannes et al., 2001; de Bruijn et al., 2004, in press; Zirnheld et al., 2004; Riba et al., 2005) with respect to their influence on performance monitoring and cognitive control. While most results were interpreted with respect to the putative role of dopamine in performance monitoring, it should be noted that the majority of the drugs investigated so far acts on several transmitter systems at the same time. This makes the use of these findings for creating theories of performance monitoring more difficult. In addition, a number of findings suggest roles of other neurotransmitters as well, e.g., noradrenalin, serotonin, and GABA (Johannes et al., 2001; de Bruijn et al., 2004; Fallgatter et al., 2004; Riba et al., 2005). Therefore, studies with highly selective agents are needed, for example, with direct dopamine receptor agonists and antagonists.

The effect of pharmacological challenges can be augmented when genetic information is used. Over the last years, interest for genetic polymorphisms modulating transmitter activity has grown considerably. A growing body of evidence shows associations between common gene variants (polymorphisms) in the human population and specific cognitive processes (Goldberg and Weinberger, 2004; Meyer-Lindenberg et al., 2005). Such polymorphisms can influence the dopamine system. For example, the Catechol-O-Methyl-Transferase (COMT) Val¹⁵⁸Met polymorphism affects the availability of dopamine in synapses and extrasynaptic space and has specific effects on phasic and tonic dopamine activity (Bilder et al., 2004). Several other polymorphisms influence dopamine receptors and transporters in the brain. Comparing participant groups differing with respect to these polymorphisms using performance monitoring tests with EEG and fMRI will disentangle the roles of dopamine in signaling the need for adjustments and in biasing the mode of cognitive control. Combining this approach with pharmacological studies will yield stronger and highly informative effects (Mattay et al., 2003). They are suited to reveal the dose-action dynamics of the involved neurotransmitters.

Direct studies of the involved brain structures and specific receptors are possible using positron emission tomography (PET). Dopamine level changes in the cortex, particularly the pFMC, may and will be examined using D2-receptor radioligands suitable to image extrastriatal dopamine receptors (e.g., ¹⁸F-Fallypride, ¹¹C-FLB 457; Olsson et al., 1999, 2004; Mukherjee et al., 2002). A number of technical challenges still need to be addressed, e.g., modeling the kinetics of the new radioligands; development of dynamic designs suitable for PET studies. Recent studies of cognitive functions using dopamine receptor ligands seem very promising in this respect (e.g., Pappata et al., 2002; Aalto et al., 2005).

16.3 Individual differences and development

Regarding performance monitoring large differences between individuals can be expected. Genotyping as described above will allow a large step forward in understanding these individual differences. Moreover, the nature of these differences needs to be better characterized. Recent theories on flexible behavior suggest a dual model of cognitive

control consisting of proactive control ("early preparation") and reactive control ("late compensation") (Braver et al., in press): Under many circumstances optimal outcome can be reached by preparing the action, thereby minimizing the risk of failure and the need for performance monitoring. Unexpected changes of the environment, particularly when they interfere with automatized actions require reactive compensation and fully depend on performance monitoring. These different mutual interactions of performance monitoring and adjustments are schematically depicted in Figure VI-01. While genetic factors certainly influence whether an individual is more biased towards proactive or reactive control modes, recent studies suggest that other factors, such as, for example, physical fitness seem to modify this bias as well (Colcombe et al., 2004; Themanson et al., 2005). It needs to be elucidated how these seemingly unrelated factors can influence performance monitoring. Similarly, developmental changes in performance monitoring require more attention. Several papers reported the development of the ERN in children and adolescents (Segalowitz and Davies, 2004; Segalowitz et al., 2004; Hogan et al., 2005; Santesso et al., 2005) as well as in aging (Falkenstein et al., 2001; Mathewson et al., 2005). For example, it was shown that the ERN is reduced in older healthy people, despite their abilities to perform the tasks are not impaired. Moreover, it seems that older subjects are less prone to make errors due to premature responding. It needs to be clarified whether the decrease in the ERN reflects a deficit in performance monitoring or rather a shift of control mode. Also the underlying neuronal and molecular changes are still rather unclear, and only a combination of methods as described above can be expected shed light on these questions.

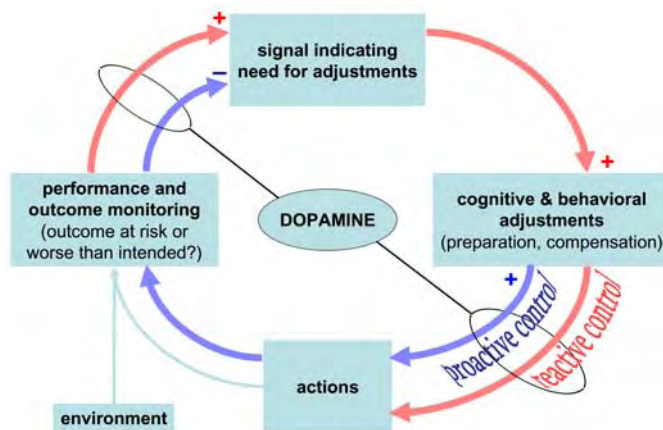


Figure VI-01.
The relationship between monitoring and adjustments with respect to the dual mode model of cognitive control and putative interactions with dopaminergic activity.

16.4 Diagnostics of performance monitoring deficits

Chapter 9 of this volume gives an overview of the findings from patient studies on performance monitoring. Currently, patient studies are particularly helpful to address the necessity of specific brain regions and transmitter systems for performance monitoring and flexible adjustments. Future clinical studies of performance monitoring need to pursue a number of further questions. In a first step, the intraindividual reliability and robustness of the correlates of performance monitoring needs to be established. Current knowledge suggests that the ERN is a robust phenomenon and a sensitive marker of the integrity of the performance monitoring network. Even in chronic lesions when the behavioral abilities have recovered to large extents the ERN can indicate the previous impairment. It needs therefore be tested whether the ERN can be used in longitudinal studies to investigate therapeutic effects and functional recovery. Most likely, a combination of behavioral (for

example error signaling) and electrophysiological measures will yield best results in this vain. Patient-friendly, robust, and easy-to-perform tests of performance monitoring are to be developed. Eventually, the goal is to advance our knowledge about brain diseases impairing performance monitoring. For a large number of brain-damaged patients it would be a great alleviation to recover their ability to flexibly adjust behavior in response to own errors and external feedback.

In summary, a great number of open questions concerning performance monitoring will be addressed in the future using a broad variety of methodological approaches. New models and hypotheses will be built, tested, and rejected or modified. And as in performance monitoring of everyday life actions, errors and unexpected results in hypothesis testing will be most informative, will inspire new theories, and will advance our knowledge most:

"Mistakes are the portals of discovery"

James Joyce

References

Cumulated papers underlying the Chapters of this volume

Chapter

- 3 Ullsperger M, von Cramon DY (2001) Subprocesses of performance monitoring: a dissociation of error processing and response competition revealed by event-related fMRI and ERPs. *Neuroimage* 14:1387-1401.
- 4 Ullsperger M, von Cramon DY (2003) Error monitoring using external feedback: specific roles of the habenular complex, the reward system, and the cingulate motor area revealed by functional magnetic resonance imaging. *J Neurosci* 23:4308-4314.
- 5 Debener S, Ullsperger M, Siegel M, Fiehler K, von Cramon DY, Engel AK (2005) Trial-by-trial coupling of concurrent electroencephalogram and functional magnetic resonance imaging identifies the dynamics of performance monitoring. *J Neurosci* 25:11730-11737.
- 6 Ridderinkhof KR, Ullsperger M, Crone EA, Nieuwenhuis S (2004) The role of the medial frontal cortex in cognitive control. *Science* 306:443-447.
- 7 Ullsperger M, von Cramon DY, Müller NG (2002) Interactions of focal cortical lesions with error processing: evidence from event-related brain potentials. *Neuropsychology* 16:548-561.
- 8 Ullsperger M, von Cramon DY (2006) The role of intact frontostriatal circuits in error processing. *Journal of Cognitive Neuroscience* 18:1-14.
- 9 Ullsperger M (2006) Performance monitoring in neurological and psychiatric patients. *Int J Psychophysiol* 59:59-69.
- 10 Fiehler K, Ullsperger M, von Cramon DY (2004) Neural correlates of error detection and error correction: is there a common neuroanatomical substrate? *Eur J Neurosci* 19:3081-3087.
- 11 Fiehler K, Ullsperger M, Von Cramon DY (2005) Electrophysiological correlates of error correction. *Psychophysiology* 42:72-82.
- 12 Ullsperger M, von Cramon DY (in press) How does error correction differ from error signaling? An event-related potential study. *Brain Research*.
- 13 Ullsperger M, Bylsma LM, Botvinick MM (2005) The conflict-adaptation effect: it's not just priming. *Cogn Affect Behav Neurosci* 5:467-472.
- 14 Ullsperger M, von Cramon DY (2004) Neuroimaging of performance monitoring: error detection and beyond. *Cortex* 40:593-604.
- 15 Ullsperger M, Szymanowski F (2004) ERP Correlates of error relevance. In: *Errors, conflicts, and the brain. Current opinions on performance monitoring.* (Ullsperger M, Falkenstein M, eds), pp 171-184. Leipzig: MPI for Human Cognitive and Brain Sciences.

Additional References

- Aalto S, Bruck A, Laine M, Nagren K, Rinne JO (2005) Frontal and temporal dopamine release during working memory and attention tasks in healthy humans: a positron emission tomography study using the high-affinity dopamine D2 receptor ligand [¹¹C]FLB 457. *J Neurosci* 25:2471-2477.
- Allain S, Carbonnell L, Falkenstein M, Burle B, Vidal F (2004b) The modulation of the Ne-like wave on correct responses foreshadows errors. *Neurosci Lett* 372:161-166.
- Allain S, Hasbroucq T, Burle B, Grapperon J, Vidal F (2004a) Response monitoring without sensory feedback. *Clin Neurophysiol* 115:2014-2020.
- Allen JD, Trujillo L, Dikman ZV (2004) Assessing moderators and mediators of error-monitoring. In: *Errors, conflicts, and the brain. Current opinions on performance monitoring.* (Ullsperger M, Falkenstein M, eds), pp 164-171. Leipzig: MPI for Human Cognitive and Brain Sciences.
- Allen JD, Trujillo L, Dikman ZV (2004) Assessing moderators and mediators of error-monitoring. In: *Errors, conflicts, and the brain. Current opinions on performance monitoring.* (Ullsperger M, Falkenstein M, eds), pp 164-171. Leipzig: MPI for Human Cognitive and Brain Sciences.
- Angel RW (1976) Efference copy in the control of movement. *Neurology* 26:1164-1168.
- Bartholow BD, Pearson MA, Dickter CL, Sher KJ, Fabiani M, Gratton G (2005) Strategic control and medial frontal negativity: Beyond errors and response conflict. *Psychophysiology* 42:33-42.
- Barto AG (1995) Adaptive Critics and the basal ganglia. In: *Models of information processing in the basal ganglia* (Houk JC, Davis JL, Beiser DG, eds), pp 215-232. Cambridge, Massachusetts.
- Bechara A, Damasio AR, Damasio H, Anderson SW (1994) Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition* 50:7-15.
- Bechara A, Damasio H, Tranel D, Anderson SW (1998) Dissociation Of working memory from decision making within the human prefrontal cortex. *J Neurosci* 18:428-437.
- Bechtereva NP (1971) Нейро-физиологические аспекты психической деятельности человека. [Neurophysiological aspects of human psychic activity]. Leningrad: Izdatelstvo Medicina.
- Bechtereva NP, Abdullaev YG (2000) Depth electrodes in clinical neurophysiology: neuronal activity and human cognitive function. *Int J Psychophysiol* 37:11-29.

- Bechtereva NP, Kropotov JD, Ponomarev VA, Etlinger SC (1990) In search of cerebral error detectors. *Int J Psychophysiol* 8:261-273.
- Bechtereva NP, Shemyakina NV, Starchenko MG, Danko SG, Medvedev SV (2005) Error detection mechanisms of the brain: background and prospects. *Int J Psychophysiol* 58:227-234.
- Berns GS, McClure SM, Pagnoni G, Montague PR (2001) Predictability modulates human brain response to reward. *J Neurosci* 21:2793-2798.
- Bilder RM, Volavka J, Lachman HM, Grace AA (2004) The catechol-O-methyltransferase polymorphism: Relations to the tonic-phasic dopamine hypothesis and neuropsychiatric phenotypes. *Neuropsychopharmacology* 29:1943-1961.
- Botvinick M, Nystrom LE, Fissell K, Carter CS, Cohen JD (1999) Conflict monitoring versus selection-for-action in anterior cingulate cortex. *Nature* 402:179-181.
- Botvinick MM, Braver TS, Barch DM, Carter CS, Cohen JD (2001) Conflict monitoring and cognitive control. *Psychol Rev* 108:624-652.
- Botvinick MM, Cohen JD, Carter CS (2004) Conflict monitoring and anterior cingulate cortex: an update. *Trends Cogn Sci* 8:539-546.
- Brass M, Ullsperger M, Knösche TR, von Cramon DY, Phillips NA (2005) Who comes first? The role of prefrontal and parietal cortex in cognitive control. *Journal of Cognitive Neuroscience* 17:1367-1375.
- Braver TS, Gray JR, Burgess GC (in press) Explaining many varieties in working memory variation: dual mechanisms of cognitive control. In: *Variation in Working Memory* (Conway A, Jarrold C, Kane M, Miyake A, eds). Oxford Univ Press: Oxford
- Brázdil M, Roman R, Daniel P, Rektor I (2005) Intracerebral Error-Related Negativity in a Simple Go/NoGo Task. *J Psychophysiol* 19:244-255.
- Brázdil M, Roman R, Falkenstein M, Daniel P, Jurak P, Rektor I (2002) Error processing--evidence from intracerebral ERP recordings. *Exp Brain Res* 146:460-466.
- Brown JW, Braver TS (2005) Learned predictions of error likelihood in the anterior cingulate cortex. *Science* 307:1118-1121.
- Carter CS, Braver TS, Barch DM, Botvinick MM, Noll D, Cohen JD (1998) Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science* 280:747-749.
- Colcombe SJ, Kramer AF, Erickson KI, Scalf P, McAuley E, Cohen NJ, Webb A, Jerome GJ, Marquez DX, Elavsky S (2004) Cardiovascular fitness, cortical plasticity, and aging. *Proc Natl Acad Sci U S A* 101:3316-3321.
- Coles MG, Scheffers MK, Holroyd CB (2001) Why is there an ERN/Ne on correct trials? Response representations, stimulus-related components, and the theory of error-processing. *Biol Psychol* 56:173-189.
- Cools R, Robbins TW (2004) Chemistry of the adaptive mind. *Philos Transact A Math Phys Eng Sci* 362:2871-2888.
- Critchley HD, Corfield DR, Chandler MP, Mathias CJ, Dolan RJ (2000) Cerebral correlates of autonomic cardiovascular arousal: a functional neuroimaging investigation in humans. *J Physiol* 523 Pt 1:259-270.
- Critchley HD, Mathias CJ, Josephs O, O'Doherty J, Zanini S, Dewar BK, Cipolotti L, Shallice T, Dolan RJ (2003) Human cingulate cortex and autonomic control: converging neuroimaging and clinical evidence. *Brain* 126:2139-2152.
- Critchley HD, Tang J, Glaser D, Butterworth B, Dolan RJ (2005) Anterior cingulate activity during error and autonomic response. *Neuroimage* 27:885-895.
- Davis KD, Taylor KS, Hutchison WD, Dostrovsky JO, McAndrews MP, Richter EO, Lozano AM (2005) Human anterior cingulate cortex neurons encode cognitive and emotional demands. *J Neurosci* 25:8402-8406.
- de Bruijn ER, Hulstijn W, Verkes RJ, Ruigt GS, Sabbe BG (2004) Drug-induced stimulation and suppression of action monitoring in healthy volunteers. *Psychopharmacology (Berl)* 177:151-160.
- de Bruijn ERA, Sabbe BGC, Hulstijn W, Ruigt GSF, Verkes RJ (in press) Effects of antipsychotic and antidepressant drugs on action monitoring in healthy volunteers. *Cognitive Brain Research*.
- Dehaene S, Posner MI, Tucker DM (1994) Localization of a neural system for error detection and compensation. *Psychological Science* 5:303-305.
- Dikman ZV, Allen JJ (2000) Error monitoring during reward and avoidance learning in high- and low-socialized individuals. *Psychophysiology* 37:43-54.
- Egner T, Hirsch J (2005) Cognitive control mechanisms resolve conflict through cortical amplification of task-relevant information. *Nat Neurosci* 8:1784-1790.
- Eisenberger NI, Lieberman MD (2004) Why rejection hurts: a common neural alarm system for physical and social pain. *Trends in Cognitive Sciences* 8:294-299.
- Endrass T, Franke C, Kathmann N (2005) Error Awareness in a Saccade Countermanding Task. *J Psychophysiol* 19:275-280.
- Eriksen BA, Eriksen CW (1974) Effects of noise letters upon the identification of a target letter in a nonsearch task. *Perception & Psychophysics* 16:143-149.
- Falkenstein M (2004) ERP correlates of erroneous performance. In: *Errors, conflicts, and the brain. Current opinions on performance monitoring.* (Ullsperger M, Falkenstein M, eds), pp 5-14. Leipzig: MPI for Human Cognitive and Brain Sciences.
- Falkenstein M, Hohnsbein J, Hoormann J (1994) Event-related potential correlates of errors in reaction tasks. In: *Perspectives of Event-Related Potentials Research (EEG Suppl. 44)* (Karmos G, Molnar M, Csepe V, Czigler I, Desmedt JE, eds), pp 287-296: Elsevier Science.
- Falkenstein M, Hohnsbein J, Hoormann J (1995) Event-related potential correlates of errors in reaction tasks. *Electroencephalogr Clin Neurophysiol Suppl.* 44 287-296.
- Falkenstein M, Hohnsbein J, Hoormann J (1996) Differential processing of motor errors. In: *Recent advances in event-related brain potential research* (Ogura C, Koga Y, Shimokochi M, eds), pp 579-585: Elsevier Science.
- Falkenstein M, Hohnsbein J, Hoormann J, Blanke L (1990) Effects of errors in choice reaction tasks on the ERP under focused and divided attention. In: *Psychophysiological Brain Research* (Brunia CHM, Gaillard AWK, Kok A, eds), pp 192-195: Tilburg University Press.

References

- Falkenstein M, Hoormann J, Christ S, Hohnsbein J (2000) ERP components on reaction errors and their functional significance: a tutorial. *Biol Psychol* 51:87-107.
- Falkenstein M, Hoormann J, Hohnsbein J (1997) [Event-related potential components related to errors]. *Z Exp Psychol* 44:117-138.
- Falkenstein M, Hoormann J, Hohnsbein J (2001) Changes of error-related ERPs with age. *Exp Brain Res* 138:258-262.
- Fallgatter AJ, Herrmann MJ, Roemmler J, Ehls AC, Wagoner A, Heidrich A, Ortega G, Zeng Y, Lesch KP (2004) Allelic variation of serotonin transporter function modulates the brain electrical response for error processing. *Neuropsychopharmacology* 29:1506-1511.
- Fiehler K, Ullsperger M, Grigutsch M, von Cramon D (2004) Cardiac responses to error processing and response conflict. In: *Errors, conflicts, and the brain. Current opinions on performance monitoring.* (Ullsperger M, Falkenstein M, eds), pp 135-140. Leipzig: MPI for Human Cognitive and Brain Sciences.
- Fiorillo CD, Tobler PN, Schultz W (2003) Discrete coding of reward probability and uncertainty by dopamine neurons. *Science* 299:1898-1902.
- Ford JM (1999) Schizophrenia: the broken P300 and beyond. *Psychophysiology* 36:667-682.
- Garavan H, Ross TJ, Murphy K, Roche RA, Stein EA (2002) Dissociable executive functions in the dynamic control of behavior: inhibition, error detection, and correction. *Neuroimage* 17:1820-1829.
- Gehring WJ, Goss B, Coles MG, Meyer DE, et al. (1993) A neural system for error detection and compensation. *Psychological Science* 4:385-390.
- Gehring WJ, Knight RT (2000) Prefrontal-cingulate interactions in action monitoring. *Nat Neurosci* 3:516-520.
- Gehring WJ, Willoughby AR (2002) The medial frontal cortex and the rapid processing of monetary gains and losses. *Science* 295:2279-2282.
- Gehring WJ, Willoughby AR (2004) Are all medial frontal negativities created equal? Toward a richer empirical basis for theories of action monitoring. In: *Errors, conflicts, and the brain. Current opinions on performance monitoring.* (Ullsperger M, Falkenstein M, eds), pp 14-20. Leipzig: MPI for Human Cognitive and Brain Sciences.
- Gemba H, Sasaki K, Brooks VB (1986) 'Error' potentials in limbic cortex (anterior cingulate area 24) of monkeys during motor learning. *Neurosci Lett* 70:223-227.
- Gerfen CR (1992) The neostriatal mosaic: multiple levels of compartmental organization in the basal ganglia. *Annu Rev Neurosci* 15:285-320.
- Goldberg TE, Weinberger DR (2004) Genes and the parsing of cognitive processes. *Trends Cogn Sci* 8:325-335.
- Gratton G, Coles MG, Donchin E (1992) Optimizing the use of information: strategic control of activation of responses. *J Exp Psychol Gen* 121:480-506.
- Graybiel AM, Aosaki T, Flaherty AW, Kimura M (1994) The basal ganglia and adaptive motor control. *Science* 265:1826-1831.
- Hajcak G, McDonald N, Simons RF (2003) To err is autonomic: Error-related brain potentials, ANS activity, and post-error compensatory behavior. *Psychophysiology* 40.
- Hämmerer, D (2004) Reward and Punishment after Correct Answers and Errors: An EEG-Study. Unpublished Diploma Thesis.
- Hester R, Fassbender C, Garavan H (2004) Individual Differences in Error Processing: A Review and Reanalysis of Three Event-related fMRI Studies Using the GO/NOGO Task. *Cereb Cortex*.
- Higgins JR, Angel RW (1970) Correction of tracking errors without sensory feedback. *J Exp Psychol* 84:412-416.
- Hogan AM, Vargha-Khadem F, Kirkham FJ, Baldeweg T (2005) Maturation of action monitoring from adolescence to adulthood: an ERP study. *Dev Sci* 8:525-534.
- Holroyd CB, Coles MG (2002) The neural basis of human error processing: reinforcement learning, dopamine, and the error-related negativity. *Psychol Rev* 109:679-709.
- Holroyd CB, Dien J, Coles MG (1998) Error-related scalp potentials elicited by hand and foot movements: evidence for an output-independent error-processing system in humans. *Neurosci Lett* 242:65-68.
- Holroyd CB, Hajcak G, Larsen JT (in press) The good, the bad and the neutral: Electrophysiological responses to feedback stimuli. *Brain Research*.
- Holroyd CB, Larsen JT, Cohen JD (2004) Context dependence of the event-related brain potential associated with reward and punishment. *Psychophysiology* 41:245-253.
- Holroyd CB, Nieuwenhuis S, Yeung N, Cohen JD (2003) Errors in reward prediction are reflected in the event-related brain potential. *Neuroreport* 14:2481-2484.
- Holroyd CB, Nieuwenhuis S, Yeung N, Nystrom L, Mars RB, Coles MG, Cohen JD (2004) Dorsal anterior cingulate cortex shows fMRI response to internal and external error signals. *Nat Neurosci* 7:497-498.
- Houk JC, Adams JL, Barto AG (1995) A model of how the basal ganglia generate and use neural signals that predict reinforcement. In: *Models of information processing in the basal ganglia* (Houk JC, Davis JL, Beiser DG, eds), pp 249-270. Cambridge, Massachusetts.
- Ito S, Stuphorn V, Brown JW, Schall JD (2003) Performance monitoring by the anterior cingulate cortex during saccade countermanding. *Science* 302:120-122.
- Johannes S, Wieringa BM, Nager W, Dengler R, Munte TF (2001) Oxazepam alters action monitoring. *Psychopharmacology (Berl)* 155:100-106.
- Kerns JG, Cohen JD, MacDonald R, A.W., Cho RY, Stenger VA, Carter CS (2004) Anterior cingulate conflict monitoring and adjustments in control. *Science* 303:1023-1026.
- Kiehl KA, Liddle PF, Hopfinger JB (2000) Error processing and the rostral anterior cingulate: an event-related fMRI study. *Psychophysiology* 37:216-223.
- Kringelbach ML, Rolls ET (2004) The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. *Prog Neurobiol* 72:341-372.

- Laming DRJ (1968) Information theory of choice-reaction times. New York: Academic Press.
- Logothetis NK (2002) The neural basis of the blood-oxygen-level-dependent functional magnetic resonance imaging signal. *Philos Trans R Soc Lond B Biol Sci* 357:1003-1037.
- Logothetis NK (2003) The Underpinnings of the BOLD Functional Magnetic Resonance Imaging Signal. *J Neurosci* 23:3963-3971.
- Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A (2001) Neurophysiological investigation of the basis of the fMRI signal. *Nature* 412:150-157.
- Lorist MM, Boksem MA, Ridderinkhof KR (2005) Impaired cognitive control and reduced cingulate activity during mental fatigue. *Brain Res Cogn Brain Res* 24:199-205.
- Luu P, Collins P, Tucker DM (2000) Mood, personality, and self-monitoring: negative affect and emotionality in relation to frontal lobe mechanisms of error monitoring. *J Exp Psychol Gen* 129:43-60.
- Luu P, Posner MI (2003) Anterior cingulate cortex regulation of sympathetic activity. *Brain* 126:2119-2120.
- Luu P, Tucker DM (2001) Regulating action: alternating activation of midline frontal and motor cortical networks. *Clin Neurophysiol* 112:1295-1306.
- Luu P, Tucker DM, Makeig S (2004) Frontal midline theta and the error-related negativity: neurophysiological mechanisms of action regulation. *Clin Neurophysiol* 115:1821-1835.
- Masaki H, Tanaka H, Takasawa N, Yamazaki K (2001) Error-related brain potentials elicited by vocal errors. *Neuroreport* 12:1851-1855.
- Mathewson KJ, Dwyan J, Segalowitz SJ (2005) Brain bases of error-related ERPs as influenced by age and task. *Biol Psychol* 70:88-104.
- Matsumoto K, Suzuki W, Tanaka K (2003) Neuronal correlates of goal-based motor selection in the prefrontal cortex. *Science* 301:229-232.
- Matsumoto K, Tanaka K (2004) The role of the medial prefrontal cortex in achieving goals. *Curr Opin Neurobiol* 14:178-185.
- Mattay VS, Goldberg TE, Fera F, Hariri AR, Tessitore A, Egan MF, Kolachana B, Callicott JH, Weinberger DR (2003) Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. *Proc Natl Acad Sci U S A* 100:6186-6191.
- Mayr U, Awh E, Laurey P (2003) Conflict adaptation effects in the absence of executive control. *Nature Neuroscience* 6:450-452.
- McClure SM, Berns GS, Montague PR (2003) Temporal prediction errors in a passive learning task activate human striatum. *Neuron* 38:339-346.
- Meyer-Lindenberg A, Kohn PD, Kolachana B, Kippenhan S, McInerney-Leo A, Nussbaum R, Weinberger DR, Berman KF (2005) Midbrain dopamine and prefrontal function in humans: interaction and modulation by COMT genotype. *Nat Neurosci* 8:594-596.
- Milham MP, Banich MT, Webb A, Barad V, Cohen NJ, Wszalek T, Kramer AF (2001) The relative involvement of anterior cingulate and prefrontal cortex in attentional control depends on nature of conflict. *Brain Res Cogn Brain Res* 12:467-473.
- Miltner WHR, Braun CH, Coles MGH (1997) Event-related brain potentials following incorrect feedback in a time-estimation task: Evidence for a "generic" neural system for error detection. *Journal of Cognitive Neuroscience* 9:788-798.
- Miltner WHR, Lemke U, Weiss T, Holroyd C, Scheffers MK, Coles MG (2003) Implementation of error-processing in the human anterior cingulate cortex: a source analysis of the magnetic equivalent of the error-related negativity. *Biol Psychol* 64:157-166.
- Montague PR, Hyman SE, Cohen JD (2004) Computational roles for dopamine in behavioural control. *Nature* 431:760-767.
- Mukherjee J, Christian BT, Dunigan KA, Shi B, Narayanan TK, Satter M, Mantil J (2002) Brain imaging of 18F-fallypride in normal volunteers: blood analysis, distribution, test-retest studies, and preliminary assessment of sensitivity to aging effects on dopamine D-2/D-3 receptors. *Synapse* 46:170-188.
- Nieuwenhuis S, Ridderinkhof KR, Blom J, Band GP, Kok A (2001) Error-related brain potentials are differentially related to awareness of response errors: evidence from an antisaccade task. *Psychophysiology* 38:752-760.
- Nieuwenhuis S, Slagter HA, von Geusau NJ, Heslenfeld DJ, Holroyd CB (2005) Knowing good from bad: differential activation of human cortical areas by positive and negative outcomes. *Eur J Neurosci* 21:3161-3168.
- Niki H, Watanabe M (1979) Prefrontal and cingulate unit activity during timing behavior in the monkey. *Brain Res* 171:213-224.
- O'Doherty J (2006) Model-based Bayesian decision making in the human brain. In: *Alpine Brain Imaging Meeting*. Champéry, Switzerland.
- O'Doherty J, Dayan P, Schultz J, Deichmann R, Friston K, Dolan RJ (2004) Dissociable roles of ventral and dorsal striatum in instrumental conditioning. *Science* 304:452-454.
- O'Doherty J, Kringelbach ML, Rolls ET, Hornak J, Andrews C (2001) Abstract reward and punishment representations in the human orbitofrontal cortex. *Nat Neurosci* 4:95-102.
- O'Doherty JP (2004) Reward representations and reward-related learning in the human brain: insights from neuroimaging. *Curr Opin Neurobiol* 14:769-776.
- Olsson H, Halldin C, Farde L (2004) Differentiation of extrastriatal dopamine D2 receptor density and affinity in the human brain using PET. *Neuroimage* 22:794-803.
- Olsson H, Halldin C, Swahn CG, Farde L (1999) Quantification of [11C]FLB 457 binding to extrastriatal dopamine receptors in the human brain. *J Cereb Blood Flow Metab* 19:1164-1173.
- Overbeek TJM, Nieuwenhuis S, Ridderinkhof KR (2005) Dissociable Components of Error Processing: On the Functional Significance of the Pe Vis-à-vis the ERN/Ne. *J Psychophysiol* 19:319-329.
- Pagnoni G, Zink CF, Montague PR, Berns GS (2002) Activity in human ventral striatum locked to errors of reward prediction. *Nat Neurosci* 5:97-98.

References

- Pailing PE, Segalowitz SJ (2004) The error-related negativity as a state and trait measure: Motivation, personality, and ERPs in response to errors. *Psychophysiology* 41:84-95.
- Pailing PE, Segalowitz SJ, Dywan J, Davies PL (2002) Error negativity and response control. *Psychophysiology* 39:198-206.
- Pappata S, Dehaene S, Poline JB, Gregoire MC, Jobert A, Delforge J, Frouin V, Bottlaender M, Dolle F, Di Giamberardino L, Syrota A (2002) In vivo detection of striatal dopamine release during reward: a PET study with [(11)C]raclopride and a single dynamic scan approach. *Neuroimage* 16:1015-1027.
- Paus T (2001) Primate anterior cingulate cortex: where motor control, drive and cognition interface. *Nat Rev Neurosci* 2:417-424.
- Rabbitt P (1967) Time to detect errors as a function of factors affecting choice-response time. *Acta Psychol (Amst)* 27:131-142.
- Rabbitt P (2002) Consciousness is slower than you think. *Q J Exp Psychol A* 55:1081-1092.
- Rabbitt P, Rodgers B (1977) What does a man do after he makes an error? An analysis of response programming. *Quarterly Journal of Experimental Psychology* 29:727-743.
- Rabbitt PM (1966a) Errors and error correction in choice-response tasks. *J Exp Psychol* 71:264-272.
- Rabbitt PM (1966b) Error correction time without external error signals. *Nature* 212:438.
- Rabbitt PMA, Phillips S (1967) Error Detection and Correction Latencies as a Function of S-R Compatibility. *Quarterly Journal of Experimental Psychology* 19:37-42.
- Reason J (1990) Human error. Cambridge: Cambridge University Press.
- Riba J, Rodriguez-Fornells A, Morte A, Munte TF, Barbanoj MJ (2005) Noradrenergic stimulation enhances human action monitoring. *J Neurosci* 25:4370-4374.
- Ridderinkhof KR (2002) Micro- and macro-adjustments of task set: activation and suppression in conflict tasks. *Psychological Research-Psychologische Forschung* 66:312-323.
- Ridderinkhof KR, de Vlugt Y, Bramlage A, Spaan M, Elton M, Snel J, Band GP (2002) Alcohol consumption impairs detection of performance errors in mediofrontal cortex. *Science* 298:2209-2211.
- Ridderinkhof KR, Nieuwenhuis S, Bashore TR (2003) Errors are foreshadowed in brain potentials associated with action monitoring in cingulate cortex in humans. *Neuroscience letters* 348:1-4.
- Rodriguez-Fornells A, Kurzbuch AR, Munte TF (2002) Time course of error detection and correction in humans: neurophysiological evidence. *J Neurosci* 22:9990-9996.
- Ruchow M, Spitzer M, Grön G, Grothe J, Kiefer M (2005) Error processing and impulsiveness in normals: Evidence from event-related potentials. *Cognitive Brain Research* 24:317-325.
- Rugg MD, Coles MGH (1995) *Electrophysiology of Mind. Event-Related Brain Potentials and Cognition*. New York: Oxford Univ. Press.
- Rushworth MFS, Walton ME, Kennerley SW, Bannerman DM (2004) Action sets and decisions in the medial frontal cortex. *Trends Cogn Sci* 8:410-417.
- Santesso DL, Segalowitz SJ, Schmidt LA (2005) ERP correlates of error monitoring in 10-year olds are related to socialization. *Biol Psychol* 70:79-87.
- Schall JD, Stuphorn V, Brown JW (2002) Monitoring and control of action by the frontal lobes. *Neuron* 36:309-322.
- Scheffers MK, Humphrey DG, Stanny RR, Kramer AF, Coles MG (1999) Error-related processing during a period of extended wakefulness. *Psychophysiology* 36:149-157.
- Scheibel AB (1997) The thalamus and neuropsychiatric illness. In: *The Neuropsychiatry of Limbic and Subcortical Disorders* (Salloway S, Malloy P, Cummings JL, eds), pp 31-43: American Psychiatric Press.
- Schultz W (1998) Predictive reward signal of dopamine neurons. *J Neurophysiol* 80:1-27.
- Schultz W (2000) Multiple reward signals in the brain. *Nat Rev Neurosci* 1:199-207.
- Schultz W (2002) Getting formal with dopamine and reward. *Neuron* 36:241-263.
- Schultz W, Dickinson A (2000) Neuronal coding of prediction errors. *Annu Rev Neurosci* 23:473-500.
- Segalowitz SJ, Davies PL (2004) Charting the maturation of the frontal lobe: an electrophysiological strategy. *Brain Cogn* 55:116-133.
- Segalowitz SJ, Davies PL, Santesso D, Gavin WJ, Schmidt LA (2004) The development of the error negativity in children and adolescents. In: *Errors, conflicts, and the brain. Current opinions on performance monitoring*. (Ullsperger M, Falkenstein M, eds), pp 177-184. Leipzig: MPI for Human Cognitive and Brain Sciences.
- Shidara M, Richmond BJ (2002) Anterior cingulate: single neuronal signals related to degree of reward expectancy. *Science* 296:1709-1711.
- Shima K, Tanji J (1998) Role for cingulate motor area cells in voluntary movement selection based on reward. *Science* 282:1335-1338.
- Simon-Thomas ER, Knight RT (2005) Affective and Cognitive Modulation of Performance Monitoring: Behavioral and ERP Evidence. *Cognitive, Affective, & Behavioral Neuroscience* 5:362-372.
- Stuphorn V, Taylor TL, Schall JD (2000) Performance monitoring by the supplementary eye field. *Nature* 408:857-860.
- Sturmer B, Leuthold H, Soetens E, Schroter H, Sommer W (2002) Control over location-based response activation in the Simon task: behavioral and electrophysiological evidence. *J Exp Psychol Hum Percept Perform* 28:1345-1363.
- Swick D, Turken AU (2002) Dissociation between conflict detection and error monitoring in the human anterior cingulate cortex. *Proc Natl Acad Sci U S A* 99:16354-16359.
- Tellegen A, Waller N (1996) Exploring personality through test construction: Development of the multidimensional personality questionnaire. In: *Personality measures: Development and evaluation*. (Briggs SR, Cheek JM, eds), pp 133-161. Greenwich, CT: JAI Press.
- Themanson JR, Hillman CH, Curtin JJ (2005) Age and physical activity influences on action monitoring during task switching. *Neurobiol Aging*.

- Tieges Z, Ridderinkhof KR, Snel J, Kok A (2004) Caffeine strengthens action monitoring: evidence from the error-related negativity. *Brain Res Cogn Brain Res* 21:87-93.
- Ullsperger M, Volz KG, von Cramon DY (2004) A common neural system signaling the need for behavioral changes. *Trends in Cognitive Sciences* 8:445-446.
- Ullsperger M, von Cramon DY (2004) Decision making, performance and outcome monitoring in frontal cortical areas. *Nature Neuroscience* 7:1173-1174.
- Ullsperger M, von Cramon DY (2006) The role of intact frontostriatal circuits in error processing. *Journal of Cognitive Neuroscience* 18:1-14.
- Van 't Ent D, Apkarian P (1999) Motoric response inhibition in finger movement and saccadic eye movement: a comparative study. *Clin Neurophysiol* 110:1058-1072.
- van Veen V, Carter CS (2002) The timing of action-monitoring processes in the anterior cingulate cortex. *J Cogn Neurosci* 14:593-602.
- van Veen V, Cohen JD, Botvinick MM, Stenger VA, Carter CS (2001) Anterior cingulate cortex, conflict monitoring, and levels of processing. *Neuroimage* 14:1302-1308.
- van Veen V, Holroyd CB, Cohen JD, Stenger VA, Carter CS (2004) Errors without conflict: Implications for performance monitoring theories of anterior cingulate cortex. *Brain Cogn* 56:267-276.
- Vidal F, Burle B, Bonnet M, Grapperon J, Hasbroucq T (2003) Error negativity on correct trials: a reexamination of available data. *Biol Psychol* 64:265-282.
- Vidal F, Hasbroucq T, Grapperon J, Bonnet M (2000) Is the 'error negativity' specific to errors? *Biol Psychol* 51:109-128.
- Volz KG, Schubotz RI, von Cramon DY (2003) Predicting events of varying probability: uncertainty investigated by fMRI. *Neuroimage* 19:271-280.
- Volz KG, Schubotz RI, von Cramon DY (2004a) Why am I unsure? Internal and external attributions of uncertainty dissociated by fMRI. *Neuroimage* 21:848-857.
- Volz KG, Schubotz RI, von Cramon DY (2004b) Variants of uncertainty in decision making and their cerebral correlates. In: *Errors, conflicts, and the brain. Current opinions on performance monitoring.* (Ullsperger M, Falkenstein M, eds), pp 84-95. Leipzig: MPI for Human Cognitive and Brain Sciences.
- Volz KG, Schubotz RI, von Cramon DY (2005) Frontomedian activation depends on both feedback validity and valence: fMRI evidence for contextual feedback evaluation. *Neuroimage* 27:564-571.
- Walton ME, Devlin JT, Rushworth MF (2004) Interactions between decision making and performance monitoring within prefrontal cortex. *Nat Neurosci* 7:1259-1265.
- Wang C, Ulbert I, Schomer DL, Marinkovic K, Halgren E (2005) Responses of human anterior cingulate cortex microdomains to error detection, conflict monitoring, stimulus-response mapping, familiarity, and orienting. *J Neurosci* 25:604-613.
- Watson D, Clark L, Tellegen A (1988) Development and validation of brief measures of positive and negative affect: the PANAS scales. *Journal of Personality and Social Psychology* 54:1063-1070.
- Williams ZM, Bush G, Rauch SL, Cosgrove GR, Eskandar EN (2004) Human anterior cingulate neurons and the integration of monetary reward with motor responses. *Nat Neurosci* 7:1370-1375.
- Yeung N (2004) Relating cognitive and affective theories of the error-related negativity. In: *Errors, conflicts, and the brain. Current opinions on performance monitoring.* (Ullsperger M, Falkenstein M, eds), pp 63-70. Leipzig: MPI for Human Cognitive and Brain Sciences.
- Yeung N, Cohen JD, Botvinick MM (2004) The neural basis of error detection: conflict monitoring and the error-related negativity. *Psychol Rev* 111:931-959.
- Yeung N, Sanfey AG (2004) Independent coding of reward magnitude and valence in the human brain. *J Neurosci* 24:6258-6264.
- Yordanova J, Falkenstein M, Hohnsbein J, Koley V (2004) Parallel systems of error processing in the brain. *Neuroimage* 22:590-602.
- Yordanova J, Koley V (2004) Error-specific signals in the brain: Evidence from a time-frequency decomposition of event-related potentials. In: *Errors, conflicts, and the brain. Current opinions on performance monitoring.* (Ullsperger M, Falkenstein M, eds), pp 35-41. Leipzig: MPI for Human Cognitive and Brain Sciences.
- Zirnheld PJ, Carroll CA, Kieffaber PD, O'Donnell BF, Shekhar A, Hetrick WP (2004) Haloperidol impairs learning and error-related negativity in humans. *J Cogn Neurosci* 16:1098-1112.

Abbreviations

| | |
|---------|---|
| ACC | anterior cingulate cortex |
| ANOVA | analysis of variance |
| BA | Brodmann area |
| BG | basal ganglia |
| CCZ | caudal cingulate zone |
| CMA | cingulate motor area |
| COMT | catechol-O-methyl transferase |
| CoRN | correction-related negativity |
| CRN | correct-related negativity |
| DA | dopamine |
| EEG | electroencephalography |
| ERN | error-related negativity |
| ERP | event-related potential |
| fMRI | functional magnetic resonance imaging |
| FRN | feedback-related negativity |
| GABA | γ -aminobutyric acid |
| LPFC | lateral prefrontal cortex |
| LRP | lateralized readiness potential |
| MRI | magnetic resonance image |
| Ne | error negativity, equivalent to ERN |
| OFC | orbitofrontal cortex |
| Pe | error positivity |
| pFMC | posterior frontomedian cortex |
| pMFC | posterior mesial frontal cortex, equivalent to pFMC |
| pre-SMA | pre-supplementary motor area |
| RCZ | rostral cingulate zone |
| SMA | supplementary motor area |
| SN | substantia nigra |
| VTA | ventral tegmental area |

All units of measurements are abbreviated according to the SI system, except for seconds and milliseconds which are abbreviated as sec and msec in some Chapters according to the requirements of the publisher of the respective journal.

Kurzfassung in deutscher Sprache

Die funktionelle Neuroanatomie der Handlungsüberwachung: fMRT-, EKP-, und Patientenstudien

Handlungsüberwachung

Die Fähigkeit zu zielstrebigem Handeln und flexibler Anpassung an eine sich ständig verändernde Umwelt gehört zu den wichtigsten kognitiven Funktionen des Menschen. Häufig führen Handlungen nicht auf direktem Wege zu ihrem Ziel, sondern enden zunächst in Fehlern. Werden Fehler erkannt, können diese jedoch sofort durch geeignete Anpassungen oder zusätzliche Handlungen kompensiert werden. Auch das Lernen und die Aneignung motorischer Fähigkeiten werden durch eine permanente Fehlererkennung ermöglicht. Somit hängt erfolgreiches zielgerichtetes Verhalten entscheidend von einer intakten *Handlungsüberwachung* ab. Dysfunktionale Handlungsüberwachung äußert sich in der Unfähigkeit, Fehler zu erkennen und/oder zu korrigieren, dem Verharren in nicht mehr zielführenden Verhaltensweisen (Perseveration) und spontanen Regelbrüchen.

Für die Erforschung der Handlungsüberwachung sind Fehler besonders informativ. James Reason (1990) unterscheidet verschiedene Fehlerarten anhand ihrer Entstehung. Besonders relevant für die vorliegende Arbeit sind zwei Fehlertypen, die sich in ihrer Detektierbarkeit durch die handelnde Person unterscheiden. So finden sich bei Routinehandlungen häufig so genannte "Schnitzer" (*action slips*). Die korrekte Handlung ist dabei bekannt, aber bei der Umsetzung kommt es zu Ungenauigkeiten, insbesondere, wenn Routineabläufe plötzlich leicht modifiziert werden müssen. Der Fehler kann durch das kognitive System erkannt werden, indem intendierte (korrekte) und tatsächlich ausgeführte Handlung miteinander verglichen werden (interne Fehlerdetektion). In unsicheren Entscheidungssituationen treten dagegen so genannte Irrtümer (*mistakes*) auf. Dabei reicht die vorliegende Information nicht aus, die korrekte Wahl zwischen verschiedenen Handlungsmöglichkeiten zu treffen. Erst anhand des Handlungsergebnisses kann entschieden werden, ob die gewählte Handlung korrekt war oder nicht. Wird das gewünschte Ergebnis nicht erreicht, liegt ein Fehler vor.

Die vorliegende Arbeit befasst sich mit der Implementierung der Handlungsüberwachung im menschlichen Gehirn. Mittels funktioneller Magnetresonanztomographie (fMRT) und Elektroenzephalographie (EEG), insbesondere ereigniskorrelierter Hirnpotentiale (EKP), wurde die funktionelle Neuroanatomie und die Dynamik der bei der Handlungsüberwachung ablaufenden kognitiven Prozesse untersucht. Zur genaueren Beschreibung der für diese Funktion *notwendigen* Hirnareale wurden EKP-Studien bei definierten Patientengruppen durchgeführt.

Korrelate und Manifestationen der Handlungsüberwachung

Manifestationen im Verhalten

Seit den sechziger Jahren des zwanzigsten Jahrhunderts werden Fehler und Handlungsüberwachung systematisch erforscht. Zwar konnten die während der Überwachung

laufenden Prozesse zunächst nicht direkt untersucht werden, doch ließen sich Rückschlüsse auf Fehlererkennung und –verarbeitung durch die nach Fehlern beobachtbaren kompensatorischen Handlungen und Anpassungen ziehen. Während offene verbale und emotionale Äußerungen während des Fehlers (z.B. Grimassieren, Fluchen) in Versuchssituationen selten auftreten, kommt es häufig zu spontanen Fehlerkorrekturen (Rabbitt, 1966a, 1966b). Selbst wenn die Versuchspersonen bei psychologischen Experimenten nicht entsprechend instruiert sind, drücken sie nach fehlerhafter Reaktion häufig sofort die korrekte Antworttaste.

In Versuchsdurchgängen nach Fehlern lassen sich Anpassungen beobachten. So kommt es zu Reaktionszeitanstiegen (Abb. I-01), wenn zuvor eine fehlerhafte Reaktion ausgeführt wurde. Man nimmt an, dass diese der Fehlervermeidung dienende Verlangsamung eine vorsichtigere Handlungsweise widerspiegelt. In einigen Fällen wurden auch spezifischere Anpassungen beobachtet, zum Beispiel eine Reduktion von Interferenzeffekten nach Fehlern (Ridderinkhof et al., 2002). Die bewusste Wahrnehmung von Fehlern wird durch Fehlersignalisierung untersucht, wobei die Versuchspersonen nach jedem Fehler eine Signaltaste drücken (Nieuwenhuis et al., 2001; Rabbitt, 2002).

Intrakranielle Ableitungen

Bereits vor mehr als 35 Jahren wurden bei diagnostischen Ableitungen mittels Tiefenelektroden bei Menschen fehlerspezifische Potentiale identifiziert (Bechtereva, 1971). Bei nichtmenschlichen Primaten wurde später festgestellt, dass Neurone im Gyrus cinguli anterior (ACC) bei Fehlern die Feuerrate erhöhten (Niki und Watanabe, 1979). Dabei rückten speziell das kaudale Areal 24 und die zingulärmotorischen Areale (CMA) in den Vordergrund des Interesses (Gemba et al., 1986; Shima und Tanji, 1998; Schall et al., 2002; Ito et al., 2003). Besonders einflussreich für das heutige Verständnis der Handlungsüberwachung war der Befund, dass bestimmte Neurone in der rostralen CMA spezifisch dann ihre Aktivität erhöhen, wenn zwei Bedingungen erfüllt sind. Einerseits führte die vorherige Handlung nicht zum erwünschten Ergebnis, und andererseits wird im nachfolgenden Versuchsdurchgang eine alternative Handlung ausprobiert, um wieder die das Handlungsziel zu erreichen (Shima und Tanji, 1998). Diese Befunde wurden bei intraoperativen Einzelzellableitungen aus dem Homolog der CMA beim Menschen (der so genannten *rostral cingulate zone*, *RCZ*) bestätigt.

Ableitungen mit Tiefenelektroden bei Epilepsiepatienten zeigten, dass zusätzlich zur RCZ auch eine Reihe anderer Hirnstrukturen fehlerbezogene Potentiale generiert (Brázdil et al., 2002). Gleichzeitige Ableitung aus der RCZ und dem temporalen Kortex zeigten bei Fehlern transiente Phasenkopplungen im Thetafrequenzband, was als Interaktion dieser Hirnareale interpretiert wurde (Wang et al., 2005).

Ereigniskorrelierte Potentiale

Um 1990 wurden fehlerbezogene, an der Kopfoberfläche ableitbare EKPs entdeckt. Die *error-related negativity* (*ERN*, auch *error negativity*, *Ne*) ist eine negative Welle im reaktionsbezogen gemittelten EKP, die etwa 50 bis 100 ms nach der fehlerhaften Reaktion ihr Maximum erreicht und eine frontozentrale Skalpverteilung aufweist (Falkenstein et al., 1990; Gehring et al., 1993). Bei Mastoidreferenz erreicht sie Amplituden von bis zu 15 μ V an den Elektroden FCz und Cz (Abb. I-02, I-03). Zeit-Frequenz-Analysen haben ergeben, dass es um die fehlerhafte Antwort zu einem Leistungsanstieg im Theta- (5-7 Hz) und Deltafrequenzband (1.5-3.5 Hz) kommt (Luu und Tucker, 2001; Yordanova und Kolev, 2004). Die ERN tritt bei Fehlern vom Typ *action slip*

in Reaktionszeitaufgaben auf, unabhängig von Stimulusmodalität und Effektor (Holroyd et al., 1998; Van 't Ent und Apkarian, 1999; Falkenstein et al., 2000; Masaki et al., 2001; De Bruijn et al., 2003). Quellenlokalisationstudien legen nahe, dass die ERN im posterioren frontomedianen Kortex (pFMC) generiert wird (Dehaene et al., 1994).

Nach der ERN tritt häufig eine zweite fehlerbezogene Komponente auf, die *error positivity* (*Pe*). Sie hat ein zentroparietales Maximum und ist über einen längeren Zeitraum (etwa 300 bis 500 ms nach der Reaktion) beobachtbar. Eine kürzlich erschienene Übersichtsarbeit fand wenig unterstützende Datenpunkte für die vorherrschenden Hypothesen, dass die *Pe* ein Korrelat der affektiven Verarbeitung des Fehlers oder der Implementierung von Verhaltensanpassungen darstellt (Overbeek et al., 2005). Dagegen scheint es eher gesichert, dass die *Pe* mit der bewussten Fehlerwahrnehmung assoziiert ist (Nieuwenhuis et al., 2001; Endrass et al., 2005).

Bei Handlungen in unterdeterminierten Situationen kann das kognitive System Fehler erst nach Verarbeitung externer Rückmeldungen über das Handlungsergebnis erkennen. Bei derartigen Aufgaben tritt keine klassische ERN nach der Reaktion auf. Allerdings wurde eine Komponente ähnlicher Verteilung etwa 250 bis 300 ms nach Darbietung der Rückmeldung beschrieben (Miltner et al., 1997). Es ist derzeit umstritten, ob diese rückmeldungsbezogene Komponente equivalent zur ERN ist (Gehring und Willoughby, 2004). Allerdings ist festzuhalten, dass es eine Reihe von Ähnlichkeiten gibt, und dass bestimmte Theorien zur Handlungsüberwachung, zum Beispiel die *Reinforcement-Learning* Theorie, beide Komponenten gleichsetzen (Holroyd und Coles, 2002).

Es sollte nicht unerwähnt bleiben, dass auch bei korrekten Reaktionen gelegentlich eine frontozentrale Negativierung beobachtet wird. Diese Komponente ist deutlich kleiner als die ERN und häufig nur nach einer Laplace-Transformation der EEG-Daten sichtbar. Sie wird meist *correct-related negativity* (*CRN*) genannt (Ford, 1999; Vidal et al., 2000, 2003). Die Bedeutung dieser Komponente ist noch ziemlich unklar; sie wird als Hinweis auf generelle, ständig ablaufende Überwachungsprozesse gewertet.

Bildgebende Verfahren

FMRT-Studien zur Handlungsüberwachung weisen konsistent auf eine Beteiligung des pFMC bei der Fehlerdetektion aber auch bei der Entdeckung von Handlungskonflikten hin (Carter et al., 1998). Eine ausführliche Übersicht dieser Befunde findet sich im Kapitel 7 dieser Arbeit. Zusätzlich zu Aktivierungen im pFMC fanden sich regelmäßig Signalanstiege im lateralen präfrontalen Kortex (LPFC) sowie in der anterioren Insel. Weniger konsistent sind Befunde zur Beteiligung der (dorsalen) Basalganglien, des ventralen Striatums, des Thalamus und des Mittelhirns. Diese Aktivierungen sind stark von der Art der untersuchten Aufgabe und der spezifischen Fragestellung abhängig. Aktivierungen im orbitofrontalen Kortex (OFC) wurden selten berichtet, was wahrscheinlich technisch bedingt ist, da in diesem Areal häufig Signalverluste und -distorsionen (Suszeptibilitätsartefakte) aufgrund von Magnetfeldinhomogenitäten auftreten.

Modelle der Handlungsüberwachung

Im Folgenden werden die aktuellen Theorien zur Handlungsüberwachung kurz dargestellt.

Die Fehlerdetektionstheorie

Basierend auf dem Befund, dass Fehler (*action slips*) rasch korrigiert werden können, wurde schon frühzeitig vermutet, dass das Gehirn ein Fehlerdetektionssystem beherbergt

(Angel, 1976; Rabbitt und Rodgers, 1977). Nach der Entdeckung der ERN wurde dieser Gedanke zur Fehlerdetektionstheorie (oft auch als *Mismatch Theory* bezeichnet) weiterentwickelt. Sie besagt, dass das Handlungsüberwachungssystem nach einer Diskrepanz zwischen den Repräsentationen der korrekten (also der Intention entsprechenden) und der tatsächlich ausgeführten Handlung fahndet. Eine derartige Diskrepanz ("*mismatch*") äußert sich in erhöhter Aktivität im pFMC und einer ERN im EKP (Falkenstein et al., 1990, 2000; Gehring et al., 1993; Coles et al., 2001). Diese pFMC-Aktivität wird als Signal zur Initiierung kompensatorischer Mechanismen interpretiert. Verhaltensstudien sowie EKP-Befunde legen nahe, dass die Repräsentation der ausgeführten Handlung aus einer Efferenzkopie des motorischen Programms entsteht und nicht durch propriozeptive Rückmeldung aus der Peripherie (Higgins und Angel, 1970; Angel, 1976; Allain et al., 2004a). Die Repräsentation der intendierten Handlung entsteht durch die Verarbeitung der Stimuli, die auch nach Auslösen der vorschnellen fehlerhaften Reaktion fortgesetzt wird.

Die *Reinforcement Learning* Theorie

Basierend auf der Fehlerdetektionstheorie wurde unter Berücksichtigung der Befunde über Verstärkungslernen (*reinforcement learning*) und Belohnungsverarbeitung bei Primaten eine Theorie entwickelt, die durch Simulationen in einem computergestützten Modell unterstützt wird (Holroyd und Coles, 2002). Wegen ihres Bezuges zum Verstärkungslernen wird sie als *Reinforcement Learning* Theorie bezeichnet.

Untersuchungen bei Affen zeigten, dass Fehler in der Belohnungsvorhersage in phasische Aktivitätsänderungen in den mesenzephalen dopaminergen Neuronen reflektiert werden (Schultz, 1998, 2000, 2002; Schultz und Dickinson, 2000; Fiorillo et al., 2003). Wenn Ereignisse ein besseres Ergebnis für das Individuum anzeigen als erwartet, kommt es zu einem phasischen Anstieg der Feuerrate dopaminergischer Neurone. Dagegen führt ein unerwartet schlechteres Ergebnis zu einer phasischen Verminderung der dopaminergen Aktivität. Fehler lassen die Nichterreicherung eines Ziels, also ein schlechteres als das erwartete Ergebnis, antizipieren. Befunden bei Affen entsprechend wird angenommen, dass die Fehlererkennung mit einer phasischen Reduktion der Dopaminausschüttung assoziiert ist. Dieses dopaminerge Signal wird zum Kortex geleitet. Die RCZ ist stark dopaminerg innerviert, so dass ein Ausbleiben der Dopaminausschüttung vermutlich zu einer Aktivierung der Neurone in diesem Areal führt. Wegen der geometrischen Anordnung der RCZ ist es wahrscheinlich, dass sich diese Aktivität aufsummiert und an die Kopfoberfläche propagiert. Entsprechend sind phasische Reduktionen der Dopaminaktivität mit großen ERN-Amplituden und phasische Erhöhungen der Dopaminaktivität mit kleinen ERN-Amplituden assoziiert.

Die *Reinforcement Learning* Theorie basiert auf sogenannten Actor-Critic-Modellen die in der computergestützten Simulation mit neuronalen Netzwerken Anwendung finden. Insbesondere für das Verständnis der Basalganglienfunktionen wurden derartige Modelle entwickelt (Barto, 1995; Houk et al., 1995). Die *Reinforcement Learning* Theorie der Handlungsüberwachung lässt sich folgendermaßen vereinfacht zusammenfassen. Die Basalganglien sind an der Prädiktion des Handlungsergebnisses unter Berücksichtigung kontextueller Informationen aus dem LPFC beteiligt und gleichen dieses mit den eingehenden Informationen über das tatsächliche Handlungsergebnis (Efferenzkopie, externe Rückmeldung) ab. Ist das Ergebnis schlechter als erwartet, inhibieren Projektionen aus dem Striatum die mesenzephalen dopaminergen Kerne. Diese Theorie ist der bisher am stärksten an der Neurobiologie orientierte Erklärungsansatz für die Funktion der Handlungsüberwachung. Dennoch ist anzumerken, dass die Theorie in

Ermangelung geeigneter, beim Menschen anwendbarer Methoden nur zum Teil experimentell überprüft wurde. Pharmakologische Experimente, Genotypisierung und nuklearmedizinische Verfahren mit spezifischen Radioliganden stellen vielversprechende Ansätze zur Überprüfung und Erweiterung dieser Theorie dar.

EKP und Befunde bildgebender Verfahren haben viele Vorhersagen der *Reinforcement Learning* Theorie bestätigt. Allerdings scheinen neuere Ergebnisse darauf hinzuweisen, dass die ERN ein eher binäres Reaktionsmuster zeigt und nicht durch die Größe des Vorhersagefehlers beeinflusst wird. Das bedeutet, große ERN-Amplituden spiegeln wider, dass das Handlungsziel nicht erreicht wurde, und kleine ERN-Amplituden sind mit dem Erreichen des Ziels assoziiert (Yeung und Sanfey, 2004; Holroyd et al., in press).

Die Handlungskonflikttheorie

In den neunziger Jahren wurde eine weitere Theorie zur kognitiven Kontrolle und dem Beitrag der Handlungsüberwachung entwickelt. Diese Theorie ist ebenfalls als konnektionistisches computergestütztes Modell formalisiert, und eine Reihe von bildgebenden und EKP Befunden stimmen mit den Vorhersagen des Modells überein (Carter et al., 1998; Botvinick et al., 1999, 2001, 2004; Yeung et al., 2004). Grundannahme des Modells ist, dass das Handlungsüberwachungssystem nicht Fehler per se sondern Handlungskonflikte detektiert. Handlungskonflikt entsteht, wenn eine Aufgabe mehrere Handlungstendenzen gleichzeitig aktiviert, zum Beispiel, wenn ein Ablenkreuz eine hoch überlernte aber falsche Antwort bahnt. Meist setzt sich dennoch die korrekte Handlungstendenz durch, so dass der Konflikt sein Maximum vor der Ausführung der Handlung erreicht. Fehler (*action slips*) treten vor allem bei vorschneller Reaktion auf, wenn die Reizverarbeitung noch nicht abgeschlossen und somit die korrekte Handlungstendenz noch nicht vollständig aufgebaut ist. Da die Reizverarbeitung auch nach der Reaktion fortgesetzt und die korrekte Handlungstendenz weiter aufgebaut wird, erreicht der Handlungskonflikt erst nach der fehlerhaften Reaktion sein Maximum (siehe Abb. I-09).

Aufgrund von fMRT-Studien wird angenommen, dass die Aktivität im pFMC die Stärke des Handlungskonfliktes widerspiegelt. Ebenso schlagen Yeung et al. (2004) vor, dass die ERN ein Korrelat des Handlungskonflikts ist, der nach Fehlern auftritt. Wie im Fehlerdetektionsmodell wird vermutet, dass die pFMC-Aktivität kognitive Anpassungen bahnt.

Für unterdeterminierte Situationen, wenn mehrere Handlungsalternativen gleich geeignet erscheinen, wird ein dem Handlungskonflikt ähnlicher Prozess angenommen. Allerdings gibt es dafür noch keine überprüfbaren konnektionistischen Modelle. Die Handlungskonflikttheorie kann derzeit die Befunde zur rückmeldungsbezogenen Negativierung (*feedback ERN*) nicht integrieren.

Brown und Braver (2005) stellten ein abgewandeltes Modell vor, das die *Reinforcement Learning* Theorie und die Handlungsüberwachungstheorie integriert. Danach wird der pFMC immer dann aktiviert, wenn die Aufgabensituation eine hohe Fehlerwahrscheinlichkeit birgt, also wenn das intendierte Handlungsergebnis nur mit geringer Wahrscheinlichkeit erreicht wird.

Andere Modelle der Handlungsüberwachung

Alternativ zu den oben beschriebenen Modellen wurde vorgeschlagen, dass die ERN die Aktivität eines generellen Überwachungssystems widerspiegelt, das die motivationale Bedeutung eines Fehlers bewertet und die emotionalen Reaktionen steuert. Motivationale

Effekte auf die ERN-Amplitude wurden bereits in einer der ersten Studien beschrieben (Gehring et al., 1993). Dabei wurden zwei Bedingungen verglichen, in der durch finanzielle Anreize entweder die Wichtigkeit der Antwortgenauigkeit oder der Reaktionsgeschwindigkeit betont wurden. Die ERN-Amplitude war erhöht, wenn der Fokus auf der Antwortgenauigkeit lag.

Auch Untersuchungen zu interindividuellen Unterschieden liefern Hinweise, dass die ERN ein Korrelat motivationaler und emotionaler Überwachungsfunktionen sein könnte. Die ERN variiert mit negativem Affekt, negativer Emotionalität, Sozialisation und anderen Persönlichkeitsfaktoren (Dikman und Allen, 2000; Luu et al., 2000; Pailing et al., 2002; Pailing und Segalowitz, 2004).

Meines Erachtens sprechen diese Befunde nicht zwangsläufig für eine ausschließlich emotionale Funktion des pFMC. Wie ich weiter unten ausführen werde, bin ich der Überzeugung, dass das Handlungsüberwachungssystem nicht nur kognitive sondern auch motivationale, emotionale und das vegetative Nervensystem betreffende Anpassungen initiieren kann. Des Weiteren weisen die Befunde von Gehring und Kollegen (1993) und die im Teil V zusammengefassten Studien darauf hin, dass die Aktivität des Handlungsüberwachungssystems durch affektive und motivationale Faktoren moduliert werden kann (siehe auch Allen et al., 2004).

Die Bedeutung des posterioren frontomedianen Kortex

Ein großer Teil meiner bildgebenden und elektrophysiologischen Studien widmete sich der Aufklärung der funktionellen Rolle des pFMC bei der Handlungsüberwachung. Zunächst stellte sich die Frage, welche Hirnregionen mit der Entdeckung eigener Fehler assoziiert sind, ob diese sich vom durch Handlungskonflikte aktivierten Netzwerk unterscheiden, und ob die ERN in einer dieser Regionen generiert wird. Dazu führten Versuchspersonen eine Flankierreizaufgabe unter hohem Zeitdruck in zwei separaten Messsitzungen aus, einer EEG- und einer fMRT-Sitzung (siehe Kapitel 3). Bei dieser Aufgabe entsteht bei einem Teil der korrekten Reaktionen ein starker Handlungskonflikt, und den Versuchspersonen unterlaufen genügend Fehler, um eine statistische Analyse zu ermöglichen. Die fMRT-Daten zeigten erhöhte Aktivität im pFMC sowohl bei Fehlern als auch bei korrekten Reaktionen, die mit starkem Handlungskonflikt assoziiert waren. Die Aktivitätsmaxima wiesen allerdings auf eine Dissoziation innerhalb des pFMC hin. Während Handlungskonflikt bei korrekten Reaktionen mit Signalanstiegen in der anterioren Prä-SMA und dem mesialen BA 8 assoziiert war, führten Fehler zu einer verstärkten Aktivierung im Sulcus cinguli, speziell in der RCZ. Die in der EEG-Messung erhobene ERN konnte mit einem im fehlerbezogenen fMRT-Aktivitätsmaximum in der RCZ gelegenen Dipol mit einer Residualvarianz von unter 10% erklärt werden. Die Studie war eine der ersten das gesamte Gehirn einbeziehenden bildgebenden Studien zur Handlungsüberwachung. Sie zeigte, dass auch die Basalganglien, die anteriore Insel und der laterale frontale Kortex bei der Handlungsüberwachung aktiviert werden. Vorherige Studien zur Handlungsüberwachung fokussierten auf ein Volumen in der Frontomedianwand (Carter et al., 1998) oder verwendeten ein Go-NoGo-Paradigma, bei dem sich Prozesse der Handlungsüberwachung nicht sicher von motorischer Inhibition trennen lassen (Kiehl et al., 2000). Zur Integration von EEG- und fMRT-Befunden in dieser in Kapitel 3 berichteten Studie muss einschränkend angemerkt werden, dass durch die separate Messung starke Unterschiede in den Fehlerraten zwischen der EEG- und der fMRT-Sitzung unvermeidlich waren. Außerdem kann der Befund zur Dipolmodellierung

allenfalls als Unterstützung der Annahme nicht jedoch als Beweis gewertet werden, dass die ERN in der RCZ generiert wird. Diese Punkte wurden in einer späteren, simultan gemessenen Studie erfolgreich adressiert (siehe unten und Kapitel 5).

In zwei fMRT-Experimenten (siehe Kapitel 4) wurde untersucht, ob auch Fehler in unsicheren Situationen mit demselben Handlungsüberwachungssystem verarbeitet werden. Wie bereits erläutert, können Fehler in unsicheren Entscheidungssituationen erst durch externe Rückmeldungen als solche erkannt werden. Um eine hinreichende Entscheidungsunsicherheit zu erzeugen, wurde eine Bewegungsprädiktionsaufgabe entwickelt, bei der sich die Schwierigkeit dynamisch so an die Versuchsperson anpasste, dass eine mittlere Fehlerrate von 37% erzielt wurde. Nach ihrer Antwort erhielten die Probanden eine Rückmeldung. Das erste Experiment zeigte große Übereinstimmungen des durch die Verarbeitung negativer Rückmeldungen aktivierten Netzwerkes mit den in der Flankierreizaufgabe gefundenen Hirnarealen. Fehler, angezeigt durch negative Rückmeldung, waren mit Signalanstiegen in der RCZ und der anterioren Insel assoziiert. Der Hauptbefund der Studie, dass sowohl die interne Detektion von motorischen Fehlern (*action slips*) als auch die Fehlerdetektion auf der Basis externer Rückmeldungen (*mistakes*) die RCZ aktivieren, wurde später in einem Innersubjekt-Design repliziert (Holroyd et al., 2004). Positive Rückmeldungen führten in beiden Experimenten zu einer robusten Aktivierung im ventralen Striatum. Durch gelegentliche Darbietung nichtinformativer Stimuli anstelle der negativen und positiven Rückmeldungen konnte gezeigt werden, dass Handlungsunsicherheit mit Signalanstiegen in der Prä-SMA assoziiert ist. Nach Botvinick und Kollegen (2001) sind Handlungsunsicherheit und Handlungskonflikt ähnlich, so dass sich auch hier wieder eine Übereinstimmung mit den Befunden von der Flankierreizaufgabe fand. Des Weiteren fand sich ein interessantes Aktivitätsmuster im Habenularkomplex. Die Daten legen nahe, dass dort eine Integration aus Belohnungsvorhersage und vorliegenden Informationen über das Handlungsergebnis stattfindet. Das scheint plausibel, wenn man berücksichtigt, dass die Habenula vorwiegend inhibitorische Fasern zu den monoaminergen Kernen des Mittelhirns sendet. Somit kann die Hypothese aufgestellt werden, dass der Habenularkomplex eine Rolle bei der Steuerung der dopaminergen Aktivität spielt, was gut mit der *Reinforcement Learning* Theorie der Handlungsüberwachung in Einklang zu bringen ist.

Die technische Entwicklung der letzten Jahre machte es möglich, reliable EEG-Daten simultan zur fMRT-Messung zu erheben. Somit eröffneten sich neue Möglichkeiten, den Zusammenhang von EEG- und fMRT-Manifestationen der Handlungsüberwachung zu untersuchen. Ein weiteres Ziel der in Kapitel 5 beschriebenen Simultanstudie war, die Dynamik der Handlungsüberwachung näher zu beleuchten. Nach den Theorien zur Handlungsüberwachung ist anzunehmen, dass das Überwachungssystem ständig aktiv ist und signalisiert, wenn Handlungsanpassungen erforderlich sind. Diese Signale sollten über die Versuchsdurchgänge hinweg fluktuieren; ihre Amplitude sollte die resultierenden Anpassungen vorhersagen. Bisher war der Zusammenhang zwischen ERN-Amplitude bzw. Aktivierung in der RCZ und nachfolgenden Anpassungen nur durch wenige Studien belegt. Die Mehrzahl der Studien jedoch, die die Fluktuationen der gemessenen Korrelate auf der Einzelpersonenebene durch notwendige Mittelungen nicht berücksichtigen konnten, fanden keine derartigen Zusammenhänge. Durch simultane Messung von EEG und fMRT bei Durchführung einer Flankierreizaufgabe sowie durch die auf *Independent Component Analysis* (ICA) basierende Einzeldurchgangsanalyse konnten wir zeigen, dass die Amplitude der ERN mit dem fMRT-Signal in der RCZ korrelierte. Außerdem

sagte die ERN-Amplitude im einzelnen Fehlerdurchgang die Reaktionszeitverlangsamung im darauf folgenden Versuchsdurchgang voraus. Eine starke Negativierung war mit einem hohen fMRT-Signal und einer deutlicheren Reaktionszeitverlangsamung im nachfolgenden Versuchsdurchgang assoziiert.

Kapitel 6 gibt eine Übersicht über die bis 2004 veröffentlichten bildgebenden Studien zur Handlungsüberwachung. In der Zusammenschau dieser Metaanalyse mit den oben beschriebenen Experimenten sowie Befunden bei nichtmenschlichen Primaten erarbeiteten wir eine Hypothese zur Funktion des pFMC. Zunächst fällt auf, dass der pFMC immer dann aktiv ist, wenn ein Handlungsergebnis oder allgemeiner der Zustand des Individuums schlechter ist als intendiert, zum Beispiel bei Fehlern, aber auch bei Schmerzreizen oder sozial unerwünschten Phänomenen (z.B. bei sozialem Ausschluss, siehe (Eisenberger und Lieberman, 2004)). Außerdem aktivieren den pFMC Bedingungen, in denen ein schlechtes Handlungsergebnis wahrscheinlich ist, beispielsweise bei starkem Handlungskonflikt und Entscheidungsunsicherheit. Verallgemeinert handelt es sich um Situationen mit hoher Fehlerwahrscheinlichkeit (Brown und Braver, 2005). Diese Situationen haben gemeinsam, dass sie Anpassungen erfordern, da sonst das gewünschte Handlungsergebnis bzw. der gewünschte Zustand nicht erreicht werden. Wir vermuten daher, und die Befunde aus Kapitel 5 stützen diese These, dass der pFMC bei der Signalisierung der Notwendigkeit von Anpassungen eine entscheidende Rolle spielt. Diese Anpassungen können motorischer, kognitiver und affektiver Natur sein, betreffen auch das vegetative Nervensystem (Critchley et al., 2003, 2005), und können beliebig komplexe, selbst soziale, Verhaltensweisen beeinflussen (Ullsperger et al., 2004; Ullsperger und von Cramon, 2004).

Das Handlungsüberwachungsnetzwerk und seine Dysfunktion nach Hirnschädigung

Der pFMC kann seine Rolle bei der Handlungsüberwachung nur im Verbund mit anderen Hirnstrukturen wahrnehmen. Es stellt sich die Frage, mit welchen Arealen der pFMC interagiert, wo und wie die notwendige Kontextinformation bereitgestellt wird, welchen Arealen das Signal über nötige Anpassungen gesendet wird, und welche Hirnstrukturen die Aktivität des Handlungsüberwachungssystems modulieren. Obwohl fMRT und EEG Hinweise zu diesen Fragen geben, muss man berücksichtigen, dass beide Methoden korrelativer Natur sind und somit kausale Zusammenhänge nicht beweisen können. Damit kann die *Notwendigkeit* einer Hirnstruktur für die Handlungsüberwachung nicht geklärt werden. Hierbei sind Patientenstudien äußerst hilfreich. Kapitel 7 und 8 berichten von EEG-Studien bei Patienten mit lokalisierten Hirnläsionen. Es wurden Gruppen mit unilateralen Schädigungen des LPFC, der Basalganglien (insbesondere des Neostriatums), des temporalen Kortex und mit bilateralen Läsionen des frontopolaren Kortex, die sich in den anterioren OFC erstreckten, mit einem Flankierreizparadigma untersucht. Bei den Patientengruppen mit chronischen Läsionen des LPFC und der Basalganglien fand sich eine starke Reduktion der ERN. Es scheint, als würden die die ERN generierenden Strukturen nicht mehr zwischen korrekten und inkorrekten Reaktionen unterscheiden. Dennoch war die Leistung der Patienten in der Flankierreizaufgabe nicht wesentlich beeinträchtigt. Interessanterweise waren die meisten Patienten in der Lage, ihre Fehler sofort zu korrigieren. Drei Patienten mit Läsionen im LPFC fielen durch eine stark verminderte Korrekturrate auf. Eine Analyse der Läsionsmuster ergab, dass sich bei diesen Patienten die Läsionen bis ins frontale Marklager an der Basis der zweiten und

dritten Stirnhirnwindung und ins vordere subinsuläre Marklager erstreckten. Bei dieser Lokalisation kann vermutet werden, dass die Faserverbindungen zwischen RCZ und den intakten Resten des LPFC sowie die Projektionen dieser Areale ins Striatum unterbrochen wurden, was die Funktion wiederherstellende Reorganisationsprozesse verhindert haben könnte.

Die übrigen Patientengruppen mit Läsionen des frontopolaren bzw. temporalen Kortex zeigten keine Veränderungen der ERN oder der Verhaltensdaten im untersuchten Paradigma. Es kann gefolgert werden, dass die ERN ein sensibler und spezifischer Marker der funktionellen Integrität des Handlungsüberwachungssystems ist. Dabei zeigt die ERN bereits dann Auffälligkeiten, wenn das Verhalten noch weitgehend intakt ist. Zukünftige Studien werden zeigen, ob Fehlersignalisierung (siehe Kapitel 12) ein ebenso sensibler Verhaltensmaß darstellt.

Kapitel 9 gibt eine Übersicht über bisher publizierte Studien zur Handlungsüberwachung bei neurologischen und psychiatrischen Patientenpopulationen. Insgesamt ergibt sich ein noch etwas unübersichtliches Bild, was teilweise auf Unterschiede in den Untersuchungsmethoden und kleine Stichproben zurückgeführt werden kann. In der Übersicht schlage ich eine Reihe von Standards für die systematische Untersuchung der Handlungsüberwachung bei Patienten vor. Ein Ziel der weiteren Forschung ist es, robuste und einfach durchführbare Paradigmen zur gezielten Untersuchung einzelner Patienten zu entwickeln. So könnte eine spezifische Diagnostik und Therapieevaluation im Hinblick auf Handlungsüberwachung ermöglicht werden.

Anpassungen und kompensatorische Handlungen

Wenn Fehler unterlaufen sind und das Handlungsüberwachungssystem diese detektiert hat, werden kompensatorische Mechanismen angestoßen. Sofortige Korrekturhandlungen dienen der Abwehr negativer Fehlerkonsequenzen und der Verbesserung des aktuellen Handlungsergebnisses. Längerfristige kognitive Anpassungen optimieren die Ausführung einer bestimmten Aufgabe, so dass ähnliche Fehler in der Zukunft seltener auftreten.

Sofortige Fehlerkorrekturen werden schon seit den sechziger Jahren in Verhaltensexperimenten untersucht (Rabbitt, 1966a, 1966b; 1967; Rabbitt und Phillips, 1967). Bei Reaktionszeitaufgaben wurde beobachtet, dass die Versuchspersonen einen Teil der fehlerhaften Reaktionen sehr schnell durch einen zweiten Tastendruck korrigieren. Selbst wenn keine derartige Instruktion gegeben wurde, werden noch etwa 20-40% der Fehler auf diese Weise korrigiert. Die in Kapitel 10 dargestellte Studie untersucht mittels fMRT das diesen Korrekturen zugrundeliegende anatomische Substrat. Hierzu wurden führten die Versuchspersonen wiederum eine Flankierreizaufgabe aus. Die Probanden wurden in zwei Gruppen unterteilt. Eine Gruppe war instruiert, jeden bemerkten Fehler sofort durch einen zweiten Tastendruck zu korrigieren. Die andere Gruppe erhielt keine derartige Instruktion; die Teilnehmer waren sich nicht über die Möglichkeit einer Sofortkorrektur bewusst. Wie zu erwarten war, korrigierten sich die instruierten Probanden signifikant häufiger als die nichtinstruierten (82 vs. 21%). In einem Hauptkontrast, der für alle Versuchspersonen berechnet wurde, konnte die bekannten, an der Fehlerverarbeitung beteiligten Hirnareale bestätigt werden. In einem zweiten Schritt wurden nun die Aktivierungen für korrigierte Fehler in der instruierten Gruppe mit den Aktivierungen für nichtkorrigierte Fehler in der nichtinstruierten Gruppe kontrastiert. Bei Fehlerkorrektur waren folgende Areale stärker aktiv: RCZ, Prä-SMA, SMA und sekundäre somatosensorische Areale. Diese Befunde legen nahe, dass die RCZ nicht nur bei der

Fehlerdetektion, sondern auch bei der Initiierung der Korrektur eine Rolle spielt. Die mesialen prämotorischen Areale (Prä-SMA, SMA) waren vermutlich durch die zusätzliche motorische Korrekturhandlung aktiviert. Wir vermuten weiter, dass die sekundären somatosensorischen Areale für eine bei der Fehlerkorrektur verstärkte Verarbeitung somatosensorischer Rückmeldungen bedeutsam sind.

Die elektrophysiologischen Merkmale der Fehlerkorrektur wurden in einem weiteren Experiment mit gleichartiger Gruppierung der Versuchspersonen untersucht (Kapitel 11). Die Verhaltensdaten bestätigten die fMRT Studie: mit Instruktion, Fehler zu korrigieren, wurden signifikant mehr Fehler berichtigt als ohne diese Instruktion. Eine Distributionsanalyse ergab, dass dieser Zuwachs an Fehlerkorrekturen besonders durch eine Zunahme langsamer Korrekturen getrieben wurde. Des Weiteren zeigten sich auf der Verhaltensebene Ähnlichkeiten zwischen schnellen intentionalen Korrekturen bei der instruierten Gruppe und Spontankorrekturen bei der nichtinstruierten Gruppe. Das spiegelte sich auch in den Latenzen der ERN wider. Spontankorrekturen bei nichtinstruierten und schnelle Korrekturen bei instruierten Probanden waren mit einer kürzeren ERN-Latenz assoziiert als langsame Korrekturen (bei der instruierten Gruppe) und nichtkorrigierte Fehler (bei der nichtinstruierten Gruppe). Dieses Ergebnismuster stimmt mit den Vorhersagen der Handlungskonflikttheorie überein. Ein im Vergleich zu früheren EEG-Studien zur Sofortkorrektur von Fehlern (Falkenstein et al., 1994, 1996; Rodriguez-Fornells et al., 2002) überraschender Befund war, dass die nichtinstruierte Gruppe eine höhere ERN-Amplitude zeigte als die instruierte Gruppe, unabhängig davon, ob und mit welcher Geschwindigkeit die Fehler korrigiert wurden. Parallel erhobene Daten zur phasischen Herzratenänderung legten nahe, dass die Instruktion, Fehler zu korrigieren, die subjektive Bedeutung der Fehler verringert (Fiebler et al., 2004). Durch die Korrekturmöglichkeit könnten Fehler akzeptabler wirken. Eine weitere Erklärung dieses Befundes könnte die Verschiebung der motorischen Schwelle durch die Korrekturinstruktion sein (siehe unten).

In der EKP-Studie aus Kapitel 11 fanden wir außerdem eine zweite frontozentrale Negativierung, die zeitlich an die Korrekturantwort gebunden ist. Wir nennen sie daher *correction-related negativity (CoRN)*. Interessanterweise ist die CoRN auch in früher publizierten Daten sichtbar, allerdings wurde sie bisher nicht berichtet oder diskutiert. Diese EKP-Welle trat sowohl nach spontanen als auch nach intentionalen Korrekturen auf. Ihre Amplitude war bei intentionaler Korrektur erhöht. Allerdings ist die funktionelle Bedeutung der CoRN noch weitgehend unklar. Man kann annehmen, dass sie das Korrelat einer Reevaluation der Korrekturhandlung ist. Weitere Studien sind zur genauen Charakterisierung der Gemeinsamkeiten und Unterschiede der ERN, CRN und CoRN notwendig.

Bei Untersuchungen zur Sofortkorrektur fielen teilweise sehr geringe Korrekturzeiten (Zeitdauer von der fehlerhaften Reaktion bis zur Korrektur) von deutlich unter 100 ms auf. Selbst die durchschnittliche Korrekturzeit ist signifikant kürzer als die für das Anzeigen eines Fehlers durch Drücken einer Fehlersignaltaste benötigte Zeit (Rabbitt und Phillips, 1967; Rabbitt, 2002). Daher wurde wiederholt bezweifelt, ob schnelle Sofortkorrekturen aus der Fehlerdetektion resultieren. In Übereinstimmung mit dem Handlungskonfliktmodell wurde vorgeschlagen, dass es sich bei schnellen Fehlerkorrekturen eigentlich um eine verspätete korrekte Reaktion handelt (Rabbitt, 2002; Yeung et al., 2004). Wie bei einem Rennen werden demnach die inkorrekte und die korrekte Reaktion durch die Stimuli aktiviert und dicht nacheinander ausgeführt. Obwohl die Abfolge der Reaktionen (falsch →

richtig) wie ein sofort korrigierter Fehler erscheint, wäre die Fehlerverarbeitung dafür nicht notwendig. Bei der Fehlersignalisierung muss dagegen zunächst der Fehler detektiert werden, da das Drücken der Signaltaste nicht durch die Stimuli gebahnt ist. Kapitel 12 untersucht mittels EEG die Gemeinsamkeiten und Unterschiede der Sofortkorrektur mit der Fehlersignalisierung. In einem Innersubjekt-Design führten Versuchspersonen zwei Sitzungen derselben Flankierreizaufgabe durch. In einer Sitzung waren sie angehalten, jeden entdeckten Fehler sofort durch Geben der korrekten Antwort zu korrigieren. In der anderen Sitzung sollten sie Fehler durch Drücken der Signaltaste anzeigen. In der Fehlerkorrektursitzung waren die Reaktionszeiten kürzer und die Fehlerrate höher als in der Signalisierungssitzung. Die ERN-Amplitude war bei der Fehlerkorrektur niedriger als bei der Fehlersignalisierung. Dieser Amplitudenunterschied konnte nicht durch den Unterschied der Fehlerraten erklärt werden (es fand sich keine Korrelation zwischen Fehlerrate und ERN-Amplitude, und die Untersuchung einer Auswahl von Fehlerdurchgängen, denen in beiden Sitzungen vergleichbare Fehlerhäufigkeiten vorausgingen, bestätigte den Amplitudenunterschied zwischen den Sitzungen). Wie oben beschrieben, könnte die Instruktion zur Fehlerkorrektur die subjektive Fehlerbedeutung beeinflusst haben. Korrigierbare Fehler könnten weniger bedeutsam sein; die Probanden könnten mehr auf Geschwindigkeit als auf Genauigkeit geachtet haben. Allerdings fanden sich in der Nachbefragung keine Hinweise auf einen derartigen Unterschied in der subjektiven Fehlerbedeutung. Interessanterweise war den Probanden nicht bewusst, dass ihnen mehr Fehler in der Korrektursitzung unterlaufen waren. Die durch die Stimuli ausgelöste P300-Komponente unterschied sich nicht zwischen den Sitzungen, weshalb ein Unterschied der der Aufgabe gewidmeten Aufmerksamkeit unwahrscheinlich ist. Eine Alternativerklärung der Befunde wäre, dass durch die Instruktion zur sofortigen Fehlerkorrektur die motorische Schwelle gesenkt wurde. Eine derartige Schwellensenkung könnte Sofortkorrekturen erleichtern, da auch schwache oder sich spät entwickelnde korrekte Handlungstendenzen noch ausgeführt würden. Dagegen könnte ein Abwarten des Signals vom Handlungsüberwachungssystem mehr Zeit, möglicherweise auch mehr Ressourcen benötigen. Des Weiteren sagt die Handlungskonflikttheorie für eine Senkung der motorischen Schwelle die beobachteten Befunde voraus (Yeung et al., 2004). Entsprechend der Handlungskonflikttheorie wäre außerdem eine Modulation des lateralisierten Bereitschaftspotentials (*lateralized readiness potential, LRP*) zu erwarten. Die Daten bestätigten das vorhergesagte Muster: die LRPs zeigten schwächere Lateralisierungen in der Korrektursitzung, was für eine abgesenkte motorische Schwelle spricht. Insgesamt erscheint es also am wahrscheinlichsten, dass infolge der Korrekturinstruktion die motorische Reaktionsschwelle gesenkt wird, was einerseits auf ökonomischem Wege eine hohe Korrekturrate ermöglicht, andererseits Kosten in Form höherer Fehlerraten mit sich bringt. Diese Kosten bleiben aber offensichtlich unbemerkt. Aufgrund dieser Daten muss überdacht werden, ob die Instruktion zur Sofortkorrektur ein geeignetes Mittel zur Untersuchung der Fehlerverarbeitung auf der Verhaltensebene darstellt. Bisher wurde die Sofortkorrektur häufig in Patientenstudien untersucht (Gehring und Knight, 2000; Swick und Turken, 2002; Kapitel 8 [Ullsperger und von Cramon, 2006]); allerdings fand sich häufig eine Diskrepanz zwischen veränderter ERN und scheinbar intaktem Verhalten. Diese könnte sich daraus erklären, dass ein großer Anteil der Sofortkorrekturen auch ohne Fehlerdetektion ausgeführt werden kann, was die Sensitivität und Interpretierbarkeit dieses Maßes deutlich einschränkt. Es folgt also, dass zukünftige Studien zu pathologischen oder pharmakologisch induzierten Veränderung der

Handlungsüberwachung die Fehler-signalisierung als spezifischeres und sensitiveres Maß untersuchen sollten.

Kapitel 13 befasst sich mit längerfristigen Adaptationen, die durch die Handlungsüberwachung initiiert werden. Konkret geht es um Anpassungseffekte, die nach hohem Handlungskonflikt beobachtet werden. Handlungskonflikt zeigt sich häufig in so genannten Interferenzeffekten, die sich durch erhöhte Reaktionszeiten und Fehlerraten äußern. In Interferenzaufgaben wie dem Flankierreizparadigma wurde gezeigt, dass in Versuchsdurchgängen nach hoher Interferenz die Interferenzeffekte vermindert waren (Gratton et al., 1992). Nach der Handlungskonflikttheorie sendet das Handlungsüberwachungssystem bei starkem Konflikt ein Signal an andere Hirnareale (wahrscheinlich den LPFC und weiter an perzeptuelle Rindenfelder), wodurch die Verarbeitung des nachfolgenden Versuchsdurchgangs derart optimiert wird, dass der Handlungskonflikt reduziert wird. Somit sinken die Reaktionszeiten und Fehlerraten, obwohl die Reizeigenschaften potentiell eine gleich starke Interferenz hervorrufen könnten. Verhaltensexperimente und funktionelle Bildgebung unterstützten diese Theorie (Botvinick et al., 1999; Stürmer et al., 2002; Kerns et al., 2004). Allerdings wurde dieser Erklärungsansatz angezweifelt, und alternativ vorgeschlagen, dass die Effekte durch perzeptuelles *priming* aufgrund von Reizwiederholungen und nicht durch kognitive Kontrollmechanismen erklärt werden können (Mayr et al., 2003). Kapitel 13 greift diese Debatte auf und berichtet zwei Verhaltensexperimente. In Experiment 1 wird die Analyse der sequentiellen Interferenzmodulation auf Abfolgen von Durchgängen beschränkt, die keine Wiederholung identischer Reize enthielten. Experiment 2 wurde so aufgebaut, dass direkte Reizwiederholungen von vornherein ausgeschlossen waren. Beide Experimente zeigten einen deutlichen sequentiellen Adaptationseffekt. Somit konnten wir zeigen, dass perzeptuelles *priming* allein die Anpassungseffekte nicht erklären kann. Es bleibt jedoch zu klären, warum Mayr und Kollegen (2003) keine derartigen, über das *priming* hinausgehenden Effekte nachweisen konnten. Nach einem Vergleich der Experimentalparameter vermuten wir, dass zeitliche Faktoren wie Dauer der Reizdarbietung und der Zeitabstand zwischen den Versuchsdurchgängen eine entscheidende Rolle dabei spielen, wie stark *priming* und konfliktinduzierte Anpassung wirken.

Modulierende Einflüsse auf die Handlungsüberwachung

In mehreren Studien wurde gezeigt, dass die Amplitude der ERN durch affektive Faktoren moduliert werden kann (Gehring et al., 1993; Dikman und Allen, 2000; Luu et al., 2000; Allen et al., 2004). Diese Befunde bilden die Grundlage der Hypothese, dass der pFMC eine Rolle bei der affektiven Bewertung der Handlungsergebnisse und der autonomen Kontrolle spielt. Diese Hypothese wird durch bildgebende und klinische Studien gestützt (Critchley et al., 2000, 2003, 2005; Luu und Posner, 2003). Sie steht jedoch nicht im Widerspruch zu anderen, eher kognitiv orientierten Theorien zur Funktion des pFMC. In Übereinstimmung mit Yeung (2004) bin ich überzeugt, dass kognitive und affektive Theorien der Handlungsüberwachung komplementär und nicht gegensätzlich sind. Das spiegelt sich auch in der in Kapitel 6 formulierten Sicht auf die Rolle des pFMC wider. Die Anpassungen, die unter entscheidender Mitwirkung des pFMC signalisiert werden, betreffen somit motorische, kognitive, affektive und vegetative Funktionen.

Die Beeinflussung von Handlungsüberwachung und motivationalen Funktionen ist nicht unidirektional. Bei einem subjektiv weniger bedeutsamen Ziel haben auch Fehler eine geringere Bedeutung. Es ist anzunehmen, dass bei geringerer subjektiver

Fehlerbedeutung auch die Handlungsüberwachung weniger aktiv ist. Kapitel 14 und 15 berichten zwei Studien zur Manipulation der Fehlerbedeutung. Die Probanden führten eine Flankierreizaufgabe in zwei Sitzungen aus, wobei die Fehlerbedeutung durch die Instruktion variiert wurde. In einer Sitzung wurde die Reaktionsgeschwindigkeit als wichtigstes Ziel instruiert, in der anderen Sitzung sollten die Versuchspersonen besonders auf die Reaktionsgenauigkeit achten. Die Instruktion wurde jeweils durch einen unterschiedlich gewichteten finanziellen Anreiz verstärkt. Gleichzeitig wurden EEG- (Kapitel 14) bzw. fMRT- (Kapitel 15) -daten erhoben. Wie bereits zuvor gezeigt (Gehring et al., 1993; Falkenstein et al., 1995), war die ERN-Amplitude signifikant erhöht, wenn die Versuchspersonen auf die Genauigkeit (Richtigkeit) der Reaktion achteten. Unter dieser Bedingung war auch eine Reaktionszeitzunahme nach Fehlern zu beobachten, nicht jedoch in der Geschwindigkeitssitzung. Damit wurde bestätigt, dass Fehler in der Genauigkeitssitzung eine größere Bedeutung für die Versuchspersonen hatten. In Übereinstimmung mit diesen Befunden ergab die fMRT-Studie eine erhöhte fehlerbezogene RCZ Aktivität in der Genauigkeitssitzung als in der Geschwindigkeitssitzung. Entsprechend der Studie zur Fehlersignalisierung (Kapitel 12) könnte die Modulation der Gewichtung von Geschwindigkeit und Genauigkeit von den Versuchspersonen durch eine Verschiebung der motorischen Schwelle umgesetzt worden sein. Somit wäre hier ein indirekter Zusammenhang zwischen Fehlerbedeutung und Handlungsüberwachung zu konstatieren. In einer weiteren Studie fanden wir jedoch auch Hinweise auf einen direkten Zusammenhang zwischen ERN-Amplitude und subjektiver Fehlerbedeutung. Die Versuchspersonen wurden nach einer modifizierten Flankierreizaufgabe befragt, wie sehr sie sich über ihre Fehler „geärgert“ hatten. Die ERN-Amplitude korrelierte signifikant mit diesem introspektiven Maß der Fehlerbedeutung (Abb. V-01). Eine größere (also negativere) ERN war bei Versuchspersonen zu finden, die sich über Fehler stärker geärgert hatten (Hämmerer, 2004, Hämmerer und Ullsperger, in Vorbereitung).

Weitere Faktoren, die die Handlungsüberwachung beeinflussen, sind der aktuelle emotionale Zustand (Luu et al., 2000; Simon-Thomas und Knight, 2005), Persönlichkeitsmerkmale (Dikman und Allen, 2000; Allen et al., 2004; Pailing und Segalowitz, 2004), Ermüdung (Lorist et al., 2005) und Schlafentzug (Scheffers et al., 1999).

Das Handlungsüberwachungssystem agiert nicht isoliert im menschlichen Gehirn. Weitere komplexe Interaktionen mit anderen Hirnarealen und –funktionen sind also zu erwarten. Es ist somit eine wichtige Aufgabe für zukünftige Studien, diese Interaktionen zu entschlüsseln, und insbesondere ihre neurobiologische Grundlage zu erforschen.

Ausblick

Wie in der vorliegenden Arbeit dargestellt, bestehen bereits umfangreiche Kenntnisse über die Implementierung der Handlungsüberwachung im menschlichen Gehirn. Die Rolle des pFMC beim Signalisieren notwendiger Anpassungen ist gut charakterisiert, ebenso die messbaren Korrelate der pFMC-Aktivität. Das Wissen über pathologische Veränderungen der Handlungsüberwachung ist in den letzten Jahren sprunghaft angestiegen. Allerdings eröffnet sich eine große Anzahl neuer Fragen für die zukünftige Forschung. Ich möchte vier wichtige Hauptrichtungen aufzeigen, in die sich die Forschung der nächsten Jahre entwickeln sollte. Ein Hauptziel dabei ist, neurobiologisch plausible Modelle der Handlungsüberwachung und –steuerung zu entwickeln und zu testen.

Räumliche und zeitliche Dynamik der Handlungsüberwachung

Während es gesichert erscheint, dass pFMC, LPFC und Basalganglien während der Handlungsüberwachung miteinander interagieren, ist die zeitliche Abfolge dieser Interaktionen noch weitgehend unklar. Zum Beispiel könnte die LPFC-Aktivität mindestens zweimal während eines Versuchsdurchganges ansteigen. Zunächst wird angenommen, dass der LPFC am Halten und Bereitstellen der für die Prädiktion des Handlungsergebnisses notwendigen Kontextinformationen (insbesondere die Aufgabenrepräsentation) beteiligt ist. Außerdem wird der LPFC mit der Umsetzung der nach hohem Handlungskonflikt oder Fehlern notwendigen Anpassungen in Verbindung gebracht. Isoliert konnten die verwendeten Untersuchungsmethoden diesen zeitlichen Ablauf nicht charakterisieren. Das fMRT liefert zwar die notwendige räumliche Genauigkeit, jedoch keine hinreichende zeitliche Auflösung. Umgekehrt kann das EEG allein wenig Information zur funktionellen Anatomie liefern. Eine Kombination beider Methoden, wie in Kapitel 5 beschrieben, kann Vorteile aus beiden Methoden ziehen. Ein entscheidender Schritt nach vorn wäre die Untersuchung von Interaktionen innerhalb eines Versuchsdurchganges. Bisher wurden hauptsächlich Wirkungen in Abfolgen von Versuchsdurchgängen untersucht. So haben Kerns et al. (2004) und Garavan et al. (2002) gezeigt, dass die Aktivierungsstärke im LPFC durch die überwachungsspezifische Aktivierung im pFMC im vorangegangenen Durchgang beeinflusst wird. Des Weiteren wiesen Egner und Hirsch (2005) eine Modulation der Aktivität in perzeptuellen Arealen durch vorangegangenen Handlungskonflikt nach. Es bleibt jedoch zu klären, wie die Information über nötige Anpassungen vom pFMC zu den perzeptuellen Rindenfeldern gelangt. Hier können wiederum kombinierte Ansätze informativ sein. Für die Handlungsvorbereitung konnten wir mittels fMRI-getriebener Dipolmodellierung von EEG-Daten zeigen, dass die Aktivität im LPFC der im parietalen Kortex vorausgeht (Brass et al., 2005).

Eine weitere Aufgabe ist die Integrierung der Handlungsüberwachungstheorien mit Theorien zur Funktion des OFC. Neuere Studien haben Zusammenhänge zwischen diesen Systemen gezeigt (Kringelbach und Rolls, 2004; Ullsperger und von Cramon, 2004; Walton et al., 2004). Eine besondere Herausforderung ist die Untersuchung subkortikaler und kleiner Strukturen beim Menschen, z.B. der Basalganglien, des Thalamus und des Mittelhirns. Ableitungen von Tiefenelektroden bei Patienten mit Epilepsie oder tiefer Hirnstimulation können hierzu wichtige Erkenntnisse liefern.

Molekulare Grundlagen der Handlungsüberwachung

Neurobiologische Modelle der Handlungsüberwachung sollten zusätzlich zu anatomischen und zeitlichen Informationen auch Erkenntnisse über Neurotransmitter berücksichtigen. Insbesondere das Dopamin, aber auch andere Botenstoffe, wie Noradrenalin, Serotonin und Opiate scheinen entscheidend für die Handlungsüberwachung zu sein. Pharmakologische Experimente mit spezifischen Agonisten und Antagonisten sind für die Aufdeckung der Rolle der Neurotransmitter unerlässlich. Des Weiteren bedeutet die Untersuchung von genetischen Polymorphismen einen entscheidenden Schritt nach für die Erforschung kognitiver Funktionen (Goldberg und Weinberger, 2004). Insbesondere die Kombination von Genotypisierung und pharmakologischer Modulation kann die Dosis-Wirkungs-Beziehungen näher charakterisieren (Mattay et al., 2003). Auf dem Gebiet der Handlungsüberwachung sind diesbezüglich kaum Studien durchgeführt worden, so dass beispielsweise die *Reinforcement Learning* Theorie noch ihrer empirischen Überprüfung harret.

Direkt *in situ* kann die Wirkung der Neurotransmitter mittels Positronenemissionstomographie (PET) untersucht werden. Neue hochaffine Radioliganden ermöglichen nun auch die Messung des Dopaminspiegels in extrastriatalen Strukturen. Kürzlich erschienene Studien zur Anwendung von kinetischen Modellen für dynamische Untersuchungen (Pappata et al., 2002) und zur Modulation der Dopaminrezeptorbesetzung bei kognitiven Aufgaben (Aalto et al., 2005) lassen einen neuen Entwicklungsschub vorausahnen.

Interindividuelle Unterschiede und Entwicklung

Hinsichtlich der Handlungsüberwachung können deutliche interindividuelle Unterschiede angenommen werden. Diese Unterschiede müssen nicht nur charakterisiert sondern auch in einen funktionellen Kontext gestellt werden. Eine kürzlich veröffentlichte Theorie zu flexiblem Verhalten nimmt ein duales Modell der kognitiven Kontrolle bestehend aus proaktiver (Vorbereitung) und reaktiver (Kompensation) Kontrolle an (Braver et al., in press). In vielen Situationen kann das optimale Handlungsergebnis durch Vorbereitung gesichert werden. Dadurch werden das Risiko von Fehlern und die Notwendigkeit der Handlungsüberwachung minimiert. Plötzliche Veränderungen der Situation verhindern eine optimale Vorbereitung, so dass das Handlungsziel erst durch Kompensation von Fehlern und suboptimaler Ressourcenverteilung also erst durch Handlungsüberwachung erreicht werden kann. Die individuelle Gewichtung pro- und reaktiver Kontrolle scheint stark zu variieren. Einerseits gibt es sicher genetische Ursachen, andererseits scheint sich diese Gewichtung auch durch andere Faktoren, z.B. das Altern, zu verschieben. Die Entwicklung der Handlungsüberwachung und ihrer Korrelate über das gesamte Leben muss systematisch untersucht und in den Kontext der allgemeinen Steuerung flexiblen Verhaltens gestellt werden. Natürlich sind auch hierbei die molekularen und funktionell-anatomischen Grundlagen zu erforschen.

Diagnostik von Defiziten der Handlungsüberwachung

In Kapitel 9 dieser Arbeit findet sich ein Überblick über die meisten bisher veröffentlichten Patientenstudien zur Handlungsüberwachung. Viele dieser Studien waren notwendigerweise explorativ und trugen zum Verständnis der neurobiologischen Grundlagen der Handlungsüberwachung bei. Ein wichtiges Ziel für die zukünftige Forschung ist es, robuste und patientenfreundliche Untersuchungsprotokolle für die Untersuchung der Handlungsüberwachungsfunktionen bei einzelnen Patienten zu entwickeln. Es muss gezeigt werden, ob die ERN und einige Verhaltensmaße (z.B. die Fehlersignalisierung) geeignet sind, individuelle Therapieverläufe zu überwachen. Damit könnte bei vielen Patienten die Rehabilitation kognitiver Funktionen optimiert werden.

Diese und weitere Fragen werden die Forschungen zur Handlungsüberwachung und -steuerung in den kommenden Jahren beschäftigen. Die Integration mit anderen Forschungsfeldern, z.B. zur Belohnungsverarbeitung und zur Entscheidungsfindung, wird voranschreiten. Neue Hypothesen und Modelle werden entwickelt, getestet, verworfen und modifiziert werden. Wie im täglichen Leben werden Fehler und ihre Aufdeckung informativer sein als die Bestätigung etablierter Modelle. Die Falsifizierung von Hypothesen wird zu neuen Ideen inspirieren und unser Verständnis des flexiblen, zielgerichteten menschlichen Verhaltens vorantreiben.

Erklärung über die selbständige Anfertigung der Arbeit

Hiermit erkläre ich, dass ich die Habilitationsschrift selbständig angefertigt und keine anderen als die angegebenen Hilfsmittel verwendet habe. Wörtlich oder inhaltlich übernommene Stellen sind als solche gekennzeichnet.

Lebenslauf

Dr. med. Markus Ullsperger
geboren am 22. April 1970 in Berlin

Hochschulstudium

| | |
|------------|--|
| 1989–1996 | Studium der Humanmedizin |
| 1989–1993 | Medizinische Fakultät der Karlsuniversität, Pilsen, Tschechische Republik |
| 1993–1996 | Charité – Medizinische Fakultät der Humboldt-Universität zu Berlin |
| 1995–1996 | Praktisches Jahr in Berlin und am Ohio State University Medical Center, Columbus, Ohio, USA |
| 1996 | Abschluss des Studiums "mit Auszeichnung" |
| 1998–1999 | Promotionsstipendium der Gertrud-Reemtsma-Stiftung für Hirnforschung, Doktorand am Max-Planck-Institut für neuropsychologische Forschung, Leipzig, Betreuer: Prof. Dr. med. habil. D.Y. von Cramon |
| 17.10.2000 | Promotion zum Dr. med., Medizinische Fakultät, Universität Leipzig, Thema "The role of retrieval inhibition in directed forgetting – an event-related brain potential analysis." <i>summa cum laude</i> , Dr. Carl Zeise Preis 2000 |

Beruflicher Werdegang

| | |
|----------------|---|
| 1996–1998 | Arzt im Praktikum, Neurologische Abteilung, Klinik Bosse, Lutherstadt Wittenberg; Chefarzt PD Dr. med. Grünes |
| 1998 | Approbation als Arzt |
| seit Juli 1999 | wissenschaftlicher Mitarbeiter, Arbeitsbereich Kognitive Neurologie, Max-Planck-Institut für Kognitions- und Neurowissenschaften, Leipzig, Direktor: Prof. Dr. med. habil. D. Yves von Cramon; Arbeitsgruppe "Functional Neuroanatomy of the Frontal Lobes" |

Lehrerfahrungen

| | |
|-----------|---|
| seit 1999 | Dozent der Gesellschaft für Neuropsychologie (GNP) |
| seit 2000 | Vorlesungen zu Themen der Kognitiven Neurologie und Neurowissenschaften |
| seit 2004 | Kurse zur praxisorientierten Einführung in die Methoden der Kognitiven Neurologie |
| seit 2005 | Seminar Neuropsychologie |

- seit 2001 Betreuung von Medizin- und Psychologie-Doktoranden, Psychologie- und Biologie-Diplomanden sowie Praktikanten (Studenten der Psychologie und Neurowissenschaften)
- seit 2000 Kolloquien an deutschen und internationalen Universitäten, darunter Stanford, Berkeley, Yale, University College London

Herausgeberische und gutachterliche Tätigkeit

- seit 2005 Mitglied des *Board of Action Editors* bei *Brain and Cognition*

Ad Hoc Gutachter für:

| | |
|---|--|
| <i>Acta Psychologica</i> | <i>Journal of Psychiatric Research*</i> |
| <i>Behavioral Brain Research</i> | <i>Journal of Psychophysiology*</i> |
| <i>Biological Psychology*</i> | <i>NeuroImage*</i> |
| <i>Biological Psychiatry*</i> | <i>Neuropsychologia*</i> |
| <i>Brain and Cognition</i> | <i>Neuropsychology</i> |
| <i>Brain</i> | <i>Neuroscience*</i> |
| <i>Cerebral Cortex*</i> | <i>Neuroscience Letters*</i> |
| <i>Clinical Neurophysiology</i> | <i>Psychological Review</i> |
| <i>Cognitive Brain Research*</i> | <i>Psychonomic Bulletin & Review</i> |
| <i>European Journal of Neuroscience*</i> | <i>Psychophysiology*</i> |
| <i>Experimental Brain Research</i> | <i>Science*</i> |
| <i>Human Brain Mapping</i> | <i>The Journal of Neuroscience*</i> |
| <i>International Journal of Psychophysiology*</i> | <i>Visual Cognition</i> |
| * multiple Gutachten | |

Mitherausgeber des Sammelbandes:

M. Ullsperger & M. Falkenstein (eds.)
Errors, conflicts, and the Brain. Current Opinions on Performance Monitoring. Leipzig: MPI for Human Cognitive and Brain Sciences, 2004.

Mitherausgeber des *special issue* in Cognitive Brain Research

A. Kok, K. R. Ridderinkhof, M. Ullsperger (eds.)
Cognitive Control and Action (2006).

Gutachten für Organisationen:

Deutsche Forschungsgemeinschaft (DFG)
German-Israeli Foundation (GIF)
Gutachter und Prüfer (*external examiner*) am Trinity College, University of Dublin

Thesen zur Habilitationsschrift

Die funktionelle Neuroanatomie der Handlungsüberwachung: fMRT-, EKP-, und Patientenstudien

vorgelegt von Dr. Markus Ullsperger

Max-Planck-Institut für Kognitions- und Neurowissenschaften

1. Die ständige Handlungsüberwachung und daraus resultierende flexible kognitive und Verhaltensanpassungen sind eine unverzichtbare Voraussetzung für erfolgreiches zielgerichtetes Verhalten. In den letzten fünfzehn Jahren ist die Implementierung der Handlungsüberwachung im menschlichen Gehirn in den Fokus der kognitiven Neurowissenschaften gerückt. Dysfunktionen der Handlungsüberwachung können eine starke Beeinträchtigung der Aktivitäten des täglichen Lebens nach sich ziehen.
2. Die Handlungsüberwachung lässt sich nichtinvasiv mit Verhaltensmaßen, Elektroenzephalographie (EEG) und bildgebenden Verfahren, insbesondere der funktionellen Magnetresonanztomographie (fMRT) untersuchen. Besonders informativ ist die Untersuchung von Handlungsfehlern. Auf der Verhaltensebene lassen sich kompensatorische Handlungen und längerfristige Anpassungen beobachten. Im EEG finden sich fehlerspezifische ereigniskorrelierte Hirnpotentiale (EKPs). Besonders gut untersucht ist die *error-related negativity* (ERN), die innerhalb von 50 bis 100 ms nach einer fehlerhaften Reaktion an der Kopfoberfläche abgeleitet werden kann. Im fMRT findet sich bei Fehlern konsistent eine Aktivitätserhöhung im posterioren fronto-medianen Kortex (pFMC), speziell in der so genannten *rostral cingulate zone* (RCZ). Je nach Aufgabentyp zeigen weitere Hirnareale fehlerspezifische Aktivitätsanstiege.
3. Das Handlungsüberwachungssystem wird nicht nur bei Fehlern und schlechteren als den erwarteten Handlungsergebnissen aktiv, sondern auch in Situationen, wenn die Erreichung des Handlungszieles unsicher und wenig wahrscheinlich ist. Eine derartige Situation tritt beispielsweise bei Handlungskonflikten ein. Handlungskonflikt entsteht, wenn eine Aufgabe mehrere konkurrierende Handlungstendenzen gleichzeitig aktiviert.
4. Die in Kapitel 3 dargestellte Studie untersucht mittels fMRT und EEG, aufgezeichnet in getrennten Sitzungen, ob sich Unterschiede in der Aktivität des Handlungsüberwachungssystems zwischen der Fehlerverarbeitung und dem Entdecken von Handlungskonflikt finden. Die *Handlungskonflikttheorie* sagt voraus, dass bei beiden Situationen dieselbe Region des pFMC aktiv ist. Zwar zeigte die Studie sowohl bei Handlungskonflikt als auch bei Fehlern eine erhöhte Aktivität des pFMC an, aber es war eine unterschiedliche anatomische Gewichtung zu beobachten. Handlungskonflikt aktivierte stärker neokortikale Areale (mesiales Brodmann Areal [BA] 8 und prä-supplementär-motorisches Areal [prä-SMA]), während bei Fehlern die maximale Aktivität im Sulcus cinguli, speziell in der RCZ, zu finden war. Somit scheint es eine Gewichtung der Aktivität zu geben, je nachdem, ob die Handlung noch läuft oder bereits abgeschlossen ist. Die EKP-Daten legen eine Generierung der ERN in der RCZ nahe.

5. Situationen mit hoher Entscheidungsunsicherheit beinhalten, dass Fehler nur über den Vergleich der beobachteten mit den gewünschten Handlungseffekten erkannt werden können. Das Handlungsüberwachungssystem kann also erst nach externer Rückmeldung feststellen, ob ein Fehler unterlaufen ist. Kapitel 4 zeigt, dass die RCZ ebenfalls an dieser Fehlererkennung mittels externer Rückmeldung beteiligt ist. Dagegen erhöht die prä-SMA bereits bei Handlungsunsicherheit an sich ihre Aktivität. Die Aktivationsmuster im Nucleus Accumbens und im Habenularkomplex unterstützen die *Reinforcement Learning* Theorie, die eine Beteiligung des Belohnungssystems, insbesondere des dopaminergen Systems, an der Handlungsüberwachung annimmt.
6. ERN und fMRT-Signal in der RCZ spiegeln die gleichen oder sehr eng assoziierte neuronale Prozesse der Handlungsüberwachung wider. Eine Einzeldurchgangsanalyse simultan gemessener EEG- und fMRT-Daten ergab, dass die Amplitude der ERN mit dem fMRT-Signal in der RCZ korreliert. Je stärker die Negativität der ERN ausgeprägt ist, desto höher ist der Signalanstieg in der RCZ. Die Amplitude der ERN im Einzeldurchgang sagte außerdem die Reaktionszeit in Versuchsdurchgängen nach Fehlern voraus. Eine höhere ERN-Amplitude war mit Reaktionszeitverlängerung im nachfolgenden Durchgang assoziiert.
7. Basierend auf einer Metaanalyse bildgebender Studien und elektrophysiologischen Daten wird die Hypothese aufgestellt, dass der pFMC die Notwendigkeit von Anpassungen signalisiert, wenn das Handlungsergebnis einer Optimierung bedarf. Der pFMC ist immer dann aktiv, wenn das Handlungsergebnis und/oder der Zustand des Individuums schlechter ist als erwartet, und wenn die Erreichung des Handlungszieles unwahrscheinlich ist (hohe Fehlerwahrscheinlichkeit). Diese Situationen haben gemeinsam, dass sie eine Anpassung auf motorischer, kognitiver, motivationaler, und vegetativer Ebene erfordern.
8. Läsionen des lateralen frontalen Kortex oder der Basalganglien beeinträchtigen die Handlungsüberwachung. Das äußert sich vor allem in einer Reduktion bis Abwesenheit der ERN. Die ERN ist ein sensibler Marker für die funktionelle Integrität des Handlungsüberwachungssystems, der selbst bei wiederhergestelltem Verhalten Schädigungen anzeigen kann. Die Spezifität der ERN ist gezeigt, da andere Patientengruppen (z.B. mit bilateralen frontopolaren und mit temporalen Läsionen) keine Beeinträchtigung aufwiesen.
9. Handlungsüberwachung und ERN wurde bei verschiedenen neurologischen und psychiatrischen Patientengruppen untersucht. Die meisten Ergebnisse stehen im Einklang mit den derzeitigen Modellen der Handlungsüberwachung. Allerdings ist eine Standardisierung der Untersuchungen zu fordern, um eine bessere Vergleichbarkeit der Studien zu erzielen.
10. In geschwindigkeitsbetonten Reaktionszeitaufgaben treten in 20-40% der Fehler Spontankorrekturen durch rasches Drücken der korrekten Taste auf. Diese Korrekturrate lässt sich durch geeignete Instruktion auf nahezu 100% steigern. Dabei steigt vor allem die Anzahl langsamer Korrekturantworten an.
11. Die Sofortkorrektur von Fehlern involviert die Aktivität der medianen motorischen Areale. Die RCZ ist bei korrigierten Fehlern über das bei Fehlerverarbeitung beobachtete Maß hinaus aktiviert. Erhöhte Aktivierung zeigen auch Prä-SMA und SMA, sowie der sekundäre somatosensorische Kortex.

12. Schnelle intentionale, das heißt instruierte, Fehlerkorrekturen zeigen ein ähnliches EKP-Korrelat wie spontane Korrekturen. Die ERN hat eine geringere Latenz als bei langsamen intentionalen Korrekturen und bei unkorrigierten Fehlern. Dieses Muster stimmt mit den Vorhersagen der Handlungskonflikttheorie überein. Das Auftreten einer höheren ERN-Amplitude bei spontan als bei intentional korrigierten Fehlern ist durch einen Unterschied in der Fehlerbedeutung erklärbar. Die Instruktion, Fehler zu korrigieren, kann Fehler akzeptabler erscheinen lassen. Alternativ könnte auch eine Senkung der motorischen Schwelle als einfaches Mittel zur Erhöhung der Korrekturrate den Befund erklären (siehe These 14).
13. Die Sofortkorrektur ist mit einer weiteren EKP-Welle, der *correction-related negativity* (CoRN) assoziiert. Diese frontozentrale Negativierung folgt der Korrekturantwort innerhalb etwa 100 ms. Sie scheint eine weitere Evaluation der Korrektur innerhalb des prämotorischen Systems widerzuspiegeln.
14. Zur Untersuchung der Fehlerdetektion ist die Fehlersignalisierung gut geeignet. Dabei wird ein bemerkter Fehler mittels eines Tastendrucks sofortig angezeigt. Im Unterschied zur Sofortkorrektur ist für die Fehlersignalisierung eine vorherige Erkennung des Fehlers notwendig. Bei Sofortkorrekturen muss der Fehler nicht notwendigerweise erkannt werden. Es gibt mit der Handlungskonflikttheorie kompatible Erklärungsansätze, die besagen, dass schnelle Korrekturen eigentlich die verspätete Ausführung einer vorbereiteten korrekten Handlung sind. Wie bei einem Rennen treffen erst die fehlerhafte und die korrekte Handlung ein. Eine EEG-Studie, die Fehlersignalisierung und Sofortkorrektur vergleicht (Kapitel 12), legt nahe, dass die Intention Fehler sofort zu korrigieren in einer Senkung der motorischen Schwelle resultiert. Somit eignet sich die Fehlersignalisierung besser als Verhaltensmaß zur Untersuchung der Handlungsüberwachung, was in zukünftigen Patientenstudien berücksichtigt werden sollte.
15. Die Detektion von Handlungskonflikten kann zu Anpassungen führen. In Versuchsdurchgängen nach einem erhöhten Handlungskonflikt kommt es häufig zu einer Verminderung von Interferenzeffekten. Somit kann allein die erhöhte Wahrscheinlichkeit von Fehlern zu einer Verhaltensoroptimierung führen, selbst wenn keine Fehler aufgetreten sind.
16. Die Aktivität des Handlungsüberwachungssystem wird durch verschiedene Faktoren moduliert. Einerseits haben Persönlichkeitsmerkmale einen Einfluss auf die ERN. Andererseits können auch Motivation und Affekt die Handlungsüberwachung beeinflussen. Wie in den Kapiteln 14 und 15 gezeigt, steigen bei erhöhter subjektiver Bedeutsamkeit von Fehlern die ERN-Amplitude und die Aktivität in der RCZ an.
17. Die zukünftige Forschung sollte die Interaktionen der an Handlungsüberwachung und -steuerung beteiligten Hirnareale näher charakterisieren. Des Weiteren ist die Beteiligung der Neurotransmittersysteme, insbesondere des Dopamins, stärker in die Bildung und Testung der Theorien zur Handlungsüberwachung einzubeziehen. Hierfür sind pharmakologische Studien, Genotypisierung und Positronenemissionstomographie (PET) mit geeigneten Radioliganden geeignete Untersuchungsmethoden.

Danksagung

Die in dieser Schrift zusammengefassten Arbeiten wurden durch die Mithilfe und Unterstützung verschiedener Personen ermöglicht. Ich möchte allen Beteiligten herzlich danken.

Besonderer Dank gilt meinem Mentor *Professor D. Yves von Cramon*, der meine Forschung über die gesamte Zeit in vielerlei Hinsicht unterstützt und gefördert hat und immer noch fördert. Er säte mein Interesse an der Handlungsüberwachung und legte damit den Grundstein für diese Arbeit. Sein funktionell-anatomischem Wissen, die vielen intensiven Diskussionen und die Anregungen zum Querdenken waren von unschätzbarem Wert bei Entwicklung, Umsetzung und Interpretation der Studien. Gleichzeitig genoss ich immer genügend Freiheit, selbständig zu arbeiten sowie eigene Ideen zu entwickeln und umzusetzen.

Meinen Doktoranden, Diplomanden, studentischen Hilfskräften und Praktikanten möchte ich ebenfalls für die tatkräftige Unterstützung herzlich danken. Insbesondere die produktive Arbeit von *Katja Fiehler* spiegelt sich in einer Reihe von hier dargestellten Studien wider. Auch meine derzeitigen Doktoranden *Tilmann Klein* (der zuvor schon mein Praktikant und Diplomand war), *Sebastian Seifert* und *Joseph King* haben einen wichtigen Beitrag zu der vorliegenden Arbeit geleistet, selbst wenn die Studien ihrer Doktorarbeiten noch nicht enthalten sind. Meinen Diplomandinnen *Sandy Siegert*, *Dorothea Hämmerer* und *Antje Gentsch* sowie meinen Diplomanden *Friedemann Szymanowski* und *Cornelius Donat* gilt ebenfalls mein Dank. Viele von ihnen haben auch als studentische Hilfskräfte meine Forschungsarbeit deutlich erleichtert. So auch *Katrin Gille*, die meine Literatursammlung perfektioniert und viele Datenerhebungen mit betreut hat. Weiterhin möchte ich *Annette Clüver*, *Therese Lennert*, *Susanne Kamphausen*, *Corinna Klinge*, *Jacobine Torrilhon* und *Anne-Cecile Treese* für ihre Arbeit als Praktikantinnen danken.

Ohne den Austausch mit Kollegen innerhalb des Max-Planck-Institutes wäre sicher so manche Studie weniger erfolgreich verlaufen. Insbesondere den Mitgliedern der 'Exec'-Gruppe gilt mein Dank für fachlichen Austausch aber auch ein angenehmes, oft fröhliches Arbeitsklima. Besonders möchte ich *Kirsten G. Volz* für die vielen anregenden Diskussionen danken. Auch *Marcel Brass*, *Jöran Lepsien*, *André Szameitat*, *Ricarda I. Schubotz* und *Stefan Zysset* trugen maßgeblich zur Erweiterung meines Horizontes im Hinblick auf Experimentalpsychologie und Auswertemethoden bei. Besonders inspirierend war die Zusammenarbeit mit *Stefan Debener* bei der simultanen EEG- und fMRT-Studie. Ich möchte ihm auch danken, dass er mich in die Welt von EEGLAB einführte. Der *Lipsia-Gruppe* und *Maren Grigutsch* sei für die Unterstützung bei Fragen zur Datenanalyse gedankt. Und nicht zuletzt danke ich den vielen technischen Assistentinnen, die bei der Erhebung der Daten und der Einbestellung der Versuchspersonen eine unschätzbare Hilfe darstellten. *Bettina Jost* und *Sven Gutekunst* bin ich für die technische Unterstützung bei der Erstellung der Experimente dankbar.

Meine Lebensgefährtin *Elke Hoertlehner* ist eine starke motivationale Unterstützung für mich. Sie bestärkt mich, diesen Weg in der Forschung fortzusetzen. Nur gemeinsam mit ihr kann ich mich über erreichte Erfolge richtig freuen. Vielen Dank dafür! Ebenso möchte ich meinen Eltern, *Dr. Monika* und *Dr. Peter Ullsperger*, für die vielseitige Unterstützung danken. Die vielen Diskussionen mit meinem Vater und die gemeinsame Begeisterung für die kognitiven Neurowissenschaften haben meinen Weg bereichert und mich zu neuen Experimenten, Analysemethoden und alternativen Erklärungsansätzen inspiriert.