

Andreja Bubic: Violation of Expectations in Sequence Processing.
Leipzig: Max Planck Institute for Human Cognitive and Brain Sciences,
2006 (MPI Series in Human Cognitive and Brain Sciences; 114)

Impressum

Max Planck Institute for Human Cognitive and Brain Sciences, 2009



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Druck: Sächsisches Druck- und Verlagshaus Direct World, Dresden

ISBN 978 3-936816-88-3

**Violation of expectations in
sequence processing**

Von der Fakultät für Biowissenschaften, Pharmazie und Psychologie
der Universität Leipzig
genehmigte

D I S S E R T A T I O N

zur Erlangung des akademischen Grades
doctor rerum naturalium
Dr. rer. nar.

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Tag der Verteidigung: 1.10.2009

Acknowledgements

It is difficult to be short and concise in thanking everybody who has supported me during the last years. Even a much longer essay could still not express what I owe to them.

First of all, I would like to thank those who have most influenced and contributed to my scientific development during the last three years, my supervisor Ricarda I. Schubotz and Prof. D. Yves von Cramon. They have always been very generous in sharing knowledge, experience and ideas, as well as providing me with opportunities to explore all issues that I was interested in. I am very grateful to Ricarda for giving me a lot of freedom, trusting me and being always available for me. Although we spent almost half of my PhD time in different cities, I felt supported and welcome when approaching her with any issues which were relevant to me at any point in time. I could never express enough gratitude to Prof. von Cramon for occasionally making me think that “everything” can be done in science, and, in the same time, showing the importance of choosing and pursuing the right questions. I was very privileged to spend my PhD time working with Prof. von Cramon, a scientist of great knowledge, high standards and endless enthusiasm for neuroscience.

Additionally, I am very grateful to my other supervisor, Prof. Erich Schröger for his general support, valuable ideas and suggestions he made during the years. His questions usually came in the right moment and were very inspiring and motivating for my thinking and experimental work. I would also like to thank Thomas Jacobsen for his feedback and support. A significant contribution to the current thesis was made by Alexandra Bendixen who, for all practical purposes, “co-supervised” the EEG experiment conducted within this thesis. I am obviously very grateful for all the help in this particular study, but even more I would like to thank her for all other scientific encounters and discussions we have had over the years and the friendship which developed in the process. In addition, Wessel van Dam greatly helped with preparing and conducting *Experiment 3* which was for him interesting from an aspect which was not discussed within the thesis. The last (but definitely not the least) irreplaceable cornerstone of my PhD includes the

Graduiertenkolleg *Function of Attention in Cognition* which provided the means and a frame for many activities I benefited from in the last years. I have profited immensely from all schools, seminars, lectures, journal clubs and other formal and informal encounters which were organized for and by us. I was very happy to be part of the first GK cohort which was a pretty brilliant one, judging by both scientific and personal criteria. All of the students, especially Franzi, Philipp and Katja made the last years very enjoyable for me.

Additionally, I am very, very grateful to *Exec*, my research group in the Institute, all its members and friends. First of all, Anna George Abraham who was welcoming from the day I came to Leipzig and later turned out to be a great friend and a wonderful help in matters of science and beyond. An equally big thank you goes to Jane Neumann who was always more than supportive with regard to any scientific, practical or personal issue of relevance and who has, over the years, become an irreplaceable friend. A lot of practical help came in the form of Tilmann A. Klein, my long term roommate who contributed significantly to my early programming attempts, struggles with German (specially when brought together in the context of conducting experiments with German participants) and general adaptation to the standards of our daily environment. Even if this was not the case, I would still be grateful to him for his company, sense of humor and occasional wise insights. In addition, the spirit and friendship of Uta Wolfensteller, as well as her occasional scientific input, was always very much appreciated. I also have to thank Jöran Lepsien for his help in answering fMRI questions and helping me correct the motion artefacts in the fMRI data from *Experiment 4*. Maria, Franzi, Joe and Steffi with whom I shared the floor during the very last months of my PhD turned out to be more than just pleasant company. I also have to mention other people whose (sometimes even short-term) company, input or general presence I benefited from: Katja, Gabi, Derek, Flo, Stephanie, Konstanze, Markus, Marcel, Stefan and Kirsten.

Quite a few other people contributed to the experiments conducted within this thesis. Bettina Johst helped with randomization, Heike Schmidt-Duderstedt with the figures, Rosie Wallis, Tilmann and Uta with German translations, Christiane Hoffmann and Markus Ullsperger with the EEG part of the first study, while Ramona Menger and Sylvia Stasch organized participants in all behavioral experiments. A big “thank you” goes to Anna, Uta, Tilmann and Jane for proofreading (parts of) the thesis. fMRI studies would have been impossible to conduct without the MTAs, Mandy Jochemko, Simone Wipper, Annett Wiedemann, Anke Kummer and Domenica Wilfling, while Birgit Mittag and Susanne Starke pro-

vided general organizational support. In addition to those whose friendship and personal support I have already mentioned, I would like to thank a couple of other people who have consistently been there for me throughout the last years: Veseljka, Kate, Zvone, Gogich, Sandra, Mirta, Eva, Eugenia, Waltraud, and Tonca. Several others have also had a profound influence in different points in time: although I will not list them here, they all mean a lot to me and I am grateful for their support.

Of course, an immeasurable “thank you” goes to my family. Although my life decisions have managed to crush all boundaries initially acceptable and even imaginable to my parents, they have somehow learned to deal with this challenge with patience and grace. I am very happy that my brother has chosen a more reasonable lifestyle and has recently brought some balance into all of our lives with Dominik and Lara, his beautiful little babies. All in all, I have enjoyed the time spent in preparing and writing this thesis. I have learned a lot and changed more than I expected would be possible. This PhD has opened new questions, perspectives and possibilities for me and, at the end of it, I am very much looking forward to continuing the process which it initiated. I am also terribly curious to see what the future brings: es wird auf jeden Fall spannend.

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Preface

In order to efficiently function and successively adapt to the world we live in, it is crucially important to learn about our environment and capture its regularities occurring across different temporal and spatial scales. Once acquired, such knowledge is useful as it allows one not only to efficiently process current information and make decisions in the present time, but also to plan and prepare for future events. Although we often hear how important it is to live “here and now” and fully experience the current moment, it may be that our cognition and brain operate on somewhat different principles. As greatly emphasized in recent times, both cognitive and neural functioning are always oriented towards the future. Our brains constantly formulate expectations about incoming events and test such predictions by comparing them to the realized events (Bar, 2007; Butz, Sigaud, & Gerard, 2003; Schacter, Addis, & Buckner, 2007). Although important, situations in which expectations are correctly formulated have somewhat limited informative value, as they primarily confirm a successful learning process. On the other hand, cases in which events occurring in the environment do not match the postulated predictions can be extremely relevant, as they may indicate that the learning was not successful or that something changed in our surroundings. Registering and further processing events which deviate from predictions is important, because they signal a need to re-evaluate our knowledge or behavior and, if necessary, modify them to become better adapted to the surroundings. Such potential significance of deviant events for cognitive processing and behavior is reflected on the level of our nervous system which is highly sensitive to novel events, changes in the environment and other types of errors in prediction (Corbetta & Shulman, 2002; Friston, Kilner, & Harrison, 2006).

The present thesis investigates one particular class of events which violate our predictions, namely those presented in the context of purely perceptual sequences. Such sequences entail successively presented repetitive stimulus patterns which can be learned on very short temporal scales. Once acquired, knowl-

edge about the sequential structure can be used for predicting incoming stimuli. The experiments within the thesis explore the process of violating such expectations which occurs when wrongly ordered stimulus patterns, i.e., sequential deviants, are presented. Several experiments addressing the effects of introducing such events into different classes of visual sequences were conducted in order to investigate whether detecting sequential deviants represents a uniform process and, if not, to identify factors which influence its dynamics. Functional resonance magnetic imaging and electroencephalography were used for addressing these questions.

The present thesis is structured in the following fashion. Chapter 1 provides theoretical background into two themes relevant for this thesis: prediction, with a special emphasis on predictive perceptual sequencing occurring within the seconds-range, and the effects of violating such predictions. Chapter 2 shortly describes the main characteristics of methods used in the conducted experiments, namely functional magnetic resonance imaging (fMRI) and electroencephalography (EEG). In Chapters 3, 4, 5 and 6 experiments conducted within the present thesis are presented. *Experiment 1* which is described in Chapter 3 uses fMRI in order to explore the process of detecting sequential deviants presented in the context of short sequences defined by stimulus size and compare it to the process of detecting feature deviants, namely events which violate expectations related to physical properties of individual stimuli. Using different methodology, this question is further explored in *Experiment 2* which is presented in Chapter 4. In this EEG study, the temporal dynamics and the relevance of attentional involvement in detecting sequential and feature deviants are explored. *Experiment 3* is described in Chapter 5. This fMRI study explores the detection of sequential deviants introduced into more abstract sequences defined by several stimulus properties: spatial location, object properties or temporal duration (rhythm). *Experiment 4* is an fMRI study presented in Chapter 6. It explores the detection of sequential deviants in visual sequences defined by objects properties of different specificity. The last part of the dissertation presented in Chapter 7 summarizes and discusses the obtained findings and gives an outlook into future research directions.

1 Theoretical background

There are countless questions which can be asked about the principles of brain functioning and even more ways to address them. In many instances, such questions are restricted to the processing implemented within a certain brain region, cognitive function of interest or any other, well defined and partly artificially segregated topic. Even in these cases, where the topic of interest is focused and very specific, certain assumptions about the more general, fundamental nature of neural computations are made. Even if only in an implicit manner, these assumptions guide the choice of (neuro)scientific questions which get experimentally addressed and methods considered optimal for investigating them. Questioning these assumptions often triggers paradigmatic changes in the way main functions and mechanisms of brain processing are conceptualized. For example, understanding that not only the rate, but also the time of neuronal spiking (neural synchronization) could serve as a meaningful neural code drastically changed the understanding of the neural basis of perception, attention and many other cognitive functions (Gray, 1999; Singer, 1999). A whole new dimension of communication between different neurons and neuronal populations was discovered and recognized as relevant, which initiated the development of new disciplines and theories. New questions were asked, old ones reformulated and a profound shift in the way we understand the brain had been achieved.

Another recent example includes the increasing “popularity” and acceptance of embodied approaches to cognitive processing (Barsalou, 2008; Wilson, 2002). These approaches did not emerge suddenly, triggered by an incidental revolutionary finding. They represent a long tradition of thought, experimentation and theoretical postulations aimed at explaining the nature of cognition which was, for a long time, rather ignored in “mainstream” science. However, once rediscovered, these approaches started challenging and complementing decades of systematic research of rather isolated perceptual and motor functions by showing how these are inherently interconnected. The influences and constraints of our body charac-

teristics and experiences became recognized as very important determinants of all cognitive (including e.g., early sensory) functions. Understanding this did not alter or devalue previous research findings, but it provided a new perspective in interpreting some classical findings and placing them into a more comprehensive context.

A third example of a paradigmatic shift in understanding cognitive and brain processing refers to the concept of a predictive brain (Bar, 2007; Pezzulo, Hoffmann, & Falcone, 2007). In contrast to the classical view of the brain waiting for sensory input which it then processes and ultimately channels into action, the active account assumes that the brain is constantly predicting future events and comparing these predictions to outcomes, regardless of whether they occur in the sensory, cognitive or motor domain. In this view, the brain is seen as proactive, active and productive (Pezzulo, Butz, Castelfranchi, & Falcone, 2008). The current thesis is written in the spirit of this concept which underlies the framework within which the thesis is set, posed experimental questions, used experimental designs as well as interpretations of the obtained results. Therefore, before discussing the specific topics of interest within the current thesis, some of the basic assumptions and benefits of predictive processing will be presented and discussed.

1.1 The predictive brain

Anticipatory mechanisms and representations have long been recognized as relevant and beneficial for different aspects of information processing, e.g., perception, cognitive control and decision making, motor cognition and social interaction, as well as overt behavior in animals and humans. In a very broad sense, anticipatory behavior would refer to “a process, or behavior, that does not only depend on the past and present, but also on predictions, expectations, or beliefs about the future” (Butz, Sigaud, & Gerard, 2003, pg. 3). This type of behavior could be mediated through a wide range of anticipatory mechanisms, leading to several different effects following the realization of the anticipated event. Before discussing the mechanisms and beneficial effects of anticipatory processing in more detail, the relevant terminology and a short historical note will be introduced. This will illustrate how difficult it is to clearly define and delineate different terms used in the context of anticipatory processing, such as anticipation, prediction, expectation, prospection, pre-processing or preparation. While some of these terms can be at least partially differentiated and some overlap considerably, for most practical purposes they are often treated as synonyms. Within this

thesis, such somewhat liberal terminology will also be adopted, although a short attempt of differentiating between at least some aspects of these concepts will be made.

The relevance of anticipatory processing was recognized very early and investigated almost in parallel in the context of both perceptual and motor processing. The first proposal that expectations are intrinsically related to actions was formulated in the *ideomotor principle* which has recently been revisited by theories suggesting shared or common codes between perception and action (Hommel, Musseler, Aschersleben, & Prinz, 2001; James, 1890; Prinz, 1990). Additionally, in the 19th century, von Helmholtz formulated a predictive account of sensory systems suggesting that these evolved in order to infer the causes of changes in sensory inputs (c.f., Friston & Stephan, 2007). Another view of anticipatory processing came from psychologists including Wundt, Lange and James (LaBerge, 1995) who treated anticipation as a form of attention which was regarded beneficial because it allowed more pertinent reactions in the immediate situation. James even conceptualized sensory anticipation as “pre-perception” of an event, existence of which reduced the need for very elaborate processing following the actual event presentation (James, 1890). According to this view, anticipatory or preparatory attention refers to all changes in brain activity occurring prior to the expected event: these changes literally have a preparatory effect as they preactivate relevant structures expected to process the event once it actually occurs. Along these lines, LaBerge (1995) suggested that the manifestations of selective and preparatory attention are principally equivalent in a sense that they both reflect the same type of enhancement of information flow in particular brain regions. However, they differ in their temporal characteristics: preparatory attention can last for a longer time, while selective attention is usually of short duration. Furthermore, selective attention can occur before or after the occurrence of an event, irrespective of the existence of expectations prior to its appearance.

The term expectation, in contrast to anticipation or preparation which have been considered as attentional phenomena, reflects a memory component. Once formulated, the expectation represents an item which is stored in either working or long-term memory and includes the information related to all spatial and temporal characteristics of the expected event (LaBerge, 1995). Expectation does not necessarily have to include a preparation in terms of an already described preactivation, as it can also be coded in rather abstract or verbal forms. The term anticipation has often been used as a synonym to prediction, although they convey partially different meanings: while the term prediction refers to a representa-

tion of an event, anticipation describes the impact of predictions on current behavior (Butz et al., 2003). Even though not completely specified, the terms anticipation and prediction are still somewhat more clearly defined when compared to the widely used term prospection. Gilbert and Wilson (2007, pg. 1352) define prospection as an ability to “pre-experience the future by simulating it in our minds”, but without the detail and richness of genuine perceptions. Although prospection can include some aspects of both expectation and anticipation, it is not clearly specified into which extent and under which conditions. The term prospection could refer to different degrees of preactivation of relevant cortices at different moments in time prior to the expected event and could include representations of different specificity. Therefore, this term is more suited to refer to a more general orientation towards the future in a sense that stored information is constantly used to imagine, simulate and predict future events (Schacter, Addis, & Buckner, 2007).

In the present thesis the terms anticipation, prediction and expectations will be used in a somewhat interchangeable manner. Although their meaning is not exactly the same, both anticipatory / preparatory and predictive / expectancy effects could be expected within the experimental context which will later be presented in more detail. The term prediction will be somewhat favoured when discussing the expectations of individual stimuli within the experimental trials.

1.1.1 Benefits of predictive processing

As previously mentioned, the benefits of preparation have been recognized very early both in the motor and the perceptual domain. Behavioral experiments conducted by Wundt showed that attention and expectations related to the upcoming stimulus can shorten perception time, while Lange demonstrated beneficial behavioral effects triggered by the anticipation of a response (c.f., LaBerge, 1995). Ever since the 19th century, more and more advantages of predictive or anticipatory processing in contrast to pure reactive computations have been postulated. Llinas (2002) argued that predictions save both time and energy and can be identified at different levels of processing, starting from the single neuron level and generalizing across brain systems. They are principally beneficial as they save processing resources and allow the perceiver to prepare the appropriate reactions. When predictions about incoming events are made based on the stored knowledge, the repertoire of potential actions responding to the event can be predetermined prior to the occurrence of the event, leading to their faster subsequent recognition and interpretation (Bar, 2007; Nobre, 2001). Given that the information

relevant for planning and executing the appropriate reaction are available sooner, measurable benefits of anticipatory processing include increase in accuracy, speed or maintenance of information processing (LaBerge, 1995). Kveraga, Boshyan and Bar (2007) emphasize that, although important, facilitatory effects on behavior and efficiency of perception represent only one beneficial aspect of anticipatory processing. In addition, expectations allow us to construct a coherent and stable representation of the environment which is usually not easy, given the available, often impoverished (noisy and delayed) information. Moreover, they may guide top-down deployment of attention, improve information seeking as well as subsequent decision making (Butz & Pezzulo, 2008).

On a more general functional and behavioral level, the ideomotor principle suggested that anticipated sensory consequences of one's actions have a crucial role in triggering and guiding behavior (Hommel et al., 2001). In line with this idea, numerous studies of causal perception, action observation and action execution have shown that representations of events or actions include the anticipated effects of those events as well as intentions behind the actions (Kerzel, Bekkering, Wohlschlaeger, & Prinz, 2000; Schütz-Bosbach & Prinz, 2007). Therefore, Schütz-Bosbach and Prinz (2007) suggested that both perception and production of events rely on prospective codes which incorporate information about future aspects of those events. Kunde, Elsner and Kiesel (2007) similarly argued that anticipation constitutes a necessary prerequisite for action because any action or response needs to start with a response-related anticipation. Therefore, in addition to providing knowledge about ourselves and the environment, anticipation lies in the foundations of goal-directed behavior (Pezzulo, 2008).

Pertaining primarily to the level of neural processing, Friston (2005) proposed an even more fundamental role of expectations: not only is the common code of brain functioning a predictive one, but our predictions act as a form of self-fulfilling prophecy. He suggested that predictions drive our perception, cognition and behavior in a sense that we do not only passively match expected to incoming events and objectively evaluate the accuracy of our expectations, but actively try to fulfil those predictions by preferentially sampling corresponding features in the environment. Given that non-fulfilled expectations are surprising and costly, Friston and Stephan (2007) argued that our brain always tries to minimize the resulting surprise by minimizing its free energy. The terms "surprise" and "free energy" will be additionally discussed later in this chapter.

Based on all of these findings, it is possible to say that prediction represents a fundamental principle of brain functioning which is "at the core of cognition"

(Pezzulo, Hoffmann, & Falcone, 2007, pg. 68). Illustrating its importance, many cognitive functions have been considered as anticipatory in nature, e.g., motor control (Wolpert & Flanagan, 2001), visual processing and attention (Enns & Lleras, 2008; Mehta & Schaal, 2002; Riesenhuber & Poggio, 1999), imagery, action learning and understanding (Jeannerod, 2001; Kilner, Friston, & Frith, 2007), language (DeLong, Urbach, & Kutas, 2005), music (Keller & Koch, 2008), emotional processing (Herwig et al., 2007; Nitschke, Sarinopoulos, Mackiewicz, Schaefer, & Davidson, 2006; Ueda et al., 2003), general planning ability, working memory or other executive functions (Baker et al., 1996; Fuster, 2001; Partiot, Grafman, Sadato, Wachs, & Hallett, 1995; Wylie, Javitt, & Foxe, 2006), and the theory of mind (Frith & Frith, 2006). On an even more general level, simulation theories of cognition emphasize the role of internal simulations or emulations in practically all cognitive processes, arguing that many of them can be reduced to a covert simulation based on an internal model (Grush, 2004; Hesslow, 2002). Furthermore, predictive processing is not in any way restricted to human processing, but extends to different types and classes of behavior in animals, e.g., dogs, snakes or insects (Rainer, Rao, & Miller, 1999; Roitblat & Scopatz, 1983; Webb, 2004). In conclusion, anticipations and expectations do not just represent isolated phenomena, but one of the main unitary principles of cognition. In this view, the mind can be conceived of as an anticipatory device (Pezzulo et al., 2007) which incorporates numerous predictive neural mechanisms.

1.1.2 Prerequisites of prediction

Events can be predictable if they occur in a non-random fashion, allowing the brain to extract the regularity of the relationship between different events. This knowledge can later be used for predicting the occurrences of some events following the presentation of those customarily preceding them. Predictions are therefore based on learning and identifying associations between events, especially temporal dependencies between them (Bar, Aminoff, Mason, & Fenske, 2007; Butz et al., 2003). These can be made by accumulating information related to statistical regularities or analogies between events as well as applying some inference rules (Pezzulo, Butz, & Castelfranchi, 2008). Prediction of incoming events is context-dependent and may be influenced by different factors, e.g., strength of the relationship between different events, amount or type of previous exposure to these events. While, in some situations, predictions can be rather unspecific and restricted to a selected set of event features, e.g., modality or loca-

tion of an incoming stimulus, in others it is possible to formulate more specific predictions pertaining to the exact stimulus identity. In addition, it is possible to distinguish between implicit anticipations which are expressed through habits (behavior) from explicit ones which include representations of the predicted future states (Pezzulo, 2008). Prediction can take place on different temporal scales. First, expectations can be formulated based on the knowledge gained through long-term experience (Bar, 2007) or learning triggered by short-term exposure to non-random patterns (Schubotz, 2007). Second, it is possible to predict events which are expected to occur in different moments in the future, e.g., those expected to occur within seconds-range in contrast to those which may occur in distant future. Long-term predictions are usually used “offline” in a sense that they are not necessarily coupled with any immediately relevant or running process, in contrast to short-term predictions which are more likely to be used “online”. In the latter case predictions can be useful for regulating behavior, as for example in motor control where they are coupled to the current sensorimotor cycle (Pezzulo, Butz, & Castelfranchi, 2008). The temporal scale of predictions may influence their accuracy, such that short-term predictions are typically more accurate. In contrast, long-term prospection reflecting a general tendency of “looking into the future” may include quite unspecific long-term predictions. It is also possible to generate multiple predictions pertaining to different points in space and time, as done in hierarchical predictive systems (Pezzulo, Butz, & Castelfranchi, 2008). Expectations of such different type and specificity could be mediated through different mechanisms or, alternatively, could be based on the same types of processes partially implemented within different brain regions.

Regardless of the level of specificity or modality within which it is expressed, an expectation can only be formulated if a certain degree of regularity is recognized within a context, allowing the establishment of associations between individual events. Later, one of these events can serve as a cue based on which expectations about the associated event can be formulated. Such regular relation between events which affords predictability of sensory input can be defined as a rule. Different types of rules can allow predictability within the perceptual domain. On a very low level, a constant repetition of a stimulus or a specific feature represents a concrete or first-order rule. This type of rule is often used in the classical oddball paradigm in which repetition of a stimulus triggers an expectation about the continuation of its appearance in the future (Sutton, Braren, Zubin, & John, 1965). Such an expectation is formulated based on the holistic context defined by numerous stimuli: although individual events need to be related to one another in order to establish such constancy, each of them equally contributes to

the expectation and can be flexibly placed within any part of the trial. In this case, it is the “global context” of the trial which determines whether the rule is followed or not. More complex rules, however, require the extraction of relations between features of specific, mutually non-interchangeable, stimuli which are usually successively presented. Thus, a judgment regarding the conformity of the rule within each trial can be made only if the exact relation between specific stimuli is taken into account. Depending on how many features have to be considered for making this judgment, it is possible to differentiate between second-order rules which take into account just one feature, and higher-order (contingency) rules which require joint consideration of several features (Näätänen, Tervaniemi, Sussman, Paavilainen, & Winkler, 2001; Shanks, 2007). One special instance in which such knowledge of temporally structured events, characterized by a certain degree of regularity, can be used for predicting upcoming events is serial order processing (serial pattern learning, sequence processing or sequencing). Since sequence processing is of particular interest for the present thesis, it will be discussed in more detail after discussing some general mechanisms underlying predictive processing.

1.1.3 Mechanisms of prediction

Broadly stated, anticipatory and predictive processing is directed towards the future and, at the same time, highly dependent and grounded in the information from the past. This bridging over different temporal points and taking advantage of the past in order to improve behavior in the future is suggested to be the core capacity which makes our cognitive brain so efficient (Kveraga et al., 2007). Given that prediction is inherent to many different levels and types of processes, it is not easy to identify common neural mechanisms supporting such processing across all contexts. Therefore, it is not surprising that prediction is associated with a wide range of neural phenomena within different brain networks, for example changes of neuronal threshold in sensory cortices (Gomez, Vaquero, & Vazquez-Marrufo, 2004), long-range phase synchronization (Gross et al., 2006), changes in connectivity across brain regions (O'Reilly, Mesulam, & Nobre, 2008) or existence of preparatory-set cells in the prefrontal or parietal cortex (Quintana & Fuster, 1992).

In order to understand the mechanisms of predictive processing in perception, it is necessary to address the neural mechanisms within the sensory cortices which could promote more efficient processing of expected stimuli and to understand how these mechanisms could be initiated. Regarding the latter topic, it has

often been suggested that the benefits of processing predictable stimuli are mediated through changes in alertness and attention. More specifically, it was suggested that anticipatory attention involves a change in internal alertness (Brunia, 1999), which enables subsequent specific preparatory changes in the brain structures expected to be involved in processing the incoming input. In this sense, anticipation could be regarded as a bias signal (Rees & Frith, 1998) which improves the computational efficiency of a specific area.

Before exploring how this bias could, in computational terms, be imposed onto the relevant sensory areas, processing within these regions occurring in expectation of a stimulus will be shortly described. Within the relevant sensory cortices such expectancy periods are marked by, for example, a reduction of activation threshold or an increased signal-to-noise ratio associated with processing relevant stimuli (Brunia, 1999; Gomez et al., 2004). These effects are reflected in the suppression of specific brain rhythms in the sensory cortices (event-related desynchronization (ERD)) as measured using electroencephalography (EEG) (Bastiaansen & Brunia, 2001) or elicitation of particular event-related anticipatory components, e.g., contingent negative variation, stimulus preceding negativity or the readiness potential (Brunia, 1999; Praamstra, Kourtis, Kwok, & Oostenveld, 2006). Evidence for the claim that improved speed and accuracy of processing expected stimuli reflects preparatory effects in the relevant sensory cortices potentially coupled with the inhibitory effects in other sensory modalities (Brunia, 1999) comes from studies which show comparable patterns of activity in stimulus perception and anticipation. For example, findings showing that actual somatosensory stimulation and anticipation of such stimulation engage the same network (Carlsson, Petrovic, Skare, Petersson, & Ingvar, 2000) suggest a top-down modulated preactivation of sensory cortex in anticipation of a stimulus.

In addition to the expression of preparatory effects in relevant sensory cortices, it is important to understand how these effects are initiated and controlled. In an attempt to answer this question, Gomez et al. (2004) suggested that frontomedial cortical areas, namely the supplementary motor area (SMA) and anterior cingulate cortex (ACC) represent the best candidate areas responsible for initiating the process of preparing for action and perception. In this view, these areas might be able to recruit specific sensory and motor cortices needed for subsequent sensory and motor processing of the imperative stimulus. On the other hand, dorsolateral prefrontal cortex (dlPFC) was hypothesized to be implicated in sustaining activation of the sensory and motor cortices (Gomez et al., 2004). Similarly, Brunia (1999) suggested a crucial role of prefrontal cortex in organizing anticipatory

behavior by activating cortico-cortical and thalamo-cortical loops to sensory and motor areas after the preparatory set had been formulated. Once formed, the preparatory set could be communicated through changes in brain's oscillatory activity, enabling subsequent effects of anticipation. These top-down facilitatory effects have been associated with an increase in phase synchronization of neuronal populations in executive areas triggering an increase in effective synaptic gain of neurons in target sensory population (Engel, Fries, & Singer, 2001). Along these lines, Liang and Wang (2003) have shown that synchronized activity in prefrontal cortex during anticipation of a visual stimulus predicts characteristics of early visual processing and behavioral response. Therefore, they argued that synchronized oscillations in prefrontal cortex represent a plausible candidate for sustaining visual anticipation, proposing that this anticipatory control develops as a consequence of accumulating prior experience.

In addition to these accounts, an important role in mediating predictions has been posited for specific systems and regions of the brain, primarily the motor system and especially the cerebellum (Jeannerod, 2001; Schubotz, 2007; Wolpert, Doya, & Kawato, 2003; Wolpert & Flanagan, 2001) as well as the basal ganglia which are involved in timing, reinforcement learning and mediating reward processing (Graybiel, 2005; Schultz & Dickinson, 2000). Functionally, it has been proposed that the prediction of future states of the body or the environment arises from mimicking their respective dynamics through the use of internal models (Grush, 2004; Johnson-Laird, 1983; Wolpert, Ghahramani, & Jordan, 1995). The role of internal models is especially important in simulative theories of cognition which principally emphasize the role of the motor system in such simulations (Pezzulo, Butz, Castelfranchi et al., 2008). In an even wider sense, the whole brain can be conceptualized as a predictive device. In this view, the hierarchical structure of the sensory brain allows the higher functional areas to constantly formulate predictions and communicate them to lower-level areas within which they are compared to the incoming stimuli (Friston, 2005; Rao & Ballard, 1999). Once the actual stimulation fails to match predictions, these areas send prediction error signals back to those which are higher in the cortical hierarchy. Thus, mistakes in prediction have a large informative value. In contrast, pure confirmation of correctly formulated expectations does not need to be explicitly represented or communicated to higher cortical areas because those areas had already processed all relevant stimulus features prior to its occurrence.

In conclusion, anticipatory / predictive processing potentially reflects one of the core, fundamental principles of brain functioning which justifies the phrase

“the predictive brain”. Even if this statement is too strong, the relevance of prediction in cognitive and neural processing can still not be overestimated. Many cognitive functions benefit from predictive processing mediated through a very wide selection of mechanisms expressed in numerous cortical and subcortical levels. Prediction allows us to direct our behavior towards the future, while remaining well grounded and guided by the information pertaining to the present and the past. In the next chapter, one type of a context which is especially beneficial for the expression of such processing will be discussed.

1.2 Sequence processing

Serial pattern learning (serial order processing, sequence processing or sequencing) refers to the processing of temporally structured events characterized by a certain degree of regularity which is indexed by, e.g., repetitive presentation of an event pattern of any level of complexity, or predictability of their end state. In a very broad sense, examples of sequencing can be seen in many different contexts: motor, perceptual, conceptual and behavioral. We constantly sequence information in everyday life, e.g., in speech, while playing an instrument, executing a series of movements aimed at accomplishing a certain goal, etc. These sequences differ in their complexity, and in this respect it is possible to distinguish between simple linear (flat) and non-linear (hierarchical) sequences (Bapi, Pammi, Miyapuram, & Ahmed, 2005). Learning a simple linear structure can be based on learning local dependencies between neighbouring items (finite state grammar) and can be contrasted with hierarchical structures which include long-distance dependencies (phrase structure grammar). While linear sequences may be learned by all primates or phylogenetically lower animals, there have been reports showing that only humans are able to learn more complicated, hierarchically organized sequences (Conway & Christiansen, 2001; Fitch & Hauser, 2004). This phylogenetic trend is somewhat mirrored on the neural level, in a sense that simpler forms of local dependencies are processed within the phylogenetically older ventral premotor cortex in contrast to long-distance dependencies which are supported by the younger opercular portion of the inferior frontal gyrus (IFG), namely Brodmann’s area (BA) 44 of the Broca’s area (Opitz & Friederici, 2007). Although more difficult, learning of hierarchical sequences can be aided by grouping repeating elements of the pattern or chunking the sequence (Koch & Hoffmann, 2000; Sakai, Kitaguchi, & Hikosaka, 2003; Schlaghecken, Sturmer, & Eimer, 2000) which may also be useful for learning flat linear sequences. In addition to chunking, sequences can be learned by extracting statistical sequence

properties or observing the serial order and forming associations between respective elements in fixed sequences (Conway & Christiansen, 2001). In addition, learning a sequence requires acquiring knowledge about the events (stimuli) constituting the sequential pattern as well as the timing of their presentation, namely ordinal and interval sequence properties. Although it is possible to learn each one of these elements separately, sequence learning is facilitated when these two sequence features are correlated, reflecting the integration of ordinal and interval information (Shin & Ivry, 2002). The existence of independent interval and ordinal representations of a sequence is suggested by findings which show that learning a spatiotemporal sequence may facilitate learning its interval and ordinal structure alone, while learning solely interval and ordinal structures leads to facilitated learning of a sequence where both of these elements are coupled (Ullen, Bengtsson, Ehrsson, & Forssberg, 2005).

As mentioned before, sequencing can be studied in many different domains, most prominent of which is the motor one which will later be described in more detail. Outside this domain, sequencing has been studied by exploring, e.g., artificial grammar learning (Cleeremans & McClelland, 1991; Reber, 1967), serial order processing in music (Pfordresher, Palmer, & Jungers, 2007), learning task sequences without referring to the responses (Heuer, Schmidtke, & Kleinsorge, 2001; Koch, 2001) or performing sequences of cognitive tasks (Jubault, Ody, & Koehlin, 2007). All of these situations are comparable and share not only functional commonalities, but also partly overlapping neural substrate (Fiebach & Schubotz, 2006; Janata & Grafton, 2003; Jubault et al., 2007; Lelekov-Boissard & Dominey, 2002; Opitz & Friederici, 2007). This overlap may indirectly suggest shared cognitive processes across different domains which has also been proposed in a more direct fashion. For example, the shared syntactic resources hypothesis, as suggested by Patel (2003), states that processing language and music shares common syntactic processes which allow the organization and integration of elementary sensory units into coherent percepts. Since other contexts outside language and music may also share similar requirements, this theory could potentially be generalized to a wider range of phenomena. However, one has to be somewhat careful when generalizing across domains. For example, the identified overlap of brain regions across different fields does not necessarily imply the involvement of the same neuronal populations in these processes. As indicated by Marcus et al. (2003), within the Broca's region of the inferior frontal gyrus (IFG) syntactic processes may be preferentially related to its more anterior portion, namely pars triangularis (BA 45), in contrast to music syntax and imitation of actions which engage a more posterior region, pars opercularis (BA 44). All of

these domains, including sequential organisation of behavior, such as planning and executing a sequence of movements (Tanji & Shima, 1994) or tasks (Koechlin, Corrado, Pietrini, & Grafman, 2000), as well as sequential processing in both the motor (Ashe, Lungu, Basford, & Lu, 2006; Keele, Ivry, Mayr, Hazeltine, & Heuer, 2003) and perceptual domain (Hoen, Pachot-Clouard, Segebarth, & Dominey, 2006; Remillard, 2003) can greatly benefit from predictive processing. However, the level of anticipation afforded in them may depend on the type of acquired sequence knowledge. Specifically, Willingham et al. (1989) showed that the explicit knowledge is, in comparison to the implicit one, more likely to allow anticipation of the upcoming stimulus before it appears.

1.2.1 Sequencing in the motor domain

Sequencing in the motor domain has most often been investigated using the Serial reaction time task (SRTT) (Nissen & Bullemer, 1987) in which the participants are presented with a sequence of stimuli to which they have to respond by pressing corresponding keys (each stimulus is associated with one key) as fast and accurate as possible. In comparison to being presented with trains of random stimuli, participants tend to improve their reactions towards stimuli which are organized by a certain rule (Keele, Ivry, Mayr, Hazeltine, & Heuer, 2003). Alternatively, motor sequential learning can also be assessed by other paradigms, e.g., in explicit sequencing of finger taps (Mitra, Bhalerao, Summers, & Williams, 2005), discrete sequence production, immediate sequence production or other (c.f., Rhodes, Bullock, Verwey, Averbeck, & Page, 2004). There are several questions of crucial interest which pertain to the domain of motor sequencing. These include the role of attention in sequence learning, the nature of representations which are formed, and the type of information which is learned in this context. In relation to the first issue, Curran and Keele (1993) explored the role of attention in learning visuospatial sequences in SRTT and showed that attentional and nonattentional learning operate independently one from another. The resulting sequential knowledge is suggested to be represented in qualitatively different ways, allowing these two types of processes to operate in parallel without being mutually dependent. A highly related issue concerns the level of awareness of the acquired sequence knowledge, namely the distinction between implicit and explicit sequence learning. These are usually differentiated based on the involvement of intentional control in learning (Jacoby, 1991; Reingold & Merikle, 1988) which can be manipulated by, e.g., orienting participants' attention towards or away from the sequence or changing the pace of stimulus presentation. Generally,

when investigating this issue in the context of sequencing, the role of conscious knowledge as well as the development of suitable methods for dissociating explicit and implicit knowledge have mostly been pursued (Clegg, DiGirolamo, & Keele, 1998). Eimer et al. (1996) suggested a dissociation between these processes based on the identified differentiation between electrophysiological correlates of implicit and explicit sequence learning. Similarly, in a recent functional magnetic resonance imaging (fMRI) study Destrebecqz et al. (2005) used a Process dissociation procedure (Jacoby, 1991) in an attempt to dissociate the systems supporting implicit and explicit sequencing. Their findings showed a crucial role of basal ganglia in implicit and anterior cingulate / medial prefrontal cortex in explicit sequencing. Interestingly, their results also indicated that the two systems interact and that the implicit system can be controlled by conscious knowledge when the learning is explicit. Further evidence for only a partial segregation of explicit and implicit sequence learning comes from a study by Aizenstein et al. (2004) who showed the existence of overlapping parallel processes and argued for potentially complementing roles of the two systems. However, this does not imply that both types of learning always need to be present because some contexts may favor only one of these. For example, while deterministic sequences may require or evoke more explicit learning, probabilistic sequences can be learned implicitly (Remillard, 2003). Furthermore, implicit learning may be more appropriate for learning surface sequence structure in contrast to explicit learning which is needed for abstract sequential structure (Dominey, 1998).

In addition to the brain regions mentioned in the previous paragraph, primary motor and premotor cortex (especially (pre)supplementary motor area), have also been implicated in motor sequence learning (Ashe, Lungu, Basford, & Lu, 2006). Additional contributions from the parietal cortex have been interpreted as providing basic visuospatial representations of the sequence or controlling the attentional selection of spatial locations (Curran, 1995). The involvement of prefrontal cortex in sequence learning seems to be restricted to explicit motor learning where it is suggested to have one or more functional roles. Specifically, prefrontal cortex could support working memory and explicit rehearsal of sequences or even have a more abstract role in temporal coding (Ashe *et al.*, 2006). On the other hand, contributions of parietal and prefrontal regions may depend not only on the nature of learning, but also on the stage of sequence processing: while prefrontal areas may be important in acquiring, parietal areas are suggested to be more relevant for retrieving visuomotor sequences (Sakai et al., 1998). In addition, the involvement of the cerebellum and the hippocampus in learning or consolidating motor or other types of sequences (Albouy et al., 2008; Haslinger et al., 2002;

Van Opstal, Verguts, Orban, & Fias, 2008) has also been shown. In an attempt to systematically conceptualize the engagement of different brain regions in motor sequencing, Keele et al. (2003) have recently suggested the existence of two distinct systems for sequence learning. The dorsal system, comprising parietal and medial premotor areas, is described as subserving implicit learning in contrast to the ventral system comprising temporal and lateral prefrontal areas which can support either implicit or explicit learning. The former system is principally unidimensional such that processing of sequences within a specific dimension is fully encapsulated. In contrast, the ventral system is considered to be multidimensional as it allows formation of associations across dimensions and modalities. In addition to the mentioned cortical areas, subcortical regions, primarily the basal ganglia are also suggested to contribute to sequence processing within both systems. Although a valuable conceptualization, this model does not easily accommodate all of the reported findings in this research field and may be rather difficult to apply in all relevant contexts.

The question related to the types of representations being formed during sequence learning has also received a lot of attention. In principle, it could be possible that either stimulus-stimulus, stimulus-response or response-response associations are formed. Evidence for all accounts has been presented. For example, it has been shown that simple sequences can be learned by pure observation, arguing for the existence of stimulus-based representations (Howard, Mutter, & Howard, 1992; Kinder, Rolfs, & Kliegl, 2008). However, this type of learning may not always be possible. In a study using position sequences, Remillard (2003) showed successful perceptual learning only for first-order sequences which was dependent on attentional orienting towards the stimulus. In contrast to this view, Willingham et al. (1989) argued for the importance of stimulus-response representations, basing their arguments on findings showing that stimulus sequences are learned only when they are behaviorally relevant and can be mapped into responses. Finally, based on results showing that only response deviants trigger delayed reactions, Nattkemper and Prinz (1997) argued for the crucial role of response structure in sequence learning. Additional strong evidence for response anticipation in motor sequencing comes from a study from Eimer et al. (1996) who showed anticipatory deflections in the lateralized readiness potential of the EEG, suggesting pre-activation of anticipated responses. Similarly, Ziessler and Nattkemper (2001) argued that sequence learning depends primarily on response-effect learning which may be mediated by learning the relations between a stimulus and response. This learning can be quite complex, as it has been shown that it does not have to be restricted to the level of specific effectors

(Keele, Jennings, Jones, Caulton, & Cohen, 1995) and that the transfer of learning across effectors is possible (Cohen, Ivry, & Keele, 1990). These results suggest that learning can occur at a more abstract level of motor planning. In addition, this does not rule out the possibility that verbal and manual responses share a common abstract representation (Clegg *et al.*, 1998). Although there are still open questions in relation to response learning, the great majority of findings clearly confirms its importance. On the other side, controversies in relation to pure perceptual learning are still not settled. Rüsseler and Rösler (2000) have recently suggested that the task context may be important in determining which representations are formed in sequencing. More specifically, their results indicate that implicit learning includes accumulating knowledge related to response dependencies in contrast to explicit learning in which both stimulus and response properties are learned. Furthermore, when investigating the concurrent perceptual and motor learning, Mayr (1996) showed that the two types of learning can be considered as independent and can occur in parallel, leading to multi-sequence benefits (Shin & Ivry, 2002). These results indicated that, although responding to a perceptual sequence may be beneficial in enhancing learning of the perceptual sequential pattern, it is not necessary for such learning to occur.

The experiments within the present thesis will explore the effects of sequential violations / deviants or prediction errors occurring within purely perceptual sequences. Before giving a short overview of effects which accompany the presentation of such deviants, it is important to present some experimental findings related to this form of perceptual sequencing and the framework which was developed based on these findings. This framework suggests that regular perceptual events are represented in the form of internal models which were first described within the motor domain. In order to fully understand the framework, it may be useful to shortly discuss the importance of predictive processing within the motor domain and the usefulness of internal models in capturing some of these processes. Therefore, the internal model account which has proven to be very useful and fruitful in explaining many aspects of motor processing will be described and later extended to a more general context within the sensorimotor forward model framework.

1.2.2 Internal models in motor processing

Many aspects of motor behavior, e.g., motor control, motor learning, state estimation or coordination between motor effectors, are difficult to understand if conceptualized as a serial sequence of processing steps starting with sensory input

and ending with the expressed motor behavior. Efficient implementation of motor behavior requires a complex system which is able to account for several non-trivial problems inherent to the motor domain: delay of sensory information following a movement, constant noise present in the body and the environment, non-linear and non-stationary relationships between the motor commands and their sensory outcomes as well as the complexity of possible movements and combinations of movements available for reaching a certain goal. The internal model approach efficiently deals with those challenges: it goes beyond explaining the release of motor commands acting on the musculoskeletal system and introduces another level of computations which essentially entail internal simulations of different aspects of sensorimotor processing (Wolpert et al., 2003). This mimicking of natural processes is accomplished through the development of internal models whose outputs can subsequently be used by the “overt” sensorimotor loop for ameliorating the efficiency of the expressed behavior. More specifically, internal models are useful because they allow estimation of the current and the prediction of the future state of the system (Miall & Wolpert, 1996), estimation of more general context variables as well as the cancelation of sensory consequences of executed movements (Wolpert & Flanagan, 2001).

There are three main types of internal models: forward models of the motor dynamics, forward models of the external environment and inverse models (Miall & Wolpert, 1996). Inverse models represent a crucial feature of an efficient controller as they allow the selection of an appropriate motor command given the desired outcome state or the action goal (Miall & Wolpert, 1996). In contrast, forward models capture the forward, causal relationship between events, e.g., movements and their outcomes within the motor domain, allowing one to predict the consequences of one’s own actions (Davidson & Wolpert, 2005). Such prediction can not be accomplished by making abstract guesses about movement outcomes based on the chosen motor command. Since the same motor command can, in different contexts, result in different outcomes, accurate predictions can only be derived through combinations of different types of information originating from different sources. More specifically, in order to correctly estimate the expected movement outcomes, information regarding the state of the system and more general, slower-changing context of the movement need to be combined with the information about the released motor command (Wolpert et al., 2003). For this purpose the system needs to develop a dynamic and adaptable model capable of combining all available information and allowing updates in case of inaccurate predictions. Forward models which provide the simulation of the sensorimotor system and the environment represent one class of such dynamic solu-

tions. In computational terms, these simulations are triggered by the release of an efference copy of the motor command which acts on the sensorimotor system simultaneously with the original command, allowing movement execution (Wolpert et al., 2003). Their output includes predictions regarding the most probable outcomes of the executed actions, i.e., corollary discharge, whose correctness can be evaluated through a comparison with the actual sensory input available after the movement (Figure 1.1).

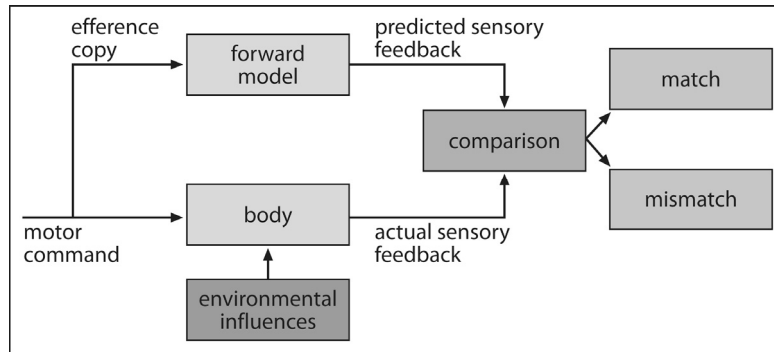


Figure 1.1: Prediction in motor control. Based on the efference copy of the motor command, a forward model is formulated and used for predicting the consequences of one's own actions. These predictions are compared with the incoming sensory input which can result either in a match when those predictions are realized, or a mismatch when the incoming input differs from the formulated expectations.

Except for its use for evaluating the correctness of model predictions and model updating, comparison between expected and realized stimulation is crucial for discriminating different types of incoming sensory input, namely information provided by the environment, i.e., exafferences, and those stemming from self-induced actions, i.e., reafferences (Miall & Wolpert, 1996). The sensory input resulting from self-produced stimulation is attenuated in comparison to external input (Blakemore, Frith, & Wolpert, 2001) which can not be explained as a general decrease in processing following any type of predictable stimulation (Blakemore, Rees, & Frith, 1998). Importantly, Bays et al. (2006) have showed strong evidence in favor of a predictive and not postdictive mechanism underlying sensory attenuation. Furthermore, the described attenuated processing allows one to discriminate and selectively process external and self-produced stimulation which is not only relevant for humans. On the contrary, these mechanisms are widespread across species: e.g., crickets inhibit the processing of incoming sensory information following their movements which initiate very loud and poten-

tially damaging noise, while bats explore their environment based on the comparisons of self-generated high-frequency sounds with the returning echoes (Crapse & Sommer, 2008).

Given the strong explanatory power of internal models, a lot of research conducted in the last two decades has tried to answer numerous questions regarding the dynamics of their acquisition, nature of representations and principles of neural implementation. Recently, a modular architecture consisting of multiple pairs of forward and inverse models jointly acquired during motor learning was proposed (Wolpert, Ghahramani, & Flanagan, 2001). According to this model, pairs of inverse and forward models are closely coupled within a particular module during the learning phase which allows them to be jointly selected within the appropriate context during execution. The selection of the appropriate module is based on relevant sensory signals used for recognizing the context and predictions from the forward model. Given the enormous spectra of motor behaviors and contexts in which any of them can be exhibited, such an architecture is suggested to represent a more efficient solution in comparison to a centralized system with one controller (Wolpert & Kawato, 1998). Evidence for this conclusion comes from studies showing that multiple pairs of forward and inverse models allow learning of multiple tasks which can later be coordinated in a flexible manner, switching between different tasks as well as generalizing learning to novel objects (Haruno, Wolpert, & Kawato, 2001).

Although the described, rather elaborated version of the internal model account is rather recent, the basic principles behind it, including the ideas about the predictive use of efference copies of motor commands and the process of matching predictions to actual stimulation are not novel. On the contrary, the importance of predictive processing within the motor system was recognized already in the 17th century by Decartes, inspiring von Helmholtz to later suggest that expectations about the effects of actions can influence subsequent perception (Bays & Wolpert, 2008). Following this, during the 1950s von Holst, Mittelstaedt and Sperry experimentally demonstrated the importance of motor-to-sensory feedback in controlling behavior (Wolpert & Flanagan, 2001). More than half a century later, the internal model framework can be considered a prevailing, widely accepted view within the motor domain which is, in recent years, being applied in explaining different phenomena well beyond this domain. For example, it was recognized rather early that internal models also include forward models outside the motor domain, namely those which mimic the behavior of the environment using the collected sensory knowledge, such as, e.g., a trajectory of an already

moving object for predicting its future behavior (Miall & Wolpert, 1996; Wolpert & Kawato, 1998). In addition, it has been suggested that the forward model account could provide a general framework for understanding prediction in a wide range or high level cognitive functions including action observation, imitation, mental practice, social interaction and the theory of mind (Wolpert et al., 2003). In a similar fashion, Schubotz and von Cramon (2003) have shown that the computations and mechanisms underlying a certain class of perceptual phenomena could be considered equivalent to those within the motor domain. Initially motivated by findings implicating the motor system in some forms of perceptual processing, they suggested a joint framework unifying the perceptual and motor domain which is grounded on the predictive nature of the motor system.

1.2.3 Sensorimotor forward model account: a unifying framework bridging motor and perceptual domains

In the previous chapter, it was argued that the nature of processing implemented within the motor domain is strongly predictive, as it is based on simulations and attempts to formulate predictions regarding future states of the system following executed movements. Given that the organization of the motor system which implements these computations supports such prospection within the seconds range, it is possible to assume that its architecture could be used in other, non-motor contexts which require or benefit from similar forms of predictive processing. For example, presented with a predictable, dynamic perceptual event or structured pattern of perceptual stimuli, the input reaching the observer at any given moment is not only useful for describing the current state of the environment, but also informative about the most probable future events.

The hypothesis that these types of events are processed in a predictive manner, which would best be instantiated through computations performed by the motor system, motivated a number of studies addressing the neural correlates of active perceptual sequencing. In order to investigate this process in an experimental setting with minimum motor requirement, Schubotz (1999) developed the serial prediction task (SPT) as a perceptual counterpart to the serial reaction time task (SRTT) (Nissen & Bullemer, 1987). Since the SPT requires participants to extract and predict repetitive sensory patterns within sequentially presented stimuli, this task is also referred to as the sequencing task. In contrast to the SRTT in which participants need to produce a motor sequence in response to the presented stimuli, motor requirements in the SPT are minimized. The only required response is delayed until the end of the trial when the participant needs to state whether a

violation of the learned pattern occurred in the last part of the trial or not. Within each experimental study the SPT is presented together with a control, non-sequencing task which is matched for attentional and perceptual demands. In addition, response and motor demands are also matched between the two tasks as they both require two-alternative forced choices from the participants. Most important features of SPT include the fact that this task provides continuous stimulation requiring anticipatory processing which is, as will later be further discussed, dependent on sensorimotor transformations provided by the premotor cortex. A schematic example of the task is provided in Figure 1.2.

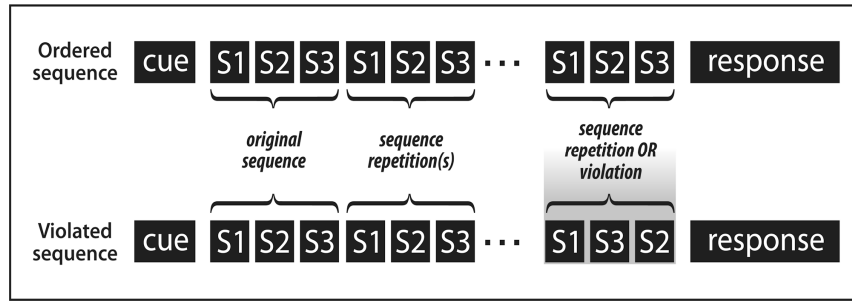


Figure 1.2: A schematic example of the serial prediction task. A pattern of n -stimuli (here 3) is presented and repeated to participants who attend to the pattern, learn it and use the acquired knowledge for predicting incoming stimuli during its subsequent repetitions. Occasionally a sequential violation (deviant) (two stimuli exchange their position; here 2nd and 3rd stimulus of the original pattern) is presented in the second part of the trial. Task of the participants is to indicate, at the end of the trial, if such a violation occurred or not. Since this task is presented together with a control task, a cue preceding each trial is given to indicate the upcoming task to the participants.

The results of numerous studies which have employed the described paradigm show that perceptual prediction required within the sequencing context relies on the premotor and connected parietal areas (Schubotz & von Cramon, 2002a, 2002b, 2002c, 2003) whose contribution is identified when the participants are actively involved in extracting and predicting the sequential structure (Schubotz & von Cramon, 2002b). While task instructions have the crucial role of engaging the premotor cortex in processing such events, stimulus properties as well as the modality of presented events only modulate this networks' involvement in the task (Schubotz & von Cramon, 2001a, 2001b; Schubotz, von Cramon, & Lohmann, 2003). These findings were interpreted taking into account basic characteristics of premotor-parietal networks as identified in the context of traditional motor processing and common processing requirements shared across the motor

and perceptual sequencing domains, namely their strong dependence on predictive processing. Based on this hypothesis, a framework was developed (Schubotz, 2007; Schubotz & von Cramon, 2003) which tries to explain the nature of predictive properties of the motor system by drawing parallels between the perceptual and the motor domain. According to this view, prediction underlies both motor and perceptual processes in which the brain can emulate expected events, regardless of whether these constitute sensory consequences of one's own actions in motor planning or expected sensory stimuli in perceptual prediction. As previously described, this emulation would be enabled by the creation of internal, sensorimotor forward models which act as models of the body and the environment and can be exploited for making predictions about future states of the modelled space. The accuracy of those predictions can be evaluated by comparing the incoming bottom-up information with predictions (top-down mediated expectations) following stimulus presentation, allowing more efficient processing of the successfully predicted stimuli. Therefore, sequence processing in perception can be taken to reflect a number of different sub-processes including the acquisition and storage of the sequence representation (i.e., forward model in computational terms) as well as the comparison of expected and presented stimuli.

A key role within the described framework is given to the lateral premotor cortex (PMC) which is hypothesized to play a major role in perceptual prediction through its role in establishing sensorimotor forward models. PMC extends over the anterior portion of the precentral and the posterior part of the superior frontal gyrus on both the lateral and medial surfaces of the brain (Chouinard & Paus, 2006). The medial premotor cortex can be subdivided into the anterior pre-supplementary motor area (pre-SMA) which is separated from the posteriorly located supplementary motor area (SMA) at the level of the anterior commissure (Picard & Strick, 2001). Although the separation of the lateral premotor cortex into clearly segregated areas has been firmly established in the monkeys' frontal cortex (Matelli, Luppino, & Rizzolatti, 1985), exact delineation of homologues in humans has proven to be a somewhat more challenging task. Nevertheless, a principal separation between the superior (dorsal) and inferior (ventral) as well as anterior (rostral) and posterior (caudal) premotor regions can still be made (c.f., Schubotz, 2004). These subregions differ in their basic connectivity patterns, such that the anterior regions are more connected with prefrontal areas in contrast to more posterior ones which are interconnected with the parietal and primary motor cortex (Barbas & Pandya, 1987; Matelli, Camarda, Glickstein, & Rizzolatti, 1986; Schubotz, 2004). A similar separation has also been established for dorsal and ventral premotor cortex which are also mutually sparsely intercon-

nected (Chouinard & Paus, 2006; Schubotz, 2004), suggesting a functional separation between these areas. As mentioned, premotor areas are reciprocally connected with parietal areas, forming multiple premotor-parietal loops with different functional significance. For example, it has been suggested that the dorsal PMC and the connecting posterior intraparietal area (IPSp) form a “reaching” circuit while ventral PM and the connecting anterior intraparietal area (AIP) represent a “grasping” circuit (Luppino, Murata, Govoni, & Matelli, 1999). In line with such diverse connectivity and functional patterns is the existence of multiple maps in premotor cortex which have been shown not just in the context of action execution, but also in action imagery and a wide range of perceptual-attentional tasks (c.f., Schubotz, 2004).

As the premotor-parietal network is known to subserve sensorimotor integration, it is plausible to suggest a similar division of functions within different components of this network in both motor planning and perceptual prediction (Schubotz, 2007). The interplay between these areas could be compared to the dynamics of parietal-premotor interactions which have been suggested to reflect the maintenance of associations between appropriate affordances and chosen movements in primate control of grasping (Fagg & Arbib, 1998) and visuomotor transformations in human grasping circuits (Jeannerod, Arbib, Rizzolatti, & Sakata, 1995). Following this view, it was suggested that the engagement of lateral premotor cortex in perceptual sequencing reflects establishment of a forward model upon which predictions about the upcoming stimuli in subsequent repetitions are formed and later compared to the presented stimuli. This process is enabled by constant interchange of information between lateral premotor and parietal areas which have access to the perceptual input provided by visual cortical areas (Ungerleider & Haxby, 1994). Providing a description of all available stimulus features, the parietal cortex supports a complex stimulus representation which can be selected by the lateral premotor cortex for specific purposes determined by the current goal or task setting (Fagg & Arbib, 1998; Fogassi et al., 2005; Rizzolatti, Fogassi, & Gallese, 1997; Rizzolatti & Luppino, 2001). Therefore, depending on whether perceptual prediction relies on full stimulus specification or only a single task-relevant stimulus dimension (e.g., size or position), lateral premotor areas can extract the appropriate information and exert a top-down modulatory influence on the parietal areas which become specifically tuned to that type of information. In addition to these “basic” findings, the conducted studies have also shown that prediction based on different stimulus features elicits the pattern of activation within which maximal loci of activation or relative contributions of different parts of this basic network partly differ (Schubotz, Kalinich, &

von Cramon, 2008; Schubotz & von Cramon, 2001a; Wolfensteller, Schubotz, & von Cramon, 2007). Specifically, predictions which are based on spatial properties of the presented stimuli activate the dorsal PMC in contrast to those based on object properties which activate the superior portion of the ventral PMC or those based on pitch and rhythm properties which engage the inferiormost portion of the ventral PMC. Comparing this pattern with the somatotopical maps outside the primary motor cortex (Fink, Frackowiak, Pietrzyk, & Passingham, 1997) and the mapping found in the action domain, where the dorsal PMC is engaged in preparing reaching movements, the superior portion of the ventral PMC in grasping and manipulation, and the inferiormost part of the PMC in vocal and auditory control (c.f., Schubotz, 2004), Schubotz and von Cramon (2003) suggested that perception of dynamic events is also referenced to the body. More specifically, it was suggested that premotor regions specialized for body parts which are habitually used to produce or be guided by a certain event are activated during perceptual prediction. Thus, spatial properties are associated with motor effectors for reaching (arm, eyes, neck), object properties with effectors related to grasping and manipulation (hand) and rhythm / pitch with articulatory effectors (mouth, tongue, larynx). Importantly, although such mapping can be used for action purposes, it is not action-specific and can not be attributed to, e.g., action imagery. The proposed stimulus-based mapping is modulated by the modality of stimulus presentation (Schubotz & von Cramon, 2001a; Schubotz et al., 2003). This modulation can not be explained by the influence of simple stimulus property in a sense that some stimulus features are more inherent to a certain modality (e.g., object properties to the visual or rhythm to the auditory modality). Instead, it has been suggested that the lateral premotor activation reflects the summed activity of both property- and modality- tuned neurons (Schubotz et al., 2008).

The described simulation of perceptual sequences needs to be coordinated and constantly updated by triggering the next entry in the forward model. This function can be subserved by supplementary motor area (SMA) and pre-supplementary motor area (pre-SMA) and implemented by different types of neuronal activity supporting serial processing which have been identified in the monkey medial premotor cortex (Shima & Tanji, 2000). In addition to the premotor and parietal areas, the cerebellum could also be relevant for the establishment of sensorimotor forward models. In the motor domain, the cerebellum has often been suggested as the most likely candidate for supporting fast, accurate and rigid pairs of forward and inverse models and providing short-cut circuits or look-up tables for mappings initially developed by cerebral unsupervised learning modules (Kawato et al., 2003; Miall & Wolpert, 1996). Given its computational speci-

ficity (Doya, 2000; Ramnani, 2006), the cerebellum could implement the suggested one-to-one or many-to-one types of mappings which are required in the motor domain. However, since this would not be optimal for perception, it was suggested that modelling the dynamics of the external environment should rely more on the premotor cortex (Schubotz, 2007) which can accommodate less specific types of mappings supported by slower but highly flexible learning mechanisms characteristic for cortical processing (Doya, 2000). This does not necessarily mean that all parts of the network are still not important for both domains: strong projections between the premotor, parietal and cerebellar areas (Dum & Strick, 2002; Kelly & Strick, 2003) can support different degrees of their interaction. The role of the cerebellum in perception could then be related to processing inverse models (Ito, 2008; Wolpert & Kawato, 1998), long-term storage of internal models (Wolpert et al., 2001), or supporting overlearned sequences by providing short-cut models for mappings developed in the premotor cortex (Ito, 1993).

Overall, according to the sensorimotor framework, prediction of both internal and external events can be supported through equivalent or highly comparable computations implemented within the motor system. Given some inherent differences between the quality of information about the body and the environment and the exact goals of prediction within the two domains, it is not automatically assumed that the models supporting perceptual and motor processing should be completely identical. While motor processing requires development of highly accurate and precise models (Blakemore, Rees et al., 1998; Miall, 2003), in perception such high precision may be either unnecessary since accurate prediction can often rely only on relational properties of external events, or even disadvantageous because it occurs in a noisy system and environment. Therefore, the specificity of perceptual forward models could be context-dependent or, alternatively, these models could always be less specific in comparison to their motor counterparts. Consequently, these differences should be reflected in neural implementation of internal models within the two domains. In addition to a stronger cortical contribution to perceptual models in contrast to the more pronounced cerebellar involvement in the motor domain, more detailed predictions in the motor domain could be reflected in a higher degree of attenuation of sensory information following self-generated actions (Blakemore, Wolpert, & Frith, 1998) in contrast to the weaker suppression of predictable external sensory stimuli.

In conclusion, although the forward models as implemented within the perceptual and the motor domain share many common computational features, they can also be differentiated on different levels. This suggestion is in line with the hy-

per-MOSAIC model (Wolpert et al., 2003) which proposes an architecture containing several levels of forward models differing in the level of specificity and function. If this is the case, sensorimotor forward models in perception are placed on a somewhat higher level and would partly differ in their underlying neural implementation when compared to those within the motor domain. Their final output would include predictions regarding the future state of the environment within a short temporal scale which could subsequently be compared to the incoming sensory information. Computationally, the expectations formulized within the internal models could be optimized in a Bayesian fashion, through weighted combinations of priors and sensory likelihoods (Kording & Wolpert, 2006).

1.3 Violating predictions

The predictive nature of the (pre)motor system in perceptual sequencing does not only resonate well with findings indicating the involvement of this system in motor functions, but is also in line with more far-reaching accounts of general brain processing as described under the Bayesian framework. Within this framework the brain is seen as a “Bayesian inference machine”, constantly building models of the environment and the body, allowing the brain to predict their respective future states and test these predictions against the incoming input (Friston & Stephan, 2007; Knill & Pouget, 2004). It was previously mentioned that the expectations based on internal models channel our perception and guide our actions in a way that we constantly sample our environment in an attempt to fulfil our predictions (Friston, Kilner, & Harrison, 2006). As already described, once formed, these predictions can be communicated from higher cortical areas to those in the lower levels of hierarchy through backward / feedback connections leading to their pre-activation during the period of stimulus expectancy.

Although the process of formulating expectations is interesting in its own right, it is also quite fascinating to consider what happens once the external event occurs, especially in cases where it does not meet the initial predictions. In the previous paragraphs it was suggested that expected stimuli are processed in a more efficient manner than the unexpected ones, as indicated by more accurate and faster reactions to these events. In contrast, unexpected events are more “costly” as they draw attentional resources towards themselves which are needed in order to check the behavioral relevance of such events (Corbetta, Kincade, & Shulman, 2002). If relevant, their occurrence might signal a need for more elaborate processing and potential behavioral adaptation. Therefore, the cost which is

related to processing these events may in the end turn to be beneficial, as it may lead to an adaptive reaction to the changing environment. In addition, prediction errors or the discrepancies between expected and realized events have been postulated as one of the main forces behind predictive learning. Specifically, associative learning theories (Rescorla & Wagner, 1972; Schultz, Dayan, & Montague, 1997) postulate that the size of the prediction error affects the rate of forming associations between events. Importantly, a predictive model can be learned by taking into account such differences between the predicted and actual outcomes. These discrepancies can be translated into changes in synaptic weights using specific learning computational rules, leading to changes in the model and subsequent more accurate predictions (Wolpert et al., 2003).

In a much more general frame, Friston (2005) suggested that “matches”, namely instances in which sensory data confirms the postulated predictions, produce non-salient, suppressed responses which are non-informative and do not require further processing. On the contrary, it is primarily the “mismatches” (prediction errors) that elicit responses which get communicated to the next level in the hierarchy using feedforward connections. Therefore, it is the accuracy of initial predictions which determines which information is processed on a higher level and what is suppressed at an earlier processing stage. Similarly, Rao and Ballard (1999) suggested that anticipatory signals are communicated from the higher cortical areas in a top-down manner in order for the expectations to be compared with the incoming stimuli in the lower-level areas. Only wrongly formulated expectations evoke signals which are then transmitted back to higher cortical areas in a bottom-up fashion. Thus, it is plausible to suggest that errors in prediction represent a surprising result for the brain and the information related to this surprise needs to be passed further along the hierarchy. The goal of this communication is not just to satisfy curiosity: knowledge about such errors can lead to modification of the internal models leading to more accurate future predictions or, in case not enough data is available, active search for information which could trigger these modifications. Therefore, the brain constantly tries to minimize surprise and maintain stability. In order to fulfil its future stability it needs to deal with inconsistencies introduced by unexpected events (Friston & Stephan, 2007).

1.3.1 Violating predictions across different contexts

Deviant detection or the effects of violating predictions have previously been studied in many different contexts: e.g., active and passive oddball paradigms

within different perceptual modalities or tasks addressing violations of temporal, linguistic (syntactic, semantic or prosodic), music and sequential structure. All of these examples include establishment of a rather stable context within which a deviating element is introduced. The established context can be either global in cases of first-level rules (as introduced in, e.g., the oddball task) or more local in cases where it is based on a certain structure defined by the relations between specific individual stimuli (e.g., in the language or music domain).

On a general level it is possible to assume that some computations underlying deviant detection could be common across different types of contexts. However, this does not necessarily imply that these computations also need to be implemented within the same brain areas, making these commonalities somewhat difficult to capture. Nevertheless, at least several “suspect regions” which might be implicated in deviant detection across different contexts can still be identified: (lower or higher level) sensory cortices coding the initial mismatch between expected and actual stimulus, frontal and parietal areas underlying attentional orientation towards the deviant as well as working memory processing, frontal areas enabling further elaboration of the deviant as well as, depending on the context, reorientation to the original context and task. The exact sensory areas which would eventually become involved in such detection depend on the modality and specificity of the expectation originally formulated. In addition, it should be emphasized that the coordination between different cortical areas (and possibly the cerebellum) during deviant detection would not be possible without the thalamus and the basal ganglia.

1.3.1.1. Violating predictions in the oddball task

The oddball paradigm represents one of the classical task contexts within which violations of expectations have been systematically studied. This task includes frequent presentation of standard stimuli among which occasional pre-defined targets are embedded (Sutton et al., 1965). Many features of this task can be varied, most important of which include attentional involvement of the subject, nature of the deviant in relation to the standard stimuli and its relevance for participant’s reaction (deviants which participants are required to detect are also called “target” in contrast to “distracter” or “novel” stimuli which violate the context but need to be ignored). Although significant, the influence of these as well as other factors (e.g., modality of the task or deviant frequency) on the involvement of different brain areas in detecting deviants will not be greatly discussed within the present thesis. Instead, only a broad overview of the most commonly reported

regions in detecting deviants in the context of the oddball task will be given. Most fMRI studies using some form of this task have consistently reported the involvement of parietal (Ardekani et al., 2002; Bledowski, Prvulovic, Goebel, Zanella, & Linden, 2004; Brazdil et al., 2005; Clark, Fannon, Lai, Benson, & Bauer, 2000; McCarthy, Luby, Gore, & Goldman-Rakic, 1997; Mulert et al., 2004) and temporal cortical areas (Kiehl, Laurens, Duty, Forster, & Liddle, 2001; Linden et al., 1999; Opitz, Mecklinger, Friederici, & von Cramon, 1999; Stevens, Skudlarski, Gatenby, & Gore, 2000; Yoshiura et al., 1999).

In an attempt to provide a functional account of these findings, Stevens et al. (2000) suggested that the involvement of bilateral inferior parietal lobule (IPL) in this context may reflect an amodal target detection network involved in early working memory processing. Alternatively, the regions in the parietal cortex around the intraparietal sulcus (IPS), in the superior and parietal lobule (SPL, IPL) and precuneus have been related to directing attention either to spatial locations or towards visual features or objects (Corbetta & Shulman, 2002; Nobre, 2001). In addition, lateral prefrontal areas have often been reported in target detection studies and suggested to reflect semantic processing of identified deviants (Opitz et al., 1999) or the orientation to rare stimuli (Kiehl et al., 2001). However, although the involvement of these areas in target detection is rather consistent, the extent of their activation is highly dependent on task demands (Kiehl et al., 2001), the degree of stimulus novelty (Kirino, Belger, Goldman-Rakic, & McCarthy, 2000), target probability (Casey et al., 2001) or degree of post-detection elaboration of the stimulus (Opitz et al., 1999). On a very general level and across different brain regions, there exists evidence regarding more pronounced involvement of the right hemisphere to both target and novel events (Stevens, Calhoun, & Kiehl, 2005).

EEG studies have, on the other hand, shown that presentation of deviants within the oddball task elicits a characteristic pattern of event-related potentials (ERP): an early negative component occurring around 200 msec and a later positive component in the 300 msec range (Linden et al., 1999; Patel & Azzam, 2005). Their exact amplitude, topography, latency as well as underlying neural generators depend on numerous task parameters, most important of which include the attentional orientation of the participant and stimulus modality. Just to give one example of how component features depend on the properties of the task and deviant stimulus, the amplitude of late components reflects the strength of expectancy which is dependent on a decaying memory trace for events within the prior stimulus sequence, the specific structure of the sequence, and the global probabil-

ity of event occurrence (Squires, Wickens, Squires, & Donchin, 1976). In line with this, a larger amplitude of late components following the presentation of a deviant stimulus is elicited by stimuli which have smaller probability of occurrence (Duncan-Johnson & Donchin, 1977). Importantly, the processing of deviants is strongly dependent on the level of participants' attentional involvement, as unattended deviants elicit event-related components of somewhat different characteristics when compared to the ones elicited by attended deviants (Escera, Alho, Schröger, & Winkler, 2000; Näätänen, Jacobsen, & Winkler, 2005; Patel & Azzam, 2005). Other examples or a more systematic overview of different ERP components will not be provided at this point, as it is not of direct relevance to the current discussion. However, some of these will be discussed in more detail in Chapter 4. It needs to be mentioned that deviant detection is not only marked by ERP effects, but also by changes in the oscillatory activity of different EEG power bands. For example, changes in the event-related gamma oscillations have been identified in the oddball task in which they follow, but show functional independence from P300 (Edwards, Soltani, Deouell, Berger, & Knight, 2005; Gurtubay et al., 2001). However, since this topic is beyond the scope of the present thesis, these effects will not be presented in more detail.

1.3.1.2. Violating predictions in other contexts

In the context of language processing, violations of semantic and syntactic structure elicit distinct brain responses and it is therefore considered that they represent separable processes. Using fMRI, it has been shown that semantic violations elicit activations primarily in posterior medial and superior temporal as well as prefrontal areas (Friederici, Rüschemeyer, Hahne, & Fiebach, 2003; Kuperberg et al., 2000). In comparison, violations of the syntactic structure in natural as well as artificial language primarily engage Broca's area (BA 44 and 45) as well as the adjacent dorsolateral prefrontal regions (Embick, Marantz, Miyashita, O'Neil, & Sakai, 2000; Indefrey, Hagoort, Herzog, Seitz, & Brown, 2001; Petersson, Forkstam, & Ingvar, 2004).

In EEG, semantic violations such as contextually inappropriate words typically elicit the N400, a negative component peaking around 400 msec after stimulus presentation, which has been suggested to reflect contextual integration (Kutas & Hillyard, 1984; McCarthy, Nobre, Bentin, & Spencer, 1995). Interestingly, N400 is not an obligatory component, as it does not necessarily need to be elicited in all contexts. As shown by Friederici et al. (1999), N400 effect is absent for semantically incongruent items which are also syntactically incorrect, which implies that

the phrase structure imposes an early influence on lexical-semantic integration processes. In contrast, violations of the syntactic structure in language elicit a positive deflection in a later time range, the so-called P600 (Friederici, Hahne, & Mecklinger, 1996) or syntactic positive shift (Hagoort, Brown, & Osterhout, 1999). In addition to this late centroparietal positivity, phrase structure and syntactic integration are reflected by a left anterior negativity (LAN) with a latency of 300-500 msec which can sometimes occur earlier, with the latency of 100-300 msec and is then referred to as an early left anterior negativity (ELAN) (Gunter, Friederici, & Hahne, 1999; Hahne & Friederici, 1999). Recently, Friederici (2002) distinguished between these effects occurring in different time points following the stimulus, relating ELAN effects to violations of word category and the later-occurring LAN component to morphosyntactic processing. Interestingly, violations of harmonic structure in music processing, similar to those in language processing, evoke a P600-like response (Patel, Gibson, Ratner, Besson, & Holcomb, 1998). In addition, semantic violations in music elicit an early negative component peaking around 180 msec, namely early right anterior negativity (ERAN) and an additional component of the same polarity peaking around 500 msec after stimulus onset (N500) (Koelsch, Gunter, Friederici, & Schröger, 2000). These components can be compared to those indexing deviant detection in language, as ELAN and ERAN share similar polarity, time course, anterior scalp distribution, underlying neural generators (contributions from Broca) and sensitivity to structural violations (Koelsch & Mulder, 2002).

1.3.1.3. Errors in overt behavior

In a sense, violations within external, perceptual events can be compared to errors of own performance which also represent a violation of a specific type of predictions, namely those related to one's own behavior. In the context of error detection, it has previously been shown that the anterior cingulate cortex (ACC), in particular the rostral cingulate zone (RCZ), plays a crucial role in processing own, as well as observed errors committed by others (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Ullsperger & von Cramon, 2004). Furthermore, a more fundamental, "generic" error-processing role in reinforcement learning for the ACC was suggested based on findings showing the involvement of the same region of the dorsal ACC in error responses as well as error feedback, showing its sensitivity to both internal and external sources of error information (Holroyd et al., 2004). In addition, other areas such as insula, pre-SMA and the dorsolateral prefrontal cortex (dlPFC) have also been related to error detection processes

(Garavan, Ross, Murphy, Roche, & Stein, 2002; Klein et al., 2007; Ullsperger & von Cramon, 2004). In the EEG, error-related negativity (ERN) or error negativity (Ne), a negative component peaking around 50-100 msec after the response has been identified as the most common event-related component associated with error-detection in overt behavior (Falkenstein, Hoormann, Christ, & Hohnsbein, 2000; Gehring, Coles, Meyer, & Donchin, 1995; Scheffers, Coles, Bernstein, Gehring, & Donchin, 1996). This component is usually followed by error positivity (Pe), a positive component peaking around 300-500 msec after the onset of the erroneous response, which might reflect post-error processing such as the conscious recognition of the error, emotional processing or strategy adaptation following the executed error (Falkenstein et al., 2000)

In the context of motor behavior, it has previously also been suggested that human error processing may be hierarchically organized, in a sense that different systems may be involved in different types of error evaluation. More specifically, in the context of motor control, Krigolson and Holroyd (2007) suggested a dissociation between two systems involved in error processing: one dealing with high-level errors in which one fails to reach a pre-defined goal, and one processing low-level errors in which a discrepancy between the desired and actual motor command is encountered. Within this account, high-level errors are reflected in the ERN component elicited by the medial prefrontal cortex in contrast to the lower-level ones which are characterized by the occurrence of other ERP components (N100, P300) reflecting the activation of posterior cortical areas.

1.3.2 Violating predictions in sequencing

Deviant detection in sequencing has most often been investigated by comparing the effects of a stimulus sequences (e.g., a simple repetition or alteration of two stimuli) terminating either in accordance with elicited expectations or in a violation (e.g., repetition in case of alternating and alternation in case of repeating sequences) and analyzing participants' behavioral performance and the elicited event-related potentials in EEG. Such violations can be termed sequential deviants as they violate the sequential structure defined by the order of stimulus presentation. These events can also be considered as one form of relational (associative) deviants, namely those encountered in situations in which a learned relation between two stimuli (in this case their order of presentation) is violated. Generally, it has been shown that sequentially correct (expected) events are processed faster and more accurately as compared with deviant items which typically elicit N200 and P300 ERP components as measured by the EEG (Rüsseler & Rösler,

2000). In a recent study Lelekov et al. (2000) used visually presented sequences in an attempt to distinguish the processing of events violating surface and abstract sequence properties. In this study violations of the abstract sequence properties evoked a late positive component rather similar to P600 which was previously described for language processing, indicating a similarity between syntax in language and abstract structure of non-linguistic sequences. Similar conclusions could also be suggested based on the fact that agrammatical patients have difficulties with abstract sequencing as well as syntactic language processing (Dominey & Lelekov, 2000). When studying violations within the context of motor sequencing, it may be very difficult to separate the two types of violation effects, namely violations within external, perceptual events from errors of own performance. As argued by Ferdinand et al. (2008), formulating and evaluating expectations about the incoming stimuli represents an important part of motor sequence learning. Furthermore, the authors suggested a unified framework for N2b and the error-related negativity (ERN) which are characterized by similar latency and scalp distribution as well as proximal neural sources. In this view, ERN and N2 reflect the same mismatch detection process which can be modified based on the demands of immediate task context. However, evidence against this interpretation comes from a study showing that ERN may better be seen as the output of an evaluative system involved in monitoring motor control (Rodriguez-Fornells, Kurzbuch, & Munte, 2002).

A recent fMRI study investigated the effect of violating expectations in sequencing by presenting participants with sequences described as random, although some of them contained ordered repetitions or alterations of stimuli (Huettel, Mack, & McCarthy, 2002). The obtained results indicated that these patterns were nevertheless identified as non-random by observers, which lead the authors to conclude that identifications of regular patterns within event sequences is obligatory. Violations of repeating patterns in this experiment elicited widespread prefrontal, insular and basal ganglia activations, similarly to violations of alternating patterns which also recruited lateral prefrontal areas. Since the respondents were instructed that the sequences were random, authors finally concluded that this activation reflects automatic identification of events that violate repeating patterns. However, in their comment of the obtained results, Ivry & Knight (2002) suggested that respondents were, despite the instructions, probably explicitly aware of the underlying sequential structure. They additionally proposed several alternative hypotheses which could possibly account for the obtained findings. These include effects of short-term memory, novelty detection mechanisms, generation of explicit predictions about forthcoming events or a

combination of all alternatives. Very distinct from these results are those showing the crucial contribution of hippocampus in detecting relational deviants (associatively novel events) which has been investigated by using familiar, slowly presented images irrelevant to the task of participants (Kumaran & Maguire, 2006, 2007).

Overall, although the detection of sequential deviants has previously been studied in several different contexts, there is not a unifying theory which could account for the obtained findings. The goal of the present thesis is not to try and provide such an account, but to study this process in a context within which it was previously not addressed, namely in the serial prediction task. This is possible as this paradigm allows investigating not only the process of learning a sequence and forming expectations related to the incoming stimuli, but also the process of detecting and evaluating the effects of violating such expectations. There are several exclusive characteristics of the serial prediction task which are mostly not shared by other, previously used paradigms in this context. It is purely perceptual and includes the obligatory attentional involvement of the respondent who is instructed to attend to the sequence. It requires explicit learning of the sequence which has to be represented in a way probably best described in the context of forward models, so that the incoming stimuli can be compared to the predicted ones resulting in a match in case of fulfilled predictions or mismatch signalling the existence of a sequence violation.

1.4 Overview of the present experiments

The goal of the experiments conducted within the current thesis was to explore the process of detecting a certain category of deviant events, namely sequential deviants, within the context of perceptual sequence processing. In order to explore this process, the previously introduced serial prediction task (SPT) was used as the principal experimental paradigm in all of the conducted studies. In all experiments, a three-stimulus pattern of successively presented stimuli defined by their order of presentation was used within the task. The violated pattern which was occasionally shown always included presentation of correct stimuli appearing in the wrong order, such that two stimuli exchanged their positions (sequential deviant). Since it was previously shown that the type of processing as evoked by the serial prediction task is by nature predictive (c.f., Schubotz, 2007), the process of detecting sequential deviants will be considered as a case of violating perceptual expectations or predictions.

Although it was in principle possible to explore the effects of other types of deviants within perceptual sequences, e.g., detection of a completely novel stimulus presented within a familiar pattern, only sequential deviants were investigated within the present thesis. Namely, it was assumed that studying this type of events would be informative not only for the process of deviant detection, but also sequence processing itself. In addition, since introducing novel events in a sequence would always introduce a large prediction error due to their smaller frequency in contrast to other stimuli, studying this phenomenon might require more restructuring of the primary paradigm used in the current experiments. Thus, the experiments conducted within the present thesis were restricted to the detection of sequential deviants.

Within *Experiment 1* sequential deviants were introduced into short perceptual sequences defined by the identity of individual stimuli which was dominantly determined by their size. The main goal of this study was to determine the degree to which detecting sequential deviants depends on the brain network previously identified in supporting regular aspects of sequence processing, primarily the medial and lateral premotor regions and the connected parietal areas (Schubotz & von Cramon, 2003), and to investigate the additional engagement of brain regions not initially involved in sequence processing. This process was compared to the detection of feature deviants, namely stimuli which differed in a pre-defined physical feature from standard stimuli presented within the target detection task. This issue was further investigated in *Experiment 2* which explored the temporal dynamics of detecting sequential and feature deviants. In addition, the relevance of participants' attentional involvement in processing both types of deviants was addressed. In *Experiment 3* the process of detecting sequential deviants was investigated within three different types of perceptual sequences organized at a somewhat more abstract level of stimulus features. Specifically, neural correlates of detecting deviants within perceptual sequences defined by spatial, object or temporal (rhythm) stimulus features were compared within this study. In *Experiment 4* deviant detection within two different levels of sequences defined by object features of different specificity was investigated. Specifically, sequential deviants were introduced into sequences in which expectations pertained to object identity (token) and those in which expectations could only be formulated on a categorical level (type). Thus, in this experiment processing of sequential deviants that violated the expectations of different specificity was compared. Before introducing individual experiments in more detail, a general overview of the methods used for exploring neural correlates of deviant detection will be given. This will mainly be restricted to the measures of brain activation, functional

magnetic resonance imaging (fMRI) and electroencephalogram (EEG). In addition, participants' behavioral performance was also measured within all experiments.

2 Introduction to the methods

The current chapter describes the methods relevant for the experiments conducted within the present thesis, namely functional magnetic resonance imaging (fMRI, Section 2.1) and event-related potentials of the electroencephalogram (EEG, Section 2.2). Both of these methods were used for investigating neural foundations of deviant detection as they each capture different aspects of the underlying processing. While electrophysiological measures provided excellent temporal resolution needed to address the temporal dynamics of processes of interest, good spatial resolution of functional imaging methods was useful in identifying the underlying neural circuitry.

In addition, in all experiments participants' behavioral performance was recorded and analyzed. Response accuracy (percentage of correct responses) was used as a measure of such performance. Because of the nature of the experimental paradigm, reaction times were not used as a complementary source of information. Namely, participants' responses were always delayed, as they were required at the end of the trial and not right after at the occurrence of the event of interest. Furthermore, since they could occur at different points in time following the event critical for participants' decision, reaction times do not represent a measure of detection or decision speed. Thus, since reaction times could not be unequivocally interpreted, they were not used as an additional measure of behavioral performance.

Statistical analyses in all experiments were performed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA). Additional software was used for recording behavioral measures and presenting the visual stimuli. Specifically, in *Experiments 1, 3 and 4* stimulus presentation and recording of participants' reactions was performed using Presentation 9.9 (*Experiment 1*) or 11.7 (*Experiments 3 and 4*) (Neurobehavioral systems, San Francisco, CA, USA). In *Experiment 2* this was realized using Cogent 2000 (developed by the Cogent 2000 team at the Functional Imaging Laboratory and the Institute of Cognitive Neuroscience, London, UK).

2.1 Functional Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is based on the interaction between an externally applied magnetic field and some types of atomic nuclei among which, especially for the purposes of biomedical brain imaging, hydrogen nuclei contained within water molecules are the most important. Thus, MRI relies on the fact that most of the human body is water-based and that the amount of water in different types of tissue is non-uniformly distributed. In order to understand the value as well as the limitations of information provided by magnetic resonance imaging, it is necessary to describe the process of acquiring the MR signal, reconstructing the obtained images and advancing from recording pure structural properties to measuring brain activity using functional magnetic imaging (fMRI). In the end, a short description of the standard analysis procedures will be provided, revealing how single subject images are analyzed and brought together in group analysis based on which all generalizations and interpretations of the obtained data can subsequently be made.

2.1.1 Obtaining an MR signal

MRI relies on some fundamental properties of atoms and their constituting protons and neutrons: first of all, since these particles rotate around their axis (spin), atomic nuclei possess a net angular momentum determined by the number of their protons and neutrons. However, only those nuclei which contain an odd number of protons and neutrons possess a net spin and can be used in magnetic resonance experiments in contrast to those containing an even number of particles in which the sum of magnetic moments of all particles is zero. Although quite a few nuclei possess this property, biomedical MRI (sometimes referred to as nuclear magnetic resonance (NMR) because it relies on described properties of atomic nuclei) commonly uses hydrogen nuclei which have a strong magnetic moment and are very abundant in the human body. Thus, MRI relies on magnetic properties of water molecules which arise from weak magnetic fields of single hydrogen proton spins.

In absence of any magnetic stimulation, spins are arranged randomly, facing different directions. When placed in an external magnetic field (e.g., MRI scanner), they align with the strong field, occupying either parallel (low-energy) or antiparallel (high-energy) state in relation to it. Since a few more spins occupy a low-energy state in the static magnetic field, net magnetization across all spins is a vector parallel to the static magnetic field (it lies in the longitudinal plane).

However, spin alignment is not fixed and spins can, as a result of energy exchange with the environment, change their state: bringing energy into the system can lead to low-to-high energy transition while high-to-low transitions are accompanied by a release of energy. It is important to emphasize that this energy can only have a certain frequency (Larmor frequency) which depends on the gyromagnetic ratio of the fields' spin (constant for each nucleus type) and the strength of the static magnetic field. If energy is introduced into the system by applying electromagnetic pulses oscillating at a resonant (Larmor) frequency of the spins, the net magnetization vector can be tipped from the longitudinal to transverse plane. This change in net magnetization induced by a radio frequency (RF) excitation pulse allows the generation of MR signals which can be measured by an external detector coil. Soon after the pulse is terminated, the spins go back into their original alignment with respect to the magnetic field in a process called free induction decay which is determined by relaxation parameters T_1 , T_2 and T_2^* . The process of relaxation is a complex one: it includes the recovery of longitudinal magnetization (reflected in T_1 relaxation) and disintegration of transverse magnetization (reflected in T_2 and T_2^* relaxation) through loss of phase coherence in the transverse plane (T_2) whose rate of decay can be increased by local field inhomogeneities (T_2^*).

It is important to emphasize that magnetic resonance imaging is not a one-pulse phenomenon. The type and quality of information which can be obtained by MRI is governed by complex procedures determining the sequences of RF pulse applications and data acquisition parameters. By varying the time periods between two excitation pulses (repetition time; TR) and the time between the pulse and start of data acquisition (echo time; TE), it is possible to create pulse sequences which are not equally sensitive to different tissue types, e.g., white or gray matter. Principally, distinguishing between different types of tissues within the recorded images is possible due to unequal rate of relaxation across these tissues. These differences are a consequence of the non-uniform distribution of water molecules within them. Since the acquired MR signal measured after an excitation pulse reflects the sum of all signals generated across a certain area, it needs to be converted into a spatially informative map. By applying different magnetic field gradients after the excitation pulse, it is possible to select the slice for imaging (slice select gradient) as well as to recover the information about the frequencies (frequency-encoding gradient) and phase (phase-encoding gradient) of the underlying signal. These gradients are oriented orthogonally along three axes: x-axis running from ear to ear, y-axis from nose to the back of the head and z-axis from top of the head down. This process allows the creation of meaningful MR images.

2.1.2 Functional magnetic resonance imaging (fMRI)

fMRI is a young cognitive neuroscience method developed in 1990 when Ogawa et al. (1990) first described the BOLD (blood oxygen level dependent) effect which reflects the dependence of T_2^* weighted contrasts on the amount of blood deoxygenation. This effect relies on the fact that oxygenated and deoxygenated hemoglobin have different magnetic properties such that only deoxygenated hemoglobin is paramagnetic. Consequently, it induces distortions or inhomogeneities into the local magnetic field which are reflected in T_2^* images: the more deoxygenated hemoglobin is present in the blood, the greater is the signal loss in T_2^* images. The fact that the level of oxygenation in the blood can be measured by MRI is interesting for the neuroscientific community because oxygen consumption reflects the metabolic activity which is closely related to the level of activation of surrounding tissue. In other words, BOLD signal can be used as an indirect indicator and measure of neural activity and brain functioning. It is generally accepted that the BOLD signal and neural activity are closely coupled and that the BOLD response primarily reflects local input of a neural population and not so much the output of a given area. Thus, it is more related to synaptic than spiking activity (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001).

It needs to be emphasized that the principles of neurovascular coupling or the relation between BOLD and neural activity are not simple. Increased neuronal activity requires energy provided through a chain of interrelated mechanisms: neural activity is coupled with an increase in blood flow, blood volume as well as the metabolic rate of oxygen consumption (Figure 2.1). Although more oxygen consumption should by itself lead to a decrease in BOLD signal due to increased amount of deoxygenated hemoglobin and faster T_2^* relaxation (it is suggested that this processes could be reflected in the initial dip, namely the first part of the BOLD response), the typically measured increase of the signal reflects oversupply of oxygen to the activated area and surrounding tissue which prolongs T_2^* relaxation time.

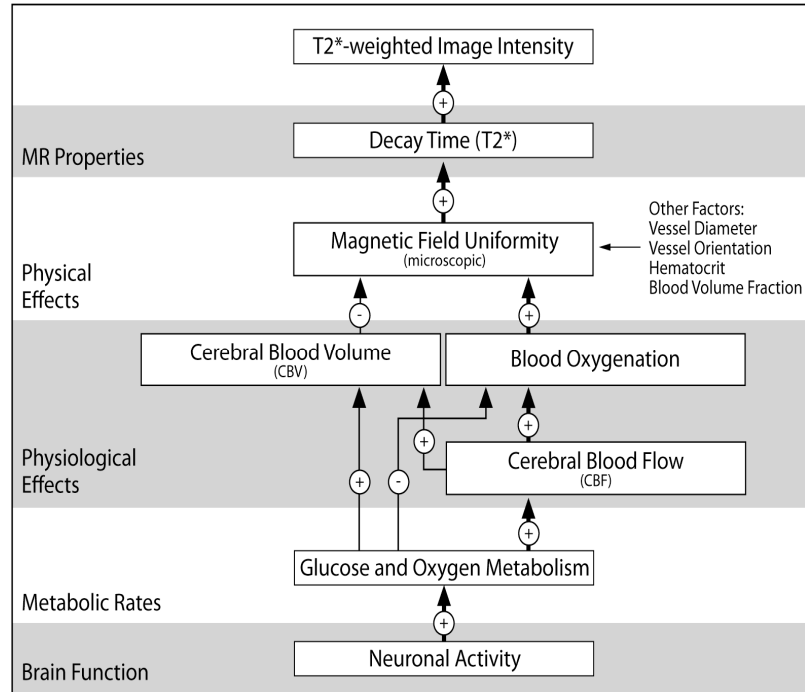


Figure 2.1: A schematic overview of the main principles of neurovascular coupling and fMRI

The way the BOLD signal evolves over time in response to a change in neural activity is described by the hemodynamic response function (HRF). HRF depends on the properties of stimulation and underlying neuronal activity and, although this is relatively stable across sessions recorded in same conditions, significant differences in HRF between individuals and different regions within individuals have been reported (Aguirre, Zarahn, & D'Esposito, 1997). However, one can still roughly describe a typical BOLD response as comprising a short-lasting initial dip, rise, peak (after 5 sec), fall and undershoot slightly below the baseline before returning to the initial value after 12-24 sec (Figure 2.2). In contrast to good spatial resolution of about 1 mm, due to the sluggish nature of the BOLD response, the temporal resolution of fMRI is typically rather low, around 5-8 sec (Horwitz, Friston, & Taylor, 2000), although fMRI images of the whole brain can be collected within higher rates, usually 1-2 sec. These values can vary across experiments as the spatial resolution depends on the voxel size while the temporal resolution is dependent on the repetition time. Increasing one of these is usually made at the expense of the other, in a sense that reducing the size of voxels in order to increase the spatial resolution leads to reduced temporal resolution because more

time is needed to acquire data from the same portion of the brain. However, the potential for improving both resolutions is limited. Therefore, when addressing temporal dynamics of cognitive processes, fMRI could best be complemented by other methods showing superior temporal resolution such as the EEG.

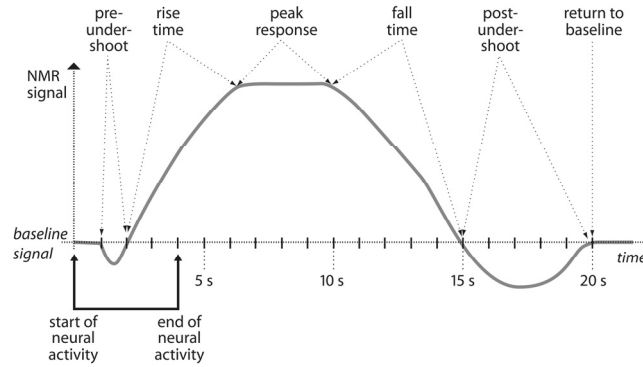


Figure 2.2: Time-course of the typical hemodynamic response

2.1.3 Standard analysis of fMRI data

Conducting an fMRI experiment results in the acquisition of a time sequence of images reflecting BOLD activity over time at discrete spatial locations. This spatial information can be used in order to identify voxels whose measured signal covaries with the changing brain states or cognitive function of interest. There are many sources of noise which influence the quality of the BOLD signal (e.g., intrinsic thermal noise within the scanner electronics and variations in participants' temperature; system noise including the subtle changes in the strength of the static magnetic field; physiological noise including e.g., motion or respiration, non-task neuronal activity) and different ways of improving the signal-to-noise ratio (e.g., increasing magnetic field strength, signal averaging or improving experimental designs). Although some of the artefacts can not easily be addressed after acquiring the data, performing several preprocessing steps prior to statistical analysis can help in discarding the unwanted variance and improving signal-to-noise ratio. Initial preprocessing steps typically include correction of artefacts which arise from motion of participants inside the scanner and compensation for different acquisition time of slices within a volume. Subsequently, the data is spatially and temporally filtered. Although useful as it increases signal-to-noise ratio and decreases variability across participants, spatial filtering may also have negative side effects as it decreases spatial resolution of the acquired data. Tem-

poral filtering is applied primarily in order to correct for low frequency drifts caused by physiological or technical reasons, although in some cases additional corrections for high frequency noise are also performed. In order to precisely match the measured activations in the functional data to the underlying anatomy and allow statistical comparisons across participants, functional images need to be registered (aligned with a reference data set, typically a high-resolution anatomical data set of the same participant or a data set averaged across a group of participants) and normalized (scaled into a standard coordinate system, e.g., Talairach stereotactic space).

Statistical analysis performed on the fMRI data can include different procedures differentiated primarily based on whether the analysis is conducted independently for each voxel or not (univariate vs. multivariate analysis) and whether they include an underlying model (model-based vs. model free approaches). The choice of the statistical analysis of fMRI data depends on the research question motivating a study and can have repercussions on the choice of preprocessing steps / parameters. Currently, the most commonly used approach is the model-based univariate analysis as implemented within the General Linear Model (GLM). GLM assumes that the measured data reflect a linear combination of different factors of interest and uncorrelated (random) noise varying independently across different voxels. Using GLM the experimenter tries to specify the model which describes how the BOLD response depends on different factors in the experiment, fit the model to the measured data (time-course of every voxel) and use it for testing the research questions of interest. Since valid inferences from the statistical analysis may be confounded by the large number of voxels being simultaneously tested within each analysis, different procedures can be used in order to deal with the potentially resulting Type I error.

2.1.4 Measurement and analysis of fMRI data in Experiments 1, 3 and 4

All fMRI experiments in the present thesis (*Experiment 1, 3 and 4*) were highly similar in terms of the data acquisition and analysis. However, since they also differed to a certain degree, it was not possible to use exactly identical acquisition or analysis parameters in all of them. Therefore, although a short summary of main acquisition / analysis steps will be provided in this Section, more details and concrete analysis parameters will be described in the methodological sections of each experiment.

2.1.4.1. Procedure

Before all experiments, participants gave informed consent for participating after being informed about potential risks and screened by the physician of the institution. The experimental standards were approved by the local ethics committee of the University of Leipzig. During the measurements, participants were supine on the scanner bed with their right and middle fingers positioned on the response buttons. In order to prevent postural adjustments, the participant's arms and hands were carefully stabilized by tape. In addition, arm, hand and head motion was prevented by using form-fitting cushions. In order to attenuate scanner noise, participants were provided with earplugs. After the measurements, a short post-experimental session was organized within which participants filled a short questionnaire rating the experimental session and tasks.

2.1.4.2. Data acquisition

The experiments were carried out on a 3T scanner (Medspec S300, Bruker, Ettlingen or Siemens Trio system, Erlangen, Germany) equipped with a standard bird cage coil. Immediately prior to the functional experiment, a set of two-dimensional anatomical images was acquired for each subject using a MDEFT sequence (256x256 pixel matrix) (Norris, 2000; Ugurbil et al., 1993). Additionally, in order to improve the localization of activation foci, high resolution whole-brain images using a T1-weighted three-dimensional segmented MDEFT sequence were acquired for the participants in a separate session. This volume data set with 160 slices and 1 mm slice thickness was standardized to the Talairach stereotactic space (Talairach & Tournoux, 1988). Parameters of the functional images in-plane which were acquired after the anatomical images will be specified for each experiment separately.

2.1.4.3. Data analysis

The processing of fMRI data was performed using the software package LIPSIA (Lohmann et al., 2001) which contains tools for pre-processing, co-registration, statistical evaluation and visualization of fMRI data. In order to align the functional data slices with a 3D stereotactic coordinate system, a rigid linear registration with six degrees of freedom (3 translational and 3 rotational parameters) was performed. The parameters were acquired on the basis on MDEFT and EPI-T1 slices to achieve an optimal match between these slices and the individual 3D reference data set. Each transformation matrix was subsequently transformed to a

standard Talairach brain size ($x=135$, $y=175$, $z=120$ mm; Talairach & Tournoux, 1988) by applying linear scaling. Finally, the normalized transformation matrices were applied to the acquired functional slices in order to align them with the stereotactic coordinate system. Transformation was performed using trilinear interpolation, thus generating data with a spatial resolution of 3 mm^3 . The purely functional analysis steps, namely preprocessing and statistical analysis were also performed in a highly comparable manner across all experiments. Preprocessing of the functional data included correction for motion artefacts and temporal offset between the slices acquired in one scan, as well as temporal and spatial filtering. The statistical evaluation was based on a least-squares estimation using the general linear model for serially autocorrelated observations (random effects model). In the first stage, autocorrelation parameters were estimated from the least squares residuals using the Yule-Walker equations and used to 'whiten' the data and the design matrix. In the second stage, the linear model was re-estimated using least squares on the whitened data to produce estimates of effects and their standard errors (Worsley et al., 2002). Data were modelled using a design matrix consisting of onset vectors with events time-locked to the violations within those conditions containing them and comparable positions within conditions without violations, with one additional vector for responses and one for the remaining stimulation periods of no interest, including the trials that were incorrectly responded to. In order to explore the process of regular sequencing, a design matrix with events time-locked to the presentation of the first stimulus within each sequence was used. Within both types of matrices the events related to each sequence type were modelled with the same duration. The design matrices were generated using a synthetic hemodynamic response function (Friston et al., 1998; Josephs, Turner, & Friston, 1997) and its first derivative for the second matrix. Contrast images of interest were then generated for each participant, after which the random effects analysis on the level of the group data was performed. Since some parameters of analysis were (due to factors such as e.g., different frequencies of the signal of interest) slightly varied across parameters, additional steps of preprocessing and statistical analysis will be provided within the methodological sections of individual experiments. Although this will be slightly redundant, it may nevertheless be a meaningful way of presenting all relevant information related to the analysis prior to presenting the respective results.

2.2 Electroencephalography

Electroencephalography (EEG) measures the electrical activity of the brain using a number of carefully placed electrodes on the head. Since the EEG signal is measured as a difference of potentials between two different recording sites, the minimum of two electrodes is required for measuring EEG: an active electrode placed at the site of neuronal activity and a reference electrode placed far from the brain activity of interest (e.g., nose, mastoids, ear lobes). EEG was first measured in humans by Hans Berger (1929) who described two basic patterns of brain waves (alpha and beta waves), thus paving the way to abundant EEG research investigating a wide range of cognitive functions, basic neurophysiological processes as well as the pathological states of the nervous system. Although the exact relationship between the signals recorded on the scalp and neurophysiological processes taking place within the brain is still not completely understood (Kandel, Schwartz, & Jessel, 2000), it is generally accepted that the physiological basis of EEG signal originates in the postsynaptic dendritic currents and not in the axonal currents which can be related to the neuron action potentials (Nunez, 1981). Signals visible on the scalp reflect the synchronized activity of a population of neurons arranged in a way which allows the summation of individual electric fields forming a dipolar field. This is usually the case when these are aligned in a parallel orientation, forming an open field, as are most pyramidal neurons whose summated postsynaptic potentials generate a signal strong enough to be recorded from the scalp electrodes. It needs to be noted that EEG may not be very successful in capturing a range of different types of neurophysiological processes, e.g., those reflecting an activation of a population of neurons which is too small, not synchronized, configured as a closed field or placed too far away from the scalp to elicit measurable signals. Regardless of this as well as its limited spatial resolution, EEG represents one of the most powerful tools of cognitive neuroscience because, by allowing continuous measurements of brain activity in the time range of a few milliseconds, it represents an excellent technique for exploring temporal dynamics of cognitive processes.

2.2.1 Analysis of the EEG data

Analysis of the event-related EEG data can be performed either in relation to the temporal or the frequency domain of the measured signal. Within the present thesis, the focus will be on the time domain of the EEG signal and the event-related potentials resulting from such analysis. Event-related potentials (ERP) are small voltage oscillations which reflect electrical activity of the brain time-locked

to a particular event, e.g. presentation of a stimulus or reaction of the participant. Since the amplitude of the ERP “locked” to the event of interest is very small in relation to the background activity, one usually needs to average ERPs recorded across many repeated presentations of the same event (epochs) in order to measure a reliable response to the desired event (Figure 2.3). This technique assumes that a certain event will always elicit a response time-locked to the stimulus / response superimposed to the randomly fluctuating background activity which will, through averaging, be cancelled out from the resulting ERP. Since some of the activity not triggered by the event of interest may be systematic or quite detrimental to data quality (e.g., artefacts evoked by movements of eyes and eyelids, muscle artefacts, etc.), several preprocessing procedures are performed prior to averaging in order to deal with these artefacts. Although minimizing some types of artefacts may be achieved by using different types of filters, e.g., low-pass filters for high-frequency artefacts (e.g., line frequency or muscle artefacts) or high-pass filters for low-frequency artefacts (e.g., DC drifts), some artefacts (e.g., those caused by eye movements and blinks) can not easily be corrected. These are often addressed by discarding epochs contaminated with eye-related activity or applying some novel procedures for estimating and removing their contribution to the measured signal, e.g., the independent component analysis (ICA).

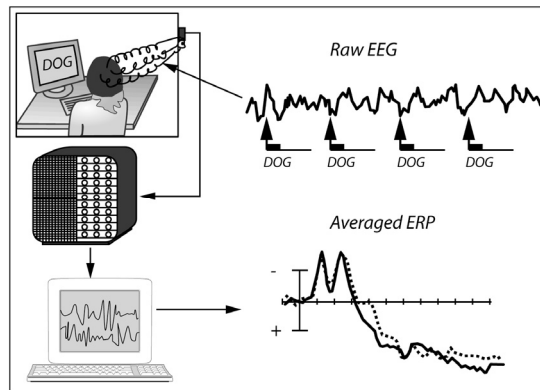


Figure 2.3: Acquisition of event-related potentials

An ERP calculated after artefact correction and averaging across all events of interest consists of a set of positive and negative voltage deflections (components) related to different stages of information processing (Rugg & Coles, 1995; Zani & Proverbio, 2003). Each ERP can be described in terms of its polarity (an indication whether curve deflection of a component is negative or positive rela-

tive to a baseline), amplitude (maximal voltage value of the component relative to a baseline), latency (time at which the onset or maximal value of the component appear relative to a critical stimulus), duration (length of time during which a component stays visible) and topography (locations at the skull and electrode positions where the component is measurable) (Donchin, Ritter, & McCallum, 1978). Identifying ERP components can be quite challenging since the activity measured on the scalp can (and often does) reflect a summation of activity generated by several sources in the brain which is only partly due to volume conduction by brain tissue, meninges, skull and scalp. Therefore, Näätänen and Picton (1987) suggested that an ERP deflection should be identified as an unique component if it can be related to only one neural generator (physiological approach). This approach can be contrasted with a more functional or psychological approach in which components are defined based on their functional role, e.g., error-related negativity (ERN) (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1990) or readiness potential (RP) (Donchin, 1979).

Overall, the quest of finding a unifying criterion for defining ERP components has proved to be a challenging one, so today several criteria are being concurrently used. First of all, many components are named in terms of their polarity and typical latency (either measured in milliseconds or given as rank order of the deflections of same polarity) which often does not reflect exact timing of the component, e.g., N200 (negative component peaking around or after 200 msec) which is also referred to as N2 (second negative component). Alternatively, some components include topographical, e.g., early left anterior negativity (ELAN) or, as previously mentioned, functional specifications, e.g., ERN. Regardless of the preferred criteria, many issues regarding clear separation of components reflecting activity of unique generators and / or well-defined cognitive processes still remain open. This is especially the case for components which occur with a longer delay after the stimulus. Namely, in contrast to early components occurring up to 100 msec after stimulus presentation (exogenous components) which primarily reflect basic sensory and perceptual processing triggered by a stimulus, those occurring after 100 msec (endogenous components) reflect more complex functions and can be modified by higher order psychological processes (Proverbio & Zani, 2003). Given the complexity of neural processes underlying some “simple” cognitive functions as well as the interdependency of such different processes evoked by commonly used cognitive neuroscience paradigms, expecting simple solutions and clear criteria in this area may not be realistic after all. However, taking this complexity into account may have beneficial effects as

it may open questions regarding the relation between different components and, in addition, hypothesized processes underlying them.

2.2.2 Measurement and analysis of EEG data in Experiment 2

2.2.2.1. Procedure

According to the declaration of Helsinki, written informed consent was obtained from each participant prior to the beginning of the experiment. Participants were seated in a sound-attenuated and electrically shielded chamber. A computer screen, visible through a glass pane, was placed outside the chamber at a distance of 100 cm. Sequences of visual stimuli were presented in the center of the screen. Participants were provided with a response keypad. After the measurement, a short post-experimental session was organized within which participants filled a short questionnaire rating the experimental session and tasks.

2.2.2.2. Data acquisition and analysis

EEG was continuously recorded with Ag/AgCl active electrodes from 128 locations radially equidistant from Cz according to the ABC layout (<http://www.biosemi.com/headcap.htm>), which roughly corresponds to the 10-5 extension of the international 10-20 system (Oostenveld & Praamstra, 2001). Electrodes were mounted in a nylon cap. Additional electrodes were placed at the tip of the nose, which served as off-line reference, and at the left and right earlobes. Eye movements were monitored by electrodes placed above and below the right eye and at the outer canthi of both eyes, which were bipolarized off-line to yield vertical and horizontal electroocular activity (EOG), respectively.

EEG and EOG signals were amplified by BioSemi Active-Two amplifiers, sampled at 512 Hz, and filtered off-line using a 0.1 Hz high pass and a 30 Hz low pass filter. Channels with technical malfunction (1 per participant on average) were replaced by interpolating the data of the surrounding electrode sites (Perrin, Pernier, Bertrand, & Echallier, 1989). For each stimulus, epochs of 900 msec duration including a 100 msec pre-stimulus baseline were averaged with reference to stimulus onset to form ERPs. Epochs with amplitude changes exceeding 100 μ V in any channel were rejected from averaging. All stimuli in a sequence with an incorrect behavioral response were also excluded from ERP averaging. Following these exclusion criteria based on which ocular artefacts were also removed, 75% of the to-be-analyzed stimuli were retained on average. Additional

analysis parameters used within the EEG experiments conducted within this thesis are provided within the respective methodological section.

3 Experiment 1. Violating expectations in perceptual sequencing

The main goal of *Experiment 1* was to investigate the detection of sequential deviants in the context of perceptual sequencing and compare it to the process of detecting deviants in one other, non-sequencing context. Thus, two different task contexts were chosen for this comparison, such that expectations about some features of the incoming stimuli could be formulated in both of them. In the sequencing or serial prediction task (SPT) those expectations could be formed based on specific relations between neighboring stimuli in contrast to the overall trial context in the target detection task. In the SPT participants were presented with a sequence consisting of three visual stimuli ordered according to their size that was repeated either correctly or with a violation in the second part of the trial. In contrast, in the target detection task participants were shown a set of six randomly ordered stimuli. Their task was to monitor these stimuli for stimuli whose color did not match that of other stimuli within the trials (size no longer being a relevant dimension). Trials within this task contained the same amount of physical information as in the sequencing task, but did not require extraction and prediction of stimulus order within the trial, making the specific relation between individual stimuli irrelevant. Within both tasks participants were occasionally presented with events which deviated from the standard context of the trial. In the SPT, this was a violation of sequential order, i.e., a sequential deviant, whereas in the target detection task the violation included the occurrence of a stimulus which was physically distinct from standard events within the trial, i.e., a feature (non-sequential) deviant. The participants' task was to indicate whether a respective deviant was present in each of the trials.

Thus, both employed tasks included the presentation of equivalently organized trials and required participants' attention to be directed at the stimulus presentation in order to detect the potential deviant. However, since the nature and speci-

ficity of expectations within the two contexts were clearly different, the involvement of rather distinct brain networks in detecting different types of deviants was expected. In particular, processing of sequential deviants was expected to engage some components of the standard sequencing network typically involved in processing temporally ordered, to-be-predicted perceptual events, primarily medial and lateral premotor cortex, with additional recruitment of areas reflecting increased attentional and working memory demands following deviation presentation. In contrast, presentation of feature deviants was expected to evoke activity in posterior temporal and parietal brain areas, which would be comparable to the pattern of results commonly reported in the oddball paradigm (e.g., Bledowski et al., 2004; Linden et al., 1999; McCarthy et al., 1997; Stevens et al., 2005a). This hypothesis was based on the similarity between the target detection task used within this study and the classical oddball paradigm, both of which include frequent presentation of standard stimuli among which occasional pre-defined stimuli deviating from the context of other presented stimuli are embedded (Sutton et al., 1965).

3.1 Methods

3.1.1 Participants

Fifteen right-handed, healthy volunteers (8 male, 7 female; age 22-31, mean age 26.6) participated in the study. One participant was excluded from further analysis due to below-chance level performance in the SPT and all subsequent analyses were performed on the data from 14 subjects.

3.1.2 Procedure

Participants were instructed and underwent a training session before the main experiment. Since continuous EEG data were simultaneously collected during the experiment, before the MRI session participants were mounted with electrode caps with sintered Ag/AgCl ring electrodes with built-in 5kOhm resistors. A high-input impedance amplifier designed for recording in high magnetic fields (Brain Amps MR plus, Brain Products, Munich, Germany) was used for collecting the EEG data and fixated beside the head coil. A rechargeable power pack placed outside the scanner bore was used to power the amplifier.

3.1.3 Stimuli and task

The stimulus material used in this study (Figure 3.1) consisted of 12 circles with diameters ranging from 0.6 to 2.8 degrees of visual angle. Each trial included successive presentation of six stimuli with the duration of 500 msec without temporal gaps, preceded by a task cue with the duration of 500 msec and followed by a 1500 msec response period. During all other periods in the experiment a fixation cross was presented at the center of the screen. Overall trial duration was 7 seconds and, in order to improve temporal resolution, each trial occurred at four different offset points (0, 500, 1000 and 1500 msec) in relation to fMRI data acquisition (Josephs et al., 1997). During the course of the experiment these stimulus trials were interspersed with empty trials during which only a fixation cross was presented and no task was given to the participants.

Serial prediction (sequencing) and target detection (feature) tasks were presented in a mixed trial design. At the beginning of each trial, subjects were informed about the upcoming task by a cue (blue square for the serial prediction and red square for the target detection task) preceding the stimuli. In the SPT, participants were instructed to attend to the size of presented stimuli in order to extract and predict the repetitive pattern contained within them. The first three stimuli of each trial formed a sequence that the participants were instructed to remember, while the last three could represent either a full repetition or a violation of the original three-stimulus sequence. The pattern of violation was always the same and included reversal in the order of 2nd and 3rd element of the original sequence. The participants' task was to indicate, in a forced-choice mode, whether a sequential violation occurred or not.

In the target detection task, participants were instructed to attend to a random set of six stimuli in order to find a predefined stimulus which was, given its clear distinctness from the remaining standards in the trial, deviating from the overall trial context (feature deviant). Feature deviant was always defined by color (stimuli with a lighter color than either the main circle or its outer rim) and participants' task was to indicate, in a forced-choice mode, whether it was presented within the trial or not. Feature deviants could be presented in any position within the trial so that each position had the same probability of containing such a stimulus. This manipulation assured that the participants would attend to all stimuli during the target detection trials, as was accomplished by the very nature of the task in the serial prediction trials.

Across all trials the order of stimuli was pseudo-randomized. The probability of each stimulus and that of transitions between stimuli were balanced with an additional constraint stating that two neighbouring stimuli within each trial always had to be dissimilar in size. Specifically, they had to be separated by at least two intermediate circle sizes so that they could be clearly differentiated during the presentation of the trial. This constraint was added based on results from a behavioural pilot study which showed differences in task difficulty with nonrestricted randomization.

In order to avoid any motor contributions to the tasks, participants' response was required after the end of each trial. The deviant events (sequential or feature) within the context of each task were presented in 50% of all trials. No feedback was given after the trials. Overall, four types of trials could be differentiated within the experiment: Ordered sequences, Violated sequences, No-target trials and Target trials (Figure 3.1). 80 trials of each type were used which, together with the 32 empty trials, amounted to the total of 352 trials presented in the course of the experiment.

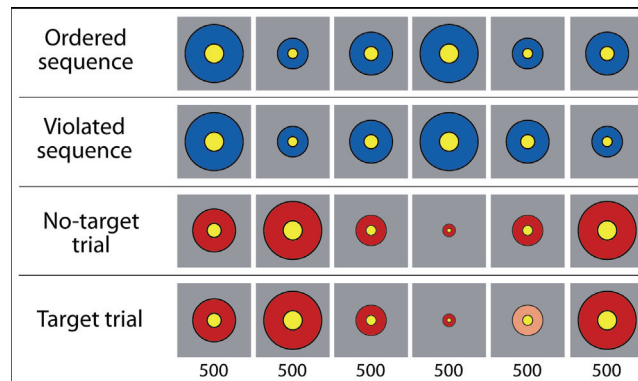


Figure 3.1: Schematic examples of four types of trials. Each trial started with a cue and was followed by six stimuli, all presented successively with the duration of 500 msec and without a temporal gap. The response was given at the end of each trial. In Ordered sequences the first three stimuli represented a sequential pattern which was then correctly repeated. Violated sequences also started with the pattern of three stimuli which was followed by the presentation of a sequential deviant (reversed order of 2nd and 3rd stimulus of the original sequence). No-target trials included the presentation of six standard stimuli of the same color and randomly varied size. Target trials included presentation of five standard stimuli among which one feature deviant was embedded (here a circle with lighter red color when compared to the standard circles presented at the 5th position within the trial).

3.1.4 Data acquisition

Imaging was performed at 3T on a Siemens Trio system (Erlangen, Germany). Functional images in-plane with the anatomical images were acquired using a gradient-echo echo planar imaging (EPI) sequence with an echo time (TE) of 30 msec, a flip angle of 90° and a repetition time (TR) of 2000 msec. 26 functional slices were acquired parallel to the bicommissural plane (AC-PC) (thickness 4 mm, interslice gap 0.4 mm) covering the whole brain. Simultaneously with the fMRI, EEG signal was also recorded.¹ In order to visually monitor this signal, acquisition of slices within the TR was arranged so that the slices were all rapidly acquired during the first 1800 msec, followed by a 200 msec period of no acquisition to complete the TR. The matrix acquired was 64 x 64 with a field of view of 192 mm, resulting in an in-plane resolution of 3 mm x 3 mm. A total of 1247 volumes was acquired.

3.1.5 Data analysis

Functional data were motion-corrected off-line with the Siemens motion correction protocol (Siemens, Erlangen, Germany). To correct for the temporal offset between the slices acquired in one scan, a cubic-spline-interpolation was applied. A temporal high pass filter with a cut-off frequency of 1/70 Hz was used for baseline correction, removing low-frequency drifts in an fMRI time series (frequencies due to global signal changes, e.g., respiration). Spatial Gaussian smoothing was applied using a Gaussian filter with 5.65 mm full width at half maximum (FWHM). Contrast images, namely estimates of the raw-score differences between specified conditions, were generated for each subject. Single-participant contrast images were entered into a second level random effects analysis for each of the contrasts. The group analysis consisted of one-sample t-tests across the contrast images of all subjects which indicated whether observed differences between conditions were significantly different from zero ($z > 3.09$, $p < 0.001$, uncorrected) (Holmes & Friston, 1998). In a second step, the results were corrected for multiple comparisons using cluster-size and cluster-value thresholds obtained by Monte Carlo simulations at a significance level of $p = 0.001$. Thus, the reported activations are significantly activated at $p < 0.001$, corrected for multiple comparisons at the cluster level.

¹ The analysis of the recorded EEG signal was not successful due to high prevalence of non-systematic artefacts identified on some of the recorded electrodes, including the one used for recording the electrocardiogram. Since this electrode was crucially important for correcting systematic artefacts arising from the recording conditions within the fMRI environment, this correction could not be performed to a satisfactory degree. Thus, this EEG data set was not further analyzed.

3.2 Results

3.2.1 Behavioral performance

Average accuracy expressed as the proportion of correct responses was 0.91 ± 0.014 for Ordered sequences, 0.88 ± 0.034 for Violated sequences, 0.89 ± 0.026 for No-target trials and 0.86 ± 0.034 for Target trials. A repeated-measures ANOVA with two two-level factors Task (SPT, target detection) and Deviant (deviant present, deviant absent) was used in order to compare the performance in different tasks. The results revealed no statistically significant main or interaction effects (Task: $F(1,13) = 0.34$, $p = 0.57$; Deviant: $F(1,13) = 1.26$, $p = 0.28$; interaction Task x Deviant: $F(1,13) = 0.01$, $p = 0.98$).

3.2.2 MRI data

Brain areas with significantly higher BOLD response during the presentation of sequential deviants in comparison to the presentation of sequence repetitions are listed in Table 3.1 (contrast Violated sequence vs. Ordered sequence). The majority of activations were distributed dominantly within the right hemisphere encompassing several lateral prefrontal and premotor areas. Additional strong foci of activations included the right frontal opercular cortex, the pre-supplementary motor area (pre-SMA) and bilateral paramedian and lateral portions of the posterior cerebellum (Figure 3.2A). Brain areas with significantly higher BOLD response during presentation of feature deviants in comparison to trials containing only standard stimuli in the target detection task are listed in Table 3.1 (contrast Target trial vs. No-target trial). Although distributed bilaterally, activations were somewhat more pronounced in the left hemisphere with the exception of frontal activations which showed a right bias. The majority of activations were located within lateral parietal and temporal cortices, encompassing middle and inferior temporal gyri (MTG and ITG) bilaterally, left inferior parietal lobule (IPL), and the bilateral superior parietal lobule (SPL) with some additional medial, frontal and subcortical activation foci (Figure 3.2B).

In order to identify brain areas involved in processing regular sequences, ordered sequencing trials were compared with the no-target trials from the control task. These results are presented in Appendix A.

Table 3.1: Activation foci related to deviant detection in Experiment 1: Anatomical brain area, hemisphere location, Talairach coordinates (x,y,z), maximal z -score and size of significant activations

Brain region (BA)	Hem	Talairach Coordinates			max z-score	mm ³
		x	y	z		
Violated vs. Ordered sequence						
pre-SMA	R	4	15	48	4.77	2160
MFG (6 / 8)	R	46	3	45	4.61	
MFG (9 / 46)	R	49	21	36	4.81	6021
	R	46	33	18	4.46	
FOP	R	34	27	0	4.18	
IFG (47)	R	41	33	3	3.15	1755
CE	R	22	-75	-21	4.57	1593
CE	L	-26	-63	-24	4.44	4509
Target-trial vs. No-target trial						
PCU (7)	L	-11	-69	57	3.80	8856
	R	13	-72	54	4.61	
SPL / OGs (7 / 19)	R	34	-75	39	5.18	
IPL / STS (39)	R	40	-51	27	3.91	8721
MTG (21 / 37)	R	55	-57	3	4.83	
	R	58	-27	-12	4.27	
ITG (20)	R	49	-30	-18	3.62	
IPL (39 / 40)	L	-47	-54	45	4.37	16983
	L	-53	-48	36	4.90	
MTG (21 / 37)	L	-53	-54	3	4.85	
	L	-53	-33	-6	4.35	
pCG (31)	R	4	-36	45	4.30	1701
SFG (6 / 8)	R	22	6	51	4.56	1458
IFG (45 / 47)	R	46	30	0	3.89	1917
CE	L	-20	-81	-27	3.92	1971

Note: BA: Brodmann area; CE: cerebellum; FOP: frontal operculum; IFG: inferior frontal gyrus; IPL: inferior parietal lobule; ITG: inferior temporal gyrus; MFG: middle frontal gyrus; MTG: middle temporal gyrus; OGs: superior occipital gyrus; pCG: posterior cingulate gyrus; PCU: precuneus; pre-SMA: pre-supplementary motor area; SFG: superior frontal gyrus; SPL: superior parietal lobule; STS: superior temporal sulcus.

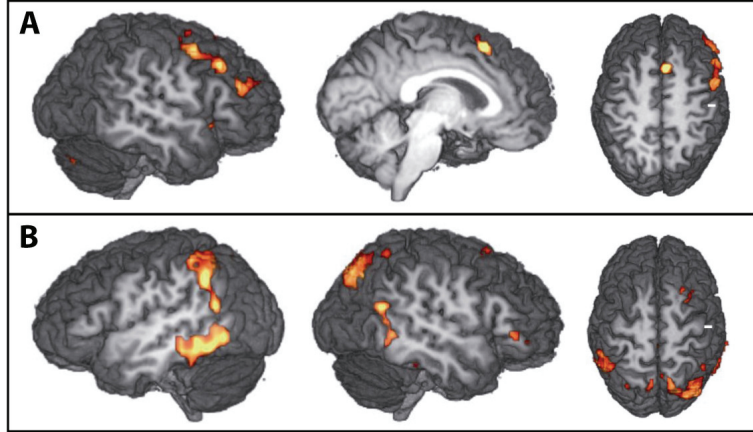


Figure 3.2: A: Brain correlates of detecting sequential deviants (Violated vs. Ordered sequence). From left to right: right hemisphere from parasagittal sections ($x=52$, $x=4$); axial section ($z=49$). B: Brain correlates of detecting feature deviants (Target trial vs. No-target trial). From left to right: left hemisphere from parasagittal section ($x=-51$); right hemisphere from parasagittal section ($x=50$); axial section ($z=58$). A and B: Group-averaged statistical maps ($N=14$) are superimposed onto an individual brain which was chosen for being the most similar to the average brain of all subjects participating in the experiment and scaled to the standard Talairach brain size (Talairach & Tournoux, 1988).

3.3 Discussion

Experiment 1 investigated the neural correlates of detecting sequential and feature deviants, namely stimuli violating two different types of expectations formulated within trials of equivalent perceptual organization. Presenting sequential violations triggered an increase of activation in the lateral and medial premotor cortex and the cerebellum, a subset of brain areas which also support regular (ordered) sequence processing (c.f., Schubotz & von Cramon, 2003). Within the medial premotor cortex, a shift of activation was identified when comparing ordered and violated sequences. Specifically, although the engagement of SMA was sufficient for supporting ordered sequence processing, a mismatch between expected and presented stimuli triggered by the presentation of a sequential deviant additionally recruited the pre-SMA (Picard & Strick, 1996, 2001). The activation of the pre-SMA has, in contrast to SMA, previously been reported in more complex aspects of hierarchical processing including sequence updating and switching (Bapi, Miyapuram, Graydon, & Doya, 2006; Jancke, Himmelbach, Shah, & Zilles, 2000; Kennerley, Sakai, & Rushworth, 2004). It is hence plausible to suggest that the involvement of pre-SMA in processing sequential deviants in the

present study reflects restructuring of the original forward model triggered by the mismatch between expected and presented stimuli. This restructuring was possible because the sequential violation always included the reversal of the order of two last stimuli within the sequence, so the observers could have, after detecting the deviant, changed the underlying forward model and correctly predicted the last stimulus in the trial. Both regular sequence processing and detecting sequential deviants additionally activated mainly the parameian and the lateral portions of the posterior cerebellum. Following the internal model account, the cerebellar activation in perceptual prediction could reflect generating a prediction about the change in sensory input (i.e., corollary discharge or expected re-afference) on the basis of the information provided by the pre-SMA, i.e., efference copy (Schubotz, 2007). In this view, the cerebellum could mediate top-down influences from the pre-SMA into specific perceptual and proprioceptive expectations within the parietal cortex which may be more pertinent in the context of deviant detection where such expectations need to be updated. On a more general level, the cerebellum has been implicated in controlling attentional resources, monitoring and adjusting the acquisition of sensory data as well as error detection and error correction (Leiner, Leiner, & Dow, 1991; Tesche & Karhu, 2000). In line with this, Tesche and Karhu (2000) suggested that the cerebellum, as a structure which can maintain a template of predictable sensory input, is specifically involved in immediate processing of temporal deviants. Given that the cerebellum was now engaged in processing deviants defined by other stimulus features, it is possible to suggest that its involvement in processing deviants is probably not restricted to those violating expectations regarding temporal patterns.

In addition to increasing the activity within areas supporting regular perceptual prediction, presentation of sequential deviants also evoked activations within brain areas outside the standard sequencing network. This primarily included the dorsolateral prefrontal cortex (dlPFC, lateral BA 9 and 46), a region implicated in working memory processes including information monitoring and manipulation (not the pure maintenance) (Petrides, 2005). The obtained results also indicate involvement of the ventrolateral prefrontal cortex, namely the inferior frontal gyrus (BA 47), which is suggested to support active selection, comparison and judgement of memorized information (Petrides, 2005). In accordance with these suggestions, the joint activation of lateral prefrontal areas in the present study may reflect a controlled process of verifying sequential regularity and active rearrangement of stimuli constituting the sequence after the deviant had been registered. In contrast, such manipulation of information was not required in regular sequence processing which could therefore be subserved by the parietal-premotor

network. The involvement of lateral prefrontal areas in violation detection most likely reflects an increased need for cognitive control (Wood & Grafman, 2003) and is not, like the contribution of the pre-SMA, lateral premotor cortex and the cerebellum, an extension of the initial involvement in supporting regular sequence processing.

Processing sequential deviants additionally activated right anterior frontal operculum (FOP), an area whose co-activation with dlPFC has previously been related to memory retrieval (Lepage, Ghaffar, Nyberg, & Tulving, 2000). Alternatively, this region could be more directly related to signalling the occurrence of a mismatch between perception and expectations which is in line with results showing its activation in detecting one's own errors (Klein et al., 2007; Ullsperger & von Cramon, 2001) and violations of rule-defined structure in artificial grammar (Friederici, Bahlmann, Heim, Schubotz, & Anwander, 2006). Most activations evoked by sequential violations were strongly right lateralized, which can be related to previous results showing a right hemispheric bias in target or violation detection (Bledowski et al., 2004; Huettel et al., 2002; Stevens et al., 2005b). In addition, it has been suggested that the right dominance may be specific to short-term violations of complex patterns requiring a substantial need for information retrieval (Tervaniemi et al., 2000) which may be more lateralized to the right cerebral hemisphere (Krause et al., 1999; Tulving, Kapur, Craik, Moscovitch, & Houle, 1994).

The target detection task as designed within the present study is similar, but not completely equivalent, to the classical oddball paradigm which entails a presentation of a train of frequent, standard stimuli in which randomly distributed infrequent events are embedded (Sutton et al., 1965). The similarity of the requirements within these two tasks was reflected in the underlying brain activations. The majority of activations obtained in contrasting trials containing the feature deviant with those which included only standard stimuli were bilaterally distributed within parietal and temporal lobes, particularly encompassing the middle and inferior temporal gyri (MTG; ITG), temporo-parietal junction (TPJ), inferior parietal lobule (IPL) and superior parietal lobule (SPL). This network is highly similar to that identified by studies which used the classical oddball task that was discussed within the *Theoretical Background* of the present thesis. The identified domination of the posterior parietal and temporal areas in the current context is in line with processing requirements in the current study. In particular, elaborate perceptual processing of the feature deviants was necessary as they were not perceptually salient or identical across all trials in the experiment. Thus,

a very pronounced involvement of bilateral posterior parieto-temporal areas in this context can be related to the suggestion from Kiehl et al. (2001), who argued that the involvement of posterior brain regions in detecting pre-defined targets is usually less pronounced when compared to the detection of novel stimuli which require more visuo-spatial processing by areas supporting object recognition, spatial attention, color and form processing. This can be related to the current experiment because feature deviants were, although clearly task-relevant, also perceptually novel. In addition to the posterior cortices, the obtained results indicate engagement of prefrontal areas in detecting feature deviants, which is also in line with findings from previous studies (Casey et al., 2001; Stevens et al., 2000).

Overall, the results of the present study indicate the involvement of distinct networks in detecting different types of events deviating from a standard context defined by stability or continuity of presented events. While requiring comparable perceptual and attentional engagement, the two tasks differently defined the standard context, basing it on sequential structure or order of stimuli in SPT in contrast to their physical similarity in the target detection task. The expectations regarding the incoming stimuli which could be formed in the two tasks differed in their specificity, type and origin, which is reflected in the dissociated pattern of activations following deviant presentation in the two task contexts.

4 Experiment 2. Temporal characteristics of violation detection in perceptual sequencing

The second study conducted within the present thesis was directly motivated by the findings from *Experiment 1* which showed that different brain networks are involved in processing sequential and feature deviants. In the present experiment the same two phenomena were investigated, with the focus now being directed to the temporal dynamics of these processes. In addition, this experiment investigated the role of attention in detecting deviants in both task contexts. In order to address these questions, an EEG study was conducted in which ERP components elicited by sequential and feature (non-sequential) deviant events under different attentional conditions were compared. In one experimental condition, the attention of participants was directed towards the property which was occasionally violated (sequential structure defined by the order of stimuli or physical characteristics of individual stimuli), while in the other the deviant occurred in the unattended stimulus dimension. The paradigm used within this study was very similar to the one described within the previous experiment. Specifically, all of the trials within the present experiment included a presentation of nine stimuli, circles with a centrally positioned fixation cross. This cross was black in the majority of stimuli which qualified these events as standard feature stimuli. Occasionally, a stimulus with a gray fixation cross was presented among these standard events, constituting a feature deviant. The order of stimulus presentation within each trial was always organized in such a way that three stimuli constituted a sequence which was later repeated two times. Thus, the number of sequence repetitions in this experiment was higher than in *Experiment 1*. In some trials the last repetition of the sequence included a reversal in the order of two stimuli, constituting a sequential deviant. In half of the trials the participants' attention was directed to-

ward the order of presented stimuli (sequential structure) which was accomplished by engaging participants in the serial prediction task (SPT) within which they had to indicate whether a sequential violation occurred during the trial or not. In the other half of the trials participants attended to the physical properties of individual stimuli while being engaged in the target detection task. Here, their task was to indicate whether a feature deviant was present within the trial or not. Therefore, the tasks employed within this study were very similar to the ones used within the previously described *Experiment 1* with the difference that the two deviant types could now occur either in the attended or ignored trial dimension. The presentation of task-relevant deviant events in both task contexts was expected to elicit an early negative (N2-like) and a late positive (P3-like) response which would, based on the described results from the fMRI study, somewhat differ in terms of their topography and potentially latency. Since the results from *Experiment 1* revealed a dominant contribution from right-lateralized prefrontal and premotor regions in detecting sequential in contrast to the identified engagement of parietal and temporal regions in detecting feature deviants, for the present experiment it was expected that the topography of ERPs elicited by sequential deviants should have a more anterior and right-lateralized distribution. In addition, it was assumed that presentation of sequential deviants in trials in which participants attended to the physical features of presented stimuli (unattended deviants) may not elicit any specific responses, because it was previously argued that attention towards the sequential structure may constitute a necessary prerequisite for the involvement of premotor-parietal system in prediction within perceptual sequences (Schubotz & von Cramon, 2002b).

4.1 Methods

4.1.1 Participants

Fourteen healthy volunteers (7 male, 2 left-handed, mean age 24.9 years) with normal or corrected-to-normal vision participated in the experiment. None were taking any medication that might affect the central nervous system.

4.1.2 Stimuli and task

Each trial included the presentation of nine visual stimuli with a duration of 500 msec each (immediately succeeding each other) and a response window of 1500 msec, during which a question mark was displayed on the screen. During the 500

msec interval until the beginning of the next trial, a fixation cross was displayed. The stimuli used in *Experiment 1* were adjusted for this study so that a fixation cross was added in the centre of the circle. As in *Experiment 1*, a sequence was defined as the pattern of three stimuli presented at the beginning of each trial. Following the initial presentation, it was repeated two times, amounting to nine stimuli within a trial. Sequential standards or ordered sequence trials included two correct repetitions of the sequence in contrast to sequential deviants which included one repetition and one reversal of order of either the 1st and 2nd or the 2nd and 3rd stimulus. As mentioned before, each circle contained a fixation cross that was colored either in black or in gray (75% color change). Feature standards refer to stimuli in which the fixation cross appeared in black color in contrast to feature (non-sequential) deviants which contained a gray fixation cross. In the case of these events, color change could occur in positions 3, 4, 5 or 6 with 5% probability each and in positions 7 or 8 with 15% probability each. Throughout the experiment, the probability of occurrence of both violations was 50%.

The occurrence of sequential and feature violations was counterbalanced within participants. Stimulation was randomized individually for each participant, and was presented twice in the experiment. In two successive parts of the experiment (experimental blocks) participants completed two different tasks on the stimuli. They either judged the sequential correctness within the serial prediction task (SPT) or monitored the sequence for feature violations in the target detection (feature) task. Examples of different types of trials are presented in Figure 4.1. In both tasks, participants responded by button presses with their left and right index fingers. Button-response assignment was counterbalanced across participants. Participants completed five blocks comprising 48 sequences of each task amounting to the total of 480 sequences presented throughout the experiment. Each sequence lasted for 6500 msec and the overall duration of an experimental session amounted to 52 minutes.

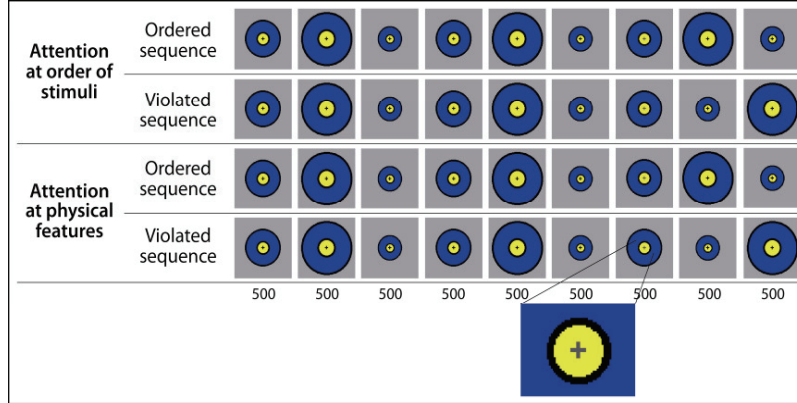


Figure 4.1: Schematic examples of four types of trials. Each trial included the presentation of nine stimuli, all presented successively with the duration of 500 msec and without a temporal gap. In Ordered sequence trials the first three stimuli represented a sequential pattern which was then correctly repeated two times. Violated sequence trials also started with the 3-stimulus sequential pattern which was followed by its one repetition and one violation (here reversed order of 2nd and 3rd stimulus of the original pattern). Majority of stimuli within the experiment were standards, namely circles with a black fixation cross among which occasional feature deviants with a gray fixation cross were presented (highlighted stimulus). In half of the trials attention of participants was directed towards the sequential structure (serial prediction task) while in the other half they attended to physical features of stimuli (target detection task). Task of the participant was to determine if a violation was presented during the trial (sequential in SPT; feature in target detection) and respond at the end of each trial.

4.1.3 Data analysis

Separately for each type of violation (sequential / feature), records were sorted as a function of stimulus type (standard / deviant), position (1-9), and participants' attentional focus as defined by task instruction (violation attended / unattended). Stimuli were analyzed only when there was no previous violation of either type in the sequence. Deviance-related difference waves per type of violation (sequential / feature) and attentional focus (attended / unattended) were formed by subtracting the ERPs elicited by standards from those elicited by deviants in corresponding positions (7-8 for sequential standards and deviants, 3-8 for feature standards and deviants). Average ERP amplitudes of the deviant-minus-standard difference waves per condition were measured in 40 msec intervals around the relevant grand-average peak. Measurements were taken over Cz, Pz and corresponding lateral electrodes (cf., Figure 4.2). Difference wave amplitudes were tested against zero in one-sample, two-tailed t-tests over Cz (N1, N2), and Pz (P3), re-

spectively. The amplitudes of components elicited by the two deviant types were mutually compared using paired, two-tailed t-tests. An analysis of topography differences for the identified N2 and P3 components was conducted using an analysis of variance (ANOVA) including the factors Task (SPT, target detection), Frontality (frontal / central / posterior), and Laterality (left / center / right). The Greenhouse-Geisser correction (Greenhouse & Geisser, 1959) was applied when the assumption of sphericity was violated. In addition, latency of N2 and P3 elicited by the two deviant types was measured. For N2 individual negative peaks were searched over Cz from 200 to 380 msec while for P3 individual positive peaks were searched over Pz from 420 to 680 msec. The latencies identified for components elicited by two deviant types were mutually compared using paired, two-tailed t-tests.

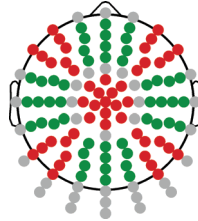


Figure 4.2. Layout of electrode positions. Highlighted are the central and lateral electrodes which were chosen for the measurement of average ERP amplitudes.

4.2 Results

4.2.1 Behavioral performance

Average accuracy expressed as the proportion of correct responses was 0.95 ± 0.012 for Ordered sequences, 0.94 ± 0.017 for Violated sequences, 0.96 ± 0.011 for No-target trials and 0.90 ± 0.028 for Target trials. A repeated-measures ANOVA with two two-level factors Task (SPT, target detection) and Deviant (deviant present, deviant absent) was used in order to compare the performance in different tasks. The results revealed a statistically significant main effect of the factor Deviant ($F(1,13) = 9.34$, $p = 0.009$) and the interaction effect Task x Deviant ($F(1,13) = 4.69$, $p = 0.049$). The main effect of factor Task was not statistically significant ($F(1,13) = 1.04$, $p = 0.33$). Pairwise post-hoc comparisons revealed higher accuracy rates in trials of the target detection task in which the feature deviant was not present in comparison to those in which it was present

($t(13) = 2.78$, $p = 0.02$), while the accuracy in violated and ordered SPT trials did not mutually differ ($t(13) = 1.79$, $p = 0.26$).

4.2.2 Electrophysiological data

Standard, deviant, and deviant-minus-standard ERPs over Cz and Pz were identified separately per task and attention condition (Figure 4.3; voltage distributions on Figure 4.4). Attended sequential violations elicited significant N2 ($t(13) = 2.238$, $p = 0.043$) and P3 ($t(13) = 5.284$, $p < 0.001$). Unattended sequential violations elicited significant N2 ($t(13) = 2.388$, $p = 0.033$), but not P3 ($t(13) = 1.377$, $p = 0.192$). Post-hoc analyses revealed that the appearance of N2 in the unattended condition was due only to those participants who had completed the attended sequential condition first (participants who first completed the SPT: $t(6) = 2.7284$, $p = 0.034$; participants who first completed the feature task: $t(6) = 0.63986$, $p = 0.54591$). Attended feature violations elicited a significant N1-enhancement ($t(13) = 2.163$, $p = 0.0497$) as well as N2 ($t(13) = 2.452$, $p = 0.029$) and P3 ($t(13) = 8.340$, $p < 0.001$) components. For unattended feature violations, no significant activation was observed in the relevant component windows (N1: $t(13) = 1.710$, $p = 0.111$; N2: $t(13) = 0.800$, $p = 0.438$; P3: $t(13) = 0.763$, $p = 0.459$).

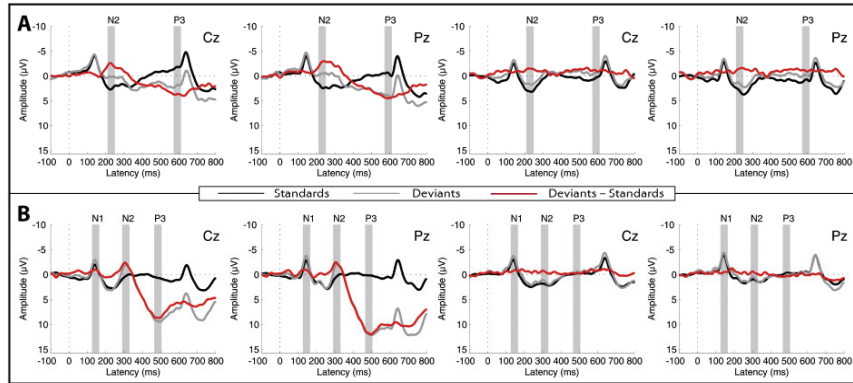


Figure 4.3: Event-related potentials (waveforms and difference waves) triggered by the presentation of different types of deviant stimuli. Electrodes Cz and Pz are presented for all conditions. A: From left to right: Sequential deviant attended and non-attended. B: From left to right: Feature deviant attended and non-attended.

A comparison of components elicited by attended sequential vs. attended feature deviants showed no amplitude difference in N2 over Cz (sequential: -2.27 ± 1.01 μV , feature -1.98 ± 0.81 μV ; $t(13) = 0.225$, $p = 0.825$), but a statistically

significant amplitude difference in P3 over Pz (sequential: $4.44 \pm 0.84 \mu\text{V}$, feature $-11.74 \pm 1.41 \mu\text{V}$; $t(13) = 5.144$, $p < 0.001$). Furthermore, a significant latency difference in N2 over Cz (sequential: $252.8 \pm 9.53 \text{ msec}$, feature $311.4 \pm 6.61 \text{ msec}$; $t(13) = 6.620$, $p < 0.001$) and in P3 over Pz (sequential: $585.2 \pm 20.01 \text{ msec}$, feature $527.1 \pm 18.39 \text{ msec}$; $t(13) = 2.638$, $p = 0.02$) was shown. An analysis of topography differences for N2 and P3 components for attended sequential and feature violations showed significant effects of interaction between factors Task and Frontality (N2: $F(1.3, 21.3) = 7.19$, $p = 0.012$; P3: $F(1.2, 15.3) = 15.71$, $p = 0.001$), Task and Laterality (N2: $F(2, 26) = 4.65$, $p = 0.019$; P3: $F(2, 26) = 3.61$, $p = 0.041$), and, in case of the P3, interaction Task, Frontality and Laterality ($F(2.6, 33.7) = 3.18$, $p = 0.043$).

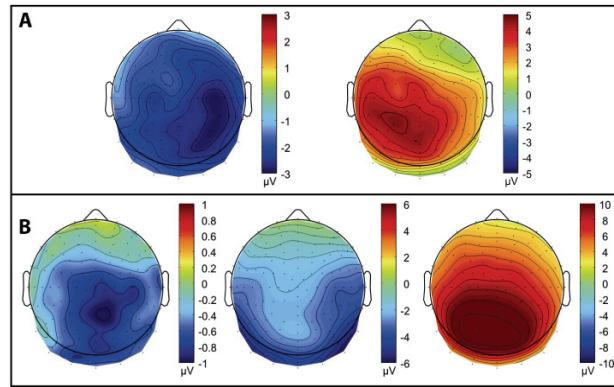


Figure 4.4: Voltage distributions for the identified ERP components in the attended conditions. A: From left to right: N2 and P3 for sequential deviants; B: From left to right: N1, N2 and P3 for feature deviants.

4.3 Discussion

The present experiment addressed the temporal course of processing violations of sequential and purely physical (feature-based; non-sequential) expectations under different attentional conditions. Specifically, the role of participants' attentional involvement in detecting sequential and feature deviants was addressed by investigating conditions in which participants' attention was directed towards the property which was occasionally violated (sequential structure or physical characteristics of stimuli) and the ones in which the deviant occurred in the unattended stimulus dimension. The obtained results indicate that both attended sequential and feature deviants elicited a negative component peaking around 250-350 msec

which is suggested to represent N2b, an ERP component which reflects voluntary processing elicited by template mismatch or the deviation from expectation of the standard when subjects selectively attend to deviations in the oddball task (Patel & Azzam, 2005). Although often associated with the oddball paradigm, N2b has previously also been identified in other contexts, including deviant detection within learned stimulus or motor sequences (Rüsseler, Kuhlicke, & Munte, 2003). Furthermore, in a study investigating explicit and implicit sequence learning, Ferdinand et al. (2008) reported an increase in the amplitude of N2b during the course of sequence learning, indicating that this component may reflect the development of knowledge about the sequential structure and the formulation of expectations which can be build based on it. In addition to the N2b, both sequential and feature deviants in the present experiment elicited a later positive component which peaked between 500-600 msec, namely P3, an ERP which reflects processing underlying the evaluation of the stimulus (Coles, Hendrikus, Scheffers, & Otten, 1995). Specifically, the component identified in the present experiment is suggested to be P3b, an ERP response which is elicited when the participants attend to the deviant stimulus (Patel & Azzam, 2005; Soltani & Knight, 2000). Its functional role has specifically been related to the updating of the underlying model of the relevant stimulus structure (Polich, 2007) or the post-categorization decision-related processing (Nieuwenhuis, Aston-Jones, & Cohen, 2005).

Although attended feature and sequential deviants in the present study elicited similar event-related components, substantial differences in their features also appeared. Specifically, the identified components differed in their latency and topography as well as the amplitude in case of P3b. Furthermore, only the appearance of features deviant elicited an enhancement of N1, an early negative component which peaked after 100 msec following stimulus presentation. This pattern of results suggests rather significant differences across several stages of processing deviant events in the two task contexts. In the very early stage, feature deviants elicited an enhanced N1 response, an obligatory ERP component peaking around 100 msec after stimulus onset which is, due to sensory adaptation, typically reduced for repetitive standard events (Näätänen & Picton, 1987). This enhanced processing of these events can be attributed to the change in physical characteristics of individual stimuli which defined feature deviants in contrast to the standards which shared the task-relevant physical feature and were therefore processed in a slightly attenuated fashion. Absence of such enhancement of N1 in case of sequential deviants can be attributed to the lack of an immediately visible physical change in the stimulus signalling this violation type.

In addition to this early difference, detection of sequential and feature deviants differed also in later processing stages. Specifically, the two event-related components which were elicited by both attended types of deviants, N2b and P3b, differed in terms of both latency and topography as well as, in case of P3b, amplitude across the two conditions. First of all, the latency of N2b was shorter for sequential deviants, indicating a somewhat faster initial registration of the mismatch between expected and presented stimuli in this condition. However, this trend then reversed in case of the P3b which had a shorter latency in case of feature deviants. Taking into account previous findings showing that latency of P3 increases with increasing difficulty of the decision (Kutas, McCarthy, & Donchin, 1977) and the suggestion that it may be used as an indicator of „stimulus evaluation time“ (Donchin & Coles, 1988), the delayed P3b elicited by sequential deviants indicates that the overall decision process was prolonged in this condition. Interestingly, P3b elicited by sequential deviants did not just show longer latency, but also a smaller amplitude in contrast to the one identified in case of feature deviants which was characterized by a very sharp onset and offset. These differences in P3b characteristics could, at least in part, arise from variable strategies employed by participants for solving the SPT. For example, as reported during the post-experimental briefing, while some participants made their decisions based on the memorized size of individual stimuli, others were more focused on the mutual relations of neighbouring stimuli. More importantly, some participants adopted the strategy of verifying the sequential deviation using two consequently presented stimuli while others made their decision right after the presentation of the first stimulus of the violated pattern. Such individual strategy differences are crucially important because they suggest that the timing of decision varied across participants. Consequently, averaging across participants could have artificially reduced the amplitude of this ERP. Except for the described differences in amplitude and latency, both N2b and P3b also showed differences in topography across the two conditions. Generally, such differences in topography suggest that the neural generators underlying the components elicited by the two deviant types are not identical. Such an interpretation is in line with findings showing that P3 does not appear to be a unitary component, but could represent activity of widely distributed sources whose coupling may depend on the task context in hand (Johnson, 1986). In the context of the present study, a more anterior and right-lateralized distribution of the identified components in case of sequential deviants is in line with the more anterior, right-lateralized distribution of regions involved in detecting sequential deviants identified in *Experiment 1*.

In addition to investigating the processing of attended sequential and feature deviants, within the design of the present study it was possible to address the processing of unattended, task-irrelevant sequential and feature deviants. The obtained results show that non-attended deviants, in contrast to the attended ones, failed to evoke a strong response in both task contexts. Although a N2 component was identified in response to the unattended sequential deviants, it was only present in those participants who had completed the attended condition before. In this subgroup of participants, previous knowledge related to the existence of an ordered trial structure was transferred to the trials in which only physical features of individual stimuli needed to be monitored. Although no longer relevant, the knowledge about the sequential structure affected the participants response to the presented deviants. This influence is in line with findings showing that informing respondents about task irrelevant aspects of presented stimuli can influence their subsequent processing and performance (Mack, Tang, Tuma, Kahn, & Rock, 1992). In contrast, the group of participants which was completely naïve with respect to the sequential structure of the trial failed to register the existence of unattended sequential deviants. Therefore, in absence of prior knowledge, attentional involvement was necessary for detecting deviants in both task contexts which indirectly suggests that it was also needed for learning the sequential structure within trials. This is in line with the suggested importance of attentional involvement in learning perceptual sequences within the sensorimotor forward model framework (Schubotz, 2007). In addition, it is in line with findings showing that explicit learning is needed for acquiring knowledge related to stimulus and response dependencies in sequence processing in contrast to implicit learning which may only lead to the learning of response contingencies (Rüsseler & Rösler, 2000) and findings showing that explicit knowledge is more likely to be used for forming expectations about incoming stimuli (Willingham et al., 1989). However, in the present experiment, existence of prior explicit knowledge allowed a certain level of sequence learning even when the sequential structure itself was no longer attended. Since this learning was not identical to the one identified in attended trials, the differences and similarities between learning perceptual sequences under different attentional conditions needs to be further explored in future experiments.

5 Experiment 3: Violating expectations of different type in perceptual sequencing

The main goal of *Experiment 3* was to compare the process of detecting sequential deviants within different classes of perceptual sequences organized at a more abstract level of stimulus features. The main paradigm used within the current experiment was equivalent to the one used in the previous studies, namely the serial prediction task (SPT) within which a sequence of stimuli was presented and repeated either fully or with a sequential violation at the end of the trial. Stimulus sequences were defined by the order of three stimuli along one of the following relevant stimulus dimensions: object identity, spatial position or temporal duration (rhythm). Each stimulus was composed of two elementary forms placed on a virtual circle: while their appearance determined object identity, positioning on the virtual circle defined their spatial position and the presentation on the screen temporal duration. The difference between this and the versions of SPT used in previously presented experiments was that in this experiment, from one sequence repetition to the next, stimulus features outside the relevant dimension were varied. Consequently, sequence repetitions included the repetition of only relevant stimulus features while the irrelevant ones differed from the original sequence. For example, if the stimulus duration was a relevant feature, a repetition of the sequence was considered ordered as long as the duration of each of three stimuli was the same as in the original sequence regardless of what elementary forms the objects were comprised of or what position on the circle they occupied. Since it was previously shown that attending to different stimulus properties modulates the relative contributions of different portions of the basic premotor-parietal network (Schubotz & von Cramon, 2001a), the present experiment investigated the similarities and differences of the deviant detection process across these sequence

classes. Based on the results from *Experiment 1*, engagement of premotor and lateral prefrontal regions was expected to support the process of detecting violations within the three SPTs. However, a different pattern of activations was expected across these tasks, such that violating expectations pertaining to a particular stimulus feature would be reflected in the activation of brain areas usually associated with processing of that particular feature. Previous findings have indicated preferential involvement of the dorsal premotor cortex (PMC) in attending to spatial properties, the superior portion of the ventral PMC in attending to object and the inferiormost portion of the ventral PMC as well as frontal operculum to temporal (rhythmic) properties (Schubotz et al., 2008; Schubotz & von Cramon, 2001). Accordingly, the engagement of more dorsal premotor and prefrontal areas was expected following the presentation of violations within the position SPT whereas more ventral areas were hypothesized to be involved in detecting deviations of object and rhythm sequences.

5.1 Methods

5.1.1 Participants

30 right-handed, healthy male volunteers (mean age 26.7) participated in the study. All subjects reported to have normal or corrected-to-normal vision. Four participants were excluded from further analysis due to below-chance level performance in the SPT and one due to movement during the experiment. All subsequent analyses were performed on the data from 25 subjects.

5.1.2 Procedure

Participants were instructed and underwent a behavioural training session several days before the fMRI measurement in which they were trained to perform the three tasks until they reached a learning criterion of 75% correct responses. Prior to the main experiment on the day of the measurement, participants were additionally presented with the instructions and a five minute behavioural training session which included all tasks.

5.1.3 Stimuli and task

The stimulus material used in this study (Figure 5.1) included twelve different objects, each composed of a 25 mm circle (0.14° of visual angle) and a slightly smaller geometrical form, either a square or a circle, placed in its centre. The

colors of both geometrical forms could be red, yellow or blue, and they always differed between the two forms. Each stimulus display consisted of two identical objects presented on opposite locations of a virtual circle with a radius of 6 cm. A fixation cross was presented at the screen centre to facilitate constant visual fixation. Each stimulus was presented for either 300, 600, 900, 1200, 1500 or 1800 msec. Responses were made by pressing the left or right key of a standard response button box with the index and middle finger of the right hand.

Three different versions of the sequencing task, namely the serial prediction task (SPT; sequencing) and a control target detection task (Control) of equal trial organization were presented in a mixed trial design. Each trial included the successive presentation of 12 stimuli without temporal gaps, preceded by a task cue with the duration of 400 msec and followed by a 1500 msec response period and performance feedback lasting for 400 msec. During all other periods in the experiment a fixation cross was presented at the center of the screen. Overall trial duration was 14 seconds and, in order to improve temporal resolution, each trial occurred at four different offset points (0, 500, 1000 and 1500 msec) in relation to fMRI data acquisition (Josephs et al., 1997). During the course of the experiment the stimulus trials were interspersed with empty trials during which only a fixation cross was presented and no task was to be performed the participants.

In all three versions of the SPT, the participants attended to the order of presented stimuli in an attempt to extract and subsequently predict a specific repetitive pattern contained within them. Each trial started with a three-stimulus pattern defining a sequence which was then fully repeated two times. The last part of the trial entailed either one additional full repetition or a violation of the original three-stimulus sequence. The pattern of violation included reversal in the order of the 1st and 2nd or 2nd and 3rd element of the original sequence. The task of the participants was to indicate, in a forced-choice manner, whether the end of the trial entailed a violation or an ordered repetition of the original sequence. The sequential violations were presented in 50% of all trials. Participants were provided with feedback concerning the correctness of their response. The three versions of SPT differed in the stimulus dimension relevant for defining the repeating sequence (object, spatial position or temporal duration (rhythm)). In each version of the SPT one dimension was task-relevant and varied in an orderly manner in contrast to the two irrelevant, randomly varying dimensions. In the object serial prediction task (SPT-O), subjects attended to the stimulus identity which was defined by the color and form of the two objects contained in each stimulus. In the position serial prediction task (SPT-P), subjects attended to the

position of the elementary forms on the virtual circle while in the rhythm serial prediction task (SPT-R) they attended to their duration which formed a distinct rhythmic pattern.

Besides the three versions of SPT, the participants were presented with a control target detection task (Control) which was organized in an equivalent fashion as the SPT, but included stimuli presented in random order. The participants were instructed to attend to these trials in order to detect the presence of occasional targets which deviated from the remaining stimulus set in one of three possible ways: the two objects that constituted a stimulus were either not identical, not presented at the exactly opposite locations on a virtual circle or had unequal duration. The participants' task was to count such stimuli and respond whether an odd or even number of them was presented during the trial.

	Deviant							
Rhythm SPT								
	600	300	1500	600	300	1500	600	1500
Object SPT								
	600	300	1500	1800	300	300	1800	300
Position SPT								
	600	300	1500	900	1200	300	900	1200
Control task								
	600	300	1500	900	1200	300	900	1200

Figure 5.1: Schematic examples of the four tasks. Each trial started with a cue and was followed by 12 stimuli (here only 9 are shown to indicate how the full repetition (stimuli 4-6) differed from the original pattern (stimuli 1-3)), all presented successively without a temporal gap. The response was given at the end of each trial. In all versions of the SPT, Ordered sequences included the presentation of a three-stimulus sequential pattern defined by object, position or rhythmic properties which was correctly repeated three times. Violated sequences also started with a three-stimulus pattern after which its two repetitions and one violation (reversal of 1st and 2nd or 2nd and 3rd stimulus of the original sequence) were presented. The task of the participants was to monitor for the occurrence of such deviants. In the control task order of stimuli was randomized and the participants monitored for the occurrence of predefined deviants.

Across all trials in the experiment the order of stimuli was pseudo-randomized. The probability of each stimulus and stimulus category and that of transitions

between stimuli were balanced across different positions within the trial. In order to avoid any motor contributions to the tasks, participants' response was always required after the end of each sequence. The experiment included eight types of trials: Ordered and Violated object SPT trials, Ordered and Violated position SPT trials, Ordered and Violated rhythm SPT trials, Control trials with a deviant and Control trials without a deviant. Examples of different types of trials are presented in Figure 5.1. 21 trials of each type were used which, together with the 15 empty trials, amounted to the total of 183 trials presented in the course of the experiment.

5.1.4 Data acquisition

The experiment was carried out on a 3T scanner (Medspec S300, Bruker, Ettlingen). Functional images in-plane with the anatomical images were acquired using a gradient-echo echo planar imaging (EPI) sequence with an echo time (TE) of 30 msec, a flip angle of 90° and a repetition time (TR) of 2000 msec. 22 functional slices were acquired parallel to the bicommissural plane (AC-PC) (thickness 4 mm, interslice gap 1 mm) covering the whole brain. The matrix acquired was 64 x 64 with a field of view of 192 mm, resulting in an in-plane resolution of 3 mm x 3 mm. A total of 1290 volumes was acquired.

5.1.5 Data analysis

After performing motion correction, to correct for the temporal offset between the slices acquired in one scan, a cubic-spline-interpolation was applied. A temporal high pass filter with a cut-off frequency of 1/130 Hz was used for baseline correction, removing low-frequency drifts in an fMRI time series (frequencies due to global signal changes). Spatial Gaussian smoothing was applied using a Gaussian filter with 5.65 mm full width at half maximum (FWHM). Contrast images, namely estimates of the raw-score differences between specified conditions, were generated for each subject. Single-participant contrast images were entered into a second level random effects analysis for each of the contrasts. The group analysis consisted of one-sample t-tests across the contrast images of all subjects that indicated whether observed differences between conditions were significantly different from zero ($z > 3.09$, $p < 0.001$, uncorrected) (Holmes & Friston, 1998). The results were corrected for multiple comparisons using cluster-size and cluster-value thresholds obtained by Monte Carlo simulations at a significance level of $p = 0.005$, that is, the reported activations are significantly activated at $p < 0.005$, corrected for multiple comparisons at the cluster level. Additionally, a conjunc-

tion analysis of the calculated contrasts (Nichols, Brett, Andersson, Wager, & Poline, 2005) was calculated in order to identify common regions supporting the two conditions of interest.

5.2 Results

5.2.1 Behavioral performance

Average accuracy expressed as the proportion of correct responses was 0.90 ± 0.015 for Ordered object sequences, 0.86 ± 0.018 for Violated object sequences, 0.93 ± 0.123 for Ordered position sequences, 0.93 ± 0.174 for Violated position sequences, 0.95 ± 0.012 for Ordered rhythm sequences, 0.80 ± 0.026 for Violated rhythm sequences, 0.93 ± 0.016 for Control trials without a deviant and 0.93 ± 0.178 for Control with a deviant. A repeated-measures ANOVA with a four-level factor Task (SPT-O, SPT-P, SPT-R, Control) and a two-level factor Deviant (deviant present, deviant absent) was used in order to compare the performance in different tasks. The obtained results showed statistically significant main effects of Task and Deviant (Task: $F(3, 72) = 6.89$, $p < 0.001$, Deviant: $F(1, 24) = 15.49$, $p < 0.001$) such that the SPT-O and SPT-R were more difficult than SPT-P and the Control task as were the violated in contrast to ordered trials ($p < 0.005$). The interaction effect was also significant (interaction Task x Deviant: $F(3, 72) = 14.06$, $p < 0.001$). Post-hoc pairwise comparisons (two-tailed t-test) revealed that the violated sequence trials differed from the ordered ones only in the context of the SPT-R ($t(25) = 5.380$, $p < 0.001$).

5.2.2 MRI data

Brain areas with significantly higher BOLD response during the presentation of sequential deviants in the three classes of SPT as revealed through the comparison of violated and ordered sequence repetitions (contrasts: Violated object sequence vs. Ordered object sequence; Violated position sequence vs. Ordered position sequence; Violated rhythm sequence vs. Ordered rhythm sequence) are listed in Table 5.1 (see also Figure 5.2). Presentation of deviants in the SPT-O triggered only posterior activations in the right hemisphere encompassing the inferior parietal lobule (IPL) and middle temporal gyrus (MTG). Bilateral IPL was also activated in processing deviants within SPT-P and SPT-R. Additionally, sequential deviants within SPT-P triggered activations in the premotor cortex (PMC) and middle frontal gyrus (MFG), while those introduced into the SPT-R

elicited activations located more ventrally along the inferior frontal gyrus (IFG). Conjunction between all three contrasts revealed no common activations. In addition, SPT-O was directly compared to the other two versions of the SPT (SPT-P and SPT-R) in order to investigate whether this task engages prefrontal cortical regions more than the other two tasks. These results are presented in Appendix B.

Table 5.1: Activation foci related to deviant detection in Experiment 3: Anatomical brain area, hemisphere location, Talairach coordinates (x,y,z), maximal z-score and size of significant activations

Anatomy	Hem	Talairach Coordinates			z-score	mm ³
		x	y	z		
Violated vs. Ordered object sequence						
IPL (39 / 40)	R	55	-50	33	4.30	2862
	R	58	-50	21	4.16	
MTG (21)	R	58	-38	-3	4.27	
Violated vs. Ordered position sequence						
PMC	R	25	13	54	4.16	2970
MFG (9)	R	52	16	30	3.48	
PMC	L	-35	4	39	3.79	1350
MFG (6 / 8)	L	-44	10	45	3.97	
PCU (7)	R	1	-65	60	3.96	2862
IPL (39 / 40)	R	43	-41	51	3.90	1458
	L	-44	-50	51	4.39	2673
Violated vs. Ordered rhythm sequence						
IFG (45 / 47)	R	52	22	6	4.35	3888
PrCG / IFG (6 / 44)	R	40	13	24	3.81	
IPL (39 / 40)	L	-53	-50	39	3.81	1404
	R	55	-38	39	4.26	1944

Note: BA: Brodmann area; IFG: inferior frontal gyrus; IPL: inferior parietal lobule; MFG: middle frontal gyrus; MTG: middle temporal gyrus; PCU: precuneus; PMC: premotor cortex; PrCG: precentral gyrus.

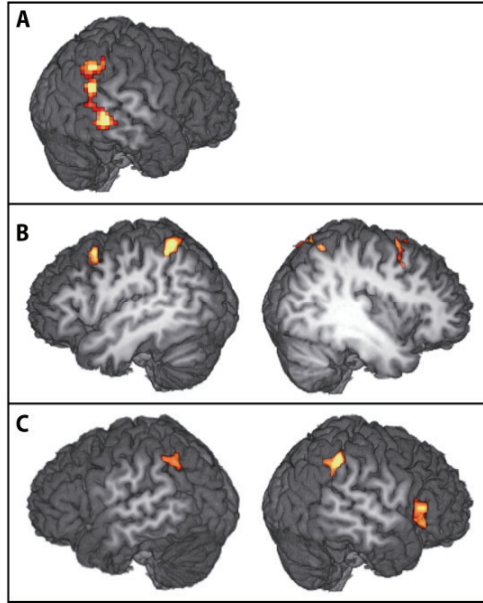


Figure 5.2: A: Brain correlates of detecting sequential deviants in SPT-O (Violated vs. Ordered object sequence). Shown is the right hemisphere from parasagittal section ($x=60$). B: Brain correlates of detecting sequential deviants in SPT-P (Violated vs. Ordered position sequence). From left to right: left hemisphere from parasagittal section ($x=-44$) and right hemisphere from parasagittal section ($x=38$). C: Brain correlates of detecting sequential deviants in SPT-R (Violated vs. Ordered rhythm sequence). From left to right: left hemisphere from parasagittal section ($x=-55$) and right hemisphere from parasagittal section ($x=46$).

5.3 Discussion

Experiment 3 investigated the process of detecting sequential deviants within different classes of perceptual sequences which differed based on the stimulus property which was used to define the sequential pattern. The obtained results indicate that deviants occurring within position and rhythm SPT triggered activations of the lateral parietal, premotor and prefrontal regions. Dissociation between these deviant types was also found: the activations within the position SPT were distributed more dorsally and posteriorly within lateral premotor and prefrontal regions in contrast to those from the rhythm SPT which were located more ventrally and anteriorly in the lateral ventral prefrontal cortex. Both types of deviants additionally triggered the activation of lateral parietal cortices. The identified dissociation between position and rhythm deviants confirmed the initial hypothesis. In contrast, detecting violations within the object SPT showed a unique pattern of parieto-temporal activation which was not accompanied by additional engagement of frontal areas.

The involvement of brain regions in detecting position and rhythm sequential deviants corresponds, to a certain degree, to the mapping which was previously identified in processing regular sequences defined by spatial or rhythmical prop-

erties of presented stimuli. Specifically, it was previously shown that perceptual predictions based on spatial stimulus properties activate the dorsal part of the premotor cortex in contrast to those based on rhythm properties which activate the inferiormost portion of the ventral premotor areas (Schubotz et al., 2008; Schubotz & von Cramon, 2001). This distribution of activations can be roughly related to findings showing that the premotor cortex contains a body representation comparable to the one contained in the primary motor cortex (Buccino et al., 2001; Corfield et al., 1999; Hamzei et al., 2002; O'Driscoll et al., 1995). A comparison of these patterns reveals that the dorsal part of the premotor cortex which is more engaged in processing spatial sequences is also associated with preparing reaching movements in contrast to the inferiormost portion of the ventral premotor areas which show a preference for rhythmic properties and are also involved in preparing actions related to vocal and auditory control (cf., Schubotz, 2004). Although these results suggest a close correspondence between categories of action and perception which are based on complementary limb and stimulus properties, this does not imply that event perception is always related to action or that it can be based on motor imagery. As suggested by Schubotz (2007), the neuro-anatomical ordering of forward models underlying different types of sequences could be based on the styles of transformations of the object or body part they describe. For example, the activation of the dorsal premotor cortex would be related to styles of transformation such as the rotation, the superior ventral premotor region to expansion or deformation and the inferiormost portion of the ventral premotor areas to pitch rising or loudening, to name just a few. Interestingly, activations triggered by the presentation of sequential deviants within the position and rhythm sequences not only showed a comparable differentiation across the dorsal-ventral dimension, but also a shift toward the more anterior prefrontal regions in comparison to more caudal and premotor regions activated in processing the respective ordered event structures. A similar shift was also observed in relation to deviant detection within *Experiment 1* in which the engagement of lateral premotor cortex in deviant detection was also identified.

When discussing the obtained results, findings showing the engagement of the dorsal premotor cortex (especially its more anterior parts together with the frontal eye fields) in attentional processing, especially spatial attention or voluntary attentional switching (Bledowski et al., 2004; Boussaoud, 2001; Chouinard & Paus, 2006) also need to be taken into account. Although the participants were constantly attending to spatial stimulus properties in position SPT, it is plausible to assume that the presentation of a deviant triggered an increase in their attentional engagement and more careful monitoring of the final stimuli which could provide

more information or confirm their initial decision related to the compromised correctness of the sequence. This could in turn lead to the involvement of dorsal premotor and posterior dorsal prefrontal areas as well as the dorsal parietal cortices in detecting such deviants. Comparable to this, violating rhythmical structure of a sequence also required more focused reassessing within this stimulus property, leading to an increase in the engagement of anterior IFG. The co-involvement of IPL in this context is plausible taking into account findings showing that this region is, together with the inferiormost portion of the ventral premotor cortex, involved in formulating temporal expectations (Coull & Nobre, 2008). The overall pattern of results pertaining to spatial and rhythm deviants is also in line with the findings from Marois et al. (2000) who have shown partial preferential activation of dorsal brain regions in detecting spatial oddball stimuli. In contrast, events which violated the rhythmical trial structure lead to the involvement of Broca's area which has previously been shown to be involved in temporal as well as music processing (Marcus et al., 2003; Patel, 2003).

Unlike the position and rhythm deviants, events which violated expectations related to object identity elicited only an activation in the inferior parietal and temporal cortices, encompassing the temporo-parietal junction (TPJ). This activation partially overlapped the one identified in processing deviants within the rhythm, but not position SPT. This region has previously been related to detection of salient and novel events, regardless of whether this salience is related to the current behavioral context or not (Downar, Crawley, Mikulis, & Davis, 2002). Kiehl et al. (2001) have previously suggested that a strong activation of posterior brain regions in detecting rare events may reflect a need for more visuo-spatial processing supporting object recognition, spatial attention, color and form processing. Since participants had to attend to detailed stimulus features in order to verify that an object deviant had been presented in the present context, such an analysis was very likely to be required in the present context. A distinct pattern of activations in processing object in contrast to position and rhythm deviants is interesting because successively presented objects of different identity are very difficult to relate one to another because they do not promote a clear transformation style. Generally, transformations afforded by position and rhythm stimulus dimensions are more natural which makes them more accessible to processing supported by premotor-parietal loops (Schubotz, 2004). For instance, while rotations, volume changes or accelerations may be smooth and therefore easily accessible to forward modelling, deformations based on changes of both form and color represent less natural transformations. Although one can imagine a slow and continuous change of only shape or color (e.g., during sunset), object proper-

ties in the present experiment were defined by a combination of these two features which changed simultaneously from one object to the next. That kind of change is discontinuous and might, even in ordered sequences, be more demanding because these stimuli incorporate more information which needs to be remembered in order to correctly solve the task. An indication that this might indeed be the case comes from the direct comparison of SPT-O and the other two tasks, revealing that the object task indeed recruits the lateral prefrontal cortical regions comparatively more than SPT-P and SPT-R (see Appendix B). If this is so, then the demands in ordered and violated sequences defined by object properties are mutually more similar than in other sequence types, leading to the observed activation pattern which revealed no prefrontal contributions. Therefore, it is possible that the distinct pattern related to the detection of object deviants only mirrors the fact that object sequences are also special when compared to those based on other stimulus features.

In conclusion, the results obtained within the present experiment showed rather distinct patterns of activation underlying the detection of deviants within different sequence types which was dependent on the relevant stimulus dimension violated by the deviant event. While the expected comparable trend was shown for detecting spatial and rhythm deviants, detecting object deviant events triggered a somewhat unique pattern of activity. Therefore, this type of deviant was further investigated in *Experiment 4*.

6 Experiment 4. Violating expectations of differing specificity in perceptual sequencing

Experiment 4 primarily focused on violations of expectations within two different classes of sequences in which object properties, namely the identity of stimuli and not any of the other previously investigated features (size, position or rhythm) were relevant for defining the repeating sequential pattern. In this experiment two different versions of the serial prediction task (SPT) were used. One of them allowed the formulation of expectations pertaining to the exact identity of incoming stimuli by presenting an ordered three-stimulus sequence which was then repeated with the exact same stimuli (token SPT). In addition to this, an additional version of SPT was developed in which the relevant feature defining the three-stimulus sequence was category membership, so that the expectations about the incoming objects could only be made on a categorical level (type SPT). In these trials, three-stimulus sequences defined by the order of stimulus categories were presented and repeated such that repetitions of the original sequence included different exemplars from the same categories. Stimuli used within this experiment included several exemplars from four arbitrary categories defined by the relation of two simple forms constituting each stimulus which the participants learned prior to the experiment.

Thus, this experiment addressed differences in neural correlates of violating expectations of equivalent type but different specificity within the context of perceptual sequence processing: in the token SPT these expectations were very specific as they pertained to the exact stimulus identity whereas in the type SPT they were restricted to a more abstract level of stimulus category. Given the results from *Experiment 3*, a significant contribution from temporal and parietal cortical regions was expected in identifying sequential deviants in both token and type

sequences. When hypothesizing about potential differences between the two deviant classes, it might be useful to consider how forward models based on expectations of different specificity might mutually differ. In relation to this, it is plausible to assume that the brain always tries to formulate the best possible internal model given the available information about past input, current context and the level of uncertainty related to it. Therefore, more specific expectations formulated within the context of token sequences could be considered as expectations of higher strength and precision. Violation of such expectations might be expected to generate a bigger prediction error in comparison to expectations which are not detailed or very specific. This view would be based on an assumption that a stronger mismatch (prediction error) following the comparison of expected and presented stimuli should elicit a stronger response which would need to be communicated to higher cortical areas (Friston et al., 2006). On the other hand, it is possible to assume that deciding on the correctness of sequential structure in the type SPT might not be as automatic as in the token SPT because more elaborate processing of all, predicted and unpredicted, stimuli might be expected in this context, leading to a relatively weaker response accompanying occasionally presented sequential deviants. Thus, although the information value of deviants in both sequence classes might be equivalent, the deviance effect identified using relatively defined fMRI contrasts might be less salient in the type SPT. Although not identical, based on both of these alternatives it would be possible to expect overall stronger activations following the detection of sequential deviants in the token SPT.

6.1 Methods

6.1.1 Participants

22 right-handed, healthy volunteers (12 male, 12 female; age 22-32, mean age 26.4) participated in the study. The measurement of one participant was interrupted at participant's demand and this partially acquired data set was excluded from any further analysis. Two participants were excluded from further analysis due to movement during the experiment and one due to poor behavioral performance, so all subsequent analyses were performed on the data from 18 subjects.

6.1.2 Procedure

Participants were instructed and underwent a 45-minute behavioral training session one day before the measurement. They were initially familiarized with all three tasks used later within the experiment (tasks described below) by undergoing a five minute general training session after which they were specifically trained with the type SPT for 25 minutes and the control task for 10 minutes. On the day of the measurement and before the main experiment they were additionally presented with the instruction and a five minute training session which included all three tasks.

6.1.3 Stimuli and task

The stimulus material used in this study included 24 different stimuli (Figure 6.1), all consisting of two basic shapes, a circle and quadrangle, presented in different sizes and positions within the picture. Four categories of stimuli were created based on an arbitrary criterion and determined by relation of two basic shapes: the two shapes could be partly overlapping, not touching each other at all or one could be contained within the other (quadrangle in circle or circle in quadrangle). Thus, each category of stimuli included six exemplars which all shared the general relative layout of the two basic shapes and differed in terms of their exact position and size within the pictures.

Two different versions of the SPT and a control serial-match-to-sample task (Control) of equivalent trial organization were presented in a mixed trial design. Each trial included successive presentation of nine stimuli with the duration of 700 msec without temporal gaps, preceded by a task cue with the duration of 700 msec and followed by a 1500 msec response period and 500 msec feedback on the accuracy of participants' response. During the course of the experiment an additional number of shorter trials containing only six stimuli were presented in order to ensure that the attention of the participant was directed at the task during the whole course of a trial (catch trials). During all other periods in the experiment a fixation cross was presented at the center of the screen. Overall trial duration was 12 seconds and, in order to improve temporal resolution, each trial occurred at four different offset points (0, 500, 1000 and 1500 msec) in relation to fMRI data acquisition (Josephs et al., 1997). During the course of the experiment the stimulus trials were interspersed with empty trials during which only a fixation cross was presented and no task was given to the participants.

At the beginning of each trial, subjects were informed about the upcoming task by a cue preceding the stimuli. In both versions of the sequencing task, participants were instructed to attend to the order of presented stimuli in order to extract and predict the repetitive pattern contained within them. The first three stimuli of each trial formed a sequence that the participants were instructed to remember, while the second part of the trial entailed either two full repetitions or one repetition and one violation of the original three-stimulus sequence. The pattern of violation included reversal in the order of the 1st and 2nd or 2nd and 3rd element of the original sequence. Sequencing catch trials included only an original sequence and its one repetition or violation. In the first version of the SPT (token sequence) participants were instructed to remember the exact stimuli of the original three-stimulus sequence which were then repeated in the second part of the trial. In the second version of SPT (type sequence) participants had to attend to the categories of stimuli of the initial sequence, because the second part of the trial entailed different exemplars from the same category of the previously presented stimuli. Thus, the type SPT could be described as a categorical version of the token SPT. In both versions of SPT, the participants' task was to indicate, in a forced-choice mode, whether a sequential violation occurred or not.

In the control, serial-match-to-sample task, participants were instructed to memorize the first stimulus within the trial and attend to the remaining stimuli in order to determine if the category of the first stimulus was later repeated. Participants' task was to indicate, in a forced-choice mode, whether the repetition occurred in any position within the trial or not. This manipulation assured that the participants would attend to all stimuli during the trial, which was accomplished by the nature of the task in the serial prediction trials.

The parameters of the three tasks were tested and chosen based on several behavioral pilot studies conducted before the experiment in which the timing of stimulus presentation, stimulus categories and exemplars as well as the amount of training prior to the experimental session were systematically varied. Since all participants initially showed significantly better performance in the token sequencing task, the performance level across the three tasks was balanced by providing preliminary training primarily aimed at type sequences.

Across all trials in the experiment the order of stimuli was pseudo-randomized. The probability of each stimulus and stimulus category and that of transitions between stimuli were balanced across different positions within the trial. In order to avoid any motor contributions to the tasks, participants' response was always required after the end of each sequence. The sequential violations in

sequencing tasks and repetitions of the first stimulus in the control task were presented in 50% of all trials. Overall, six types of trials could be differentiated within the experiment: Ordered token sequences, Violated token sequences, Ordered type sequences, Violated type sequences, Control trials without a repetition (Non-match trials) and Control trials with a repetition (Match trials) (Figure 6.1). 27 trials of each type were used which, together with the 18 catch and 18 empty trials, amounted to the total of 198 trials presented in the course of the experiment.

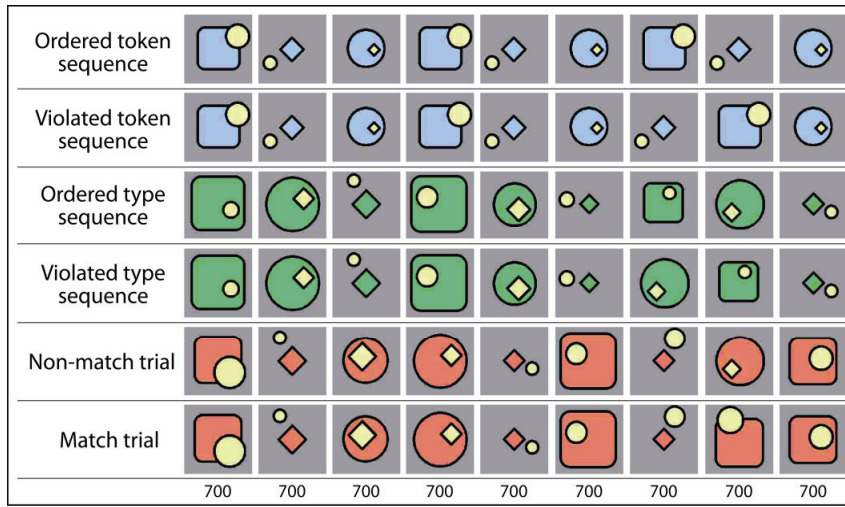


Figure 6.1: Schematic examples of six types of trials. Each trial started with a cue and was followed by 9 stimuli, all presented successively with the duration of 700 msec and without a temporal gap. The response was given at the end of each trial. In ordered sequences the first three stimuli represented a sequential pattern which was then correctly repeated two times, either with identical stimuli (Ordered token sequence) or with other exemplars from the same category (Ordered type sequence). Violated token and type sequences also started with the pattern of three stimuli which was followed by its one ordered repetition and one sequential deviant (reversed order of 1st and 2nd or 2nd and 3rd stimulus from the original sequence). The control task included the presentation of nine stimuli among which the category of the first stimulus was either repeated, here in the 8th position within the trial (Match trial), or not repeated (Non-match trial) before the end of the trial.

6.1.4 Data acquisition

The experiment was carried out on a 3T scanner (Medspec S300, Bruker, Ettlingen). Functional images in-plane with the anatomical images were acquired using a gradient-echo echo planar imaging (EPI) sequence with an echo time (TE)

of 30 msec, a flip angle of 90° and a repetition time (TR) of 2000 msec. 26 functional slices were acquired parallel to the bicommissural plane (AC-PC) (thickness 4 mm, interslice gap 1 mm) covering the whole brain. The matrix acquired was 64 x 64 with a field of view of 192 mm, resulting in an in-plane resolution of 3 mm x 3 mm. A total of 1192 volumes were acquired.

6.1.5 Data analysis

Functional data were motion-corrected off-line using the SPM5 motion correction protocol (<http://www.fil.ion.ucl.ac.uk/>). To correct for the temporal offset between the slices acquired in one scan, a cubic-spline-interpolation was applied. A temporal high pass filter with a cut-off frequency of 1/120 Hz was used for baseline correction, removing low-frequency drifts in an fMRI time series (frequencies due to global signal changes). Spatial Gaussian smoothing was applied using a Gaussian filter with 5.65 mm full width at half maximum (FWHM). Contrast images, namely estimates of the raw-score differences between specified conditions, were generated for each subject. Single-participant contrast images were entered into a second level random effects analysis for each of the contrasts. The group analysis consisted of one-sample t-tests across the contrast images of all subjects that indicated whether observed differences between conditions were significantly different from zero ($z > 3.09$, $p < 0.001$, uncorrected) (Holmes & Friston, 1998). The results were corrected for multiple comparisons using cluster-size and cluster-value thresholds obtained by Monte Carlo simulations at a significance level of $p = 0.005$, that is, the reported activations are significantly activated at $p < 0.005$, corrected for multiple comparisons at the cluster level. Additionally, conjunction analysis of the calculated contrasts (Nichols et al., 2005) was calculated in order to identify common regions supporting the two conditions of interest.

6.2 Results

6.2.1 Behavioral performance

Average accuracy expressed as the proportion of correct responses was 0.98 ± 0.004 for Ordered token sequences, 0.98 ± 0.010 for Violated token sequences, 0.97 ± 0.014 for Ordered type sequences, 0.96 ± 0.013 for Violated type sequences, 0.97 ± 0.009 for Control trials without a repetition and 0.99 ± 0.007 for Control trials with a repetition. A repeated-measures ANOVA with one three-

level factor Task (token SPT, type SPT, Control) and one two-level factor Response (violation / repetition present, violation / repetition absent) was used in order to compare the response accuracy in different tasks. The results revealed no statistically significant main or interaction effects (Task: $F(2,34) = 2,468$, $p = 0.10$; Response: $F(1,17) = 0.039$, $p = 0.845$; interaction Task x Response: $F(2,34) = 1.585$, $p = 0.22$).

6.2.2 MRI data

Brain areas with significantly higher BOLD response during the presentation of sequential deviants in the two classes of SPT as revealed through the comparison of violated and ordered sequence trials (contrasts: Violated token sequences vs. Ordered token sequences and Violated type sequences vs. Ordered type sequences) as well as the conjunction between these two contrasts are listed in Table 6.1. Presentation of deviants in the type SPT triggered bilateral frontal activations within the areas surrounding the inferior frontal junction (IFJ) at the crossing of inferior frontal and precentral sulcus, namely premotor cortex, BA 44 of the inferior frontal gyrus (IFG) and a small portion of BA 8 in the middle frontal gyrus (MFG) (Figure 6.2). Additionally, right inferior parietal lobule (IPL) was also activated in processing deviants in the type task context. In comparison, presentation of deviants in the token SPT triggered activations mainly in the right hemisphere with the dominant contribution from several lateral prefrontal areas mostly located in the IFG as well as the bilateral IPL (Figure 6.3). Conjunction between the two contrasts revealed common activation of the right IPL (BA 39/40) ($x = 52$, $y = -47$, $z = 33$; $\max z = 3.9$; size of activation 1404 mm^3) in processing sequential deviants in the token and type SPT. A time-line statistic was calculated for the regions engaged in processing deviants introduced into the token SPT ($x = 40$, $y = 34$, $z = 0$; $x = -38$, $y = 28$, $z = 0$; $x = 55$, $y = -50$, $z = 27$; $x = 55$, $y = -38$, $z = 0$; $x = -47$, $y = -56$, $z = 27$). Pair-wise comparisons between the average percent changes in the BOLD response identified within violated and ordered trials of both token and type SPT revealed statistically significant differences across all tested pairs ($p < 0.01$). The same was true for the differences between the average percent changes in the BOLD response in ordered token and type SPT trials in all regions ($p < 0.01$) except MTG ($x = 55$, $y = -38$, $z = 0$).

In order to identify brain areas involved in processing regular sequences, trials within each one of the SPT versions were compared with the Control task. These results are presented in the Appendix C.

Table 6.1: Activation foci related to deviant detection in Experiment 4: Anatomical brain area, hemisphere location, Talairach coordinates (x,y,z), maximal z-score and size of significant activations

Anatomy	Hem	Talairach Coordinates			z-score	mm ³
		x	y	z		
Violated vs. Ordered token sequence						
IFG (47)	R	40	34	0	5.00	6480
IFG (44 / 45)	R	55	16	6	3.68	
IFG (44)	R	49	13	15	4.78	
MFG (9)	R	46	19	27	3.37	
IFG (47)	L	-38	28	0	4.73	2889
IPL (39 / 40)	R	55	-50	27	4.08	5400
MTG (21)	R	55	-38	0	5.06	4752
IPL (39 / 40)	L	-47	-56	27	4.40	4320
Violated vs. Ordered type sequence						
PMC	R	37	1	27	4.22	1242
IFG (44)	R	46	10	21	3.67	
MFG (8)	L	-41	19	33	3.61	
IFG (44)	L	-44	16	21	4.50	4158
PMC	L	-41	1	36	4.12	1890
IPL / STS (39 / 40)	R	49	-44	30	4.25	
		52	-53	21	4.08	

Note: BA: Brodmann area; IFG: inferior frontal gyrus; IPL: inferior parietal lobule; STS: superior temporal sulcus; MFG: middle frontal gyrus; MTG: middle temporal gyrus; PMC: premotor cortex.

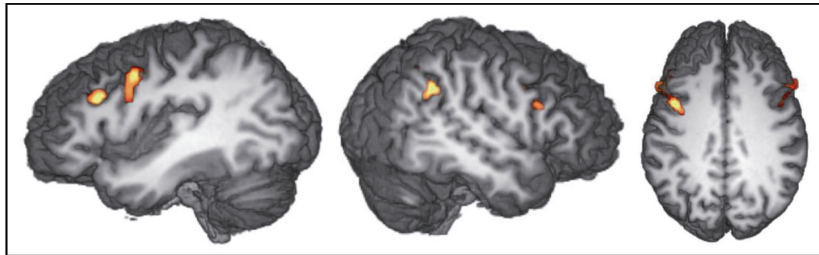


Figure 6.2: Brain correlates of detecting sequential deviants in type SPT (Violated vs. Ordered type sequence). From left to right: left hemisphere from parasagittal section (x=-40); right hemisphere from parasagittal section (x=49); axial section seen from above (z=35).

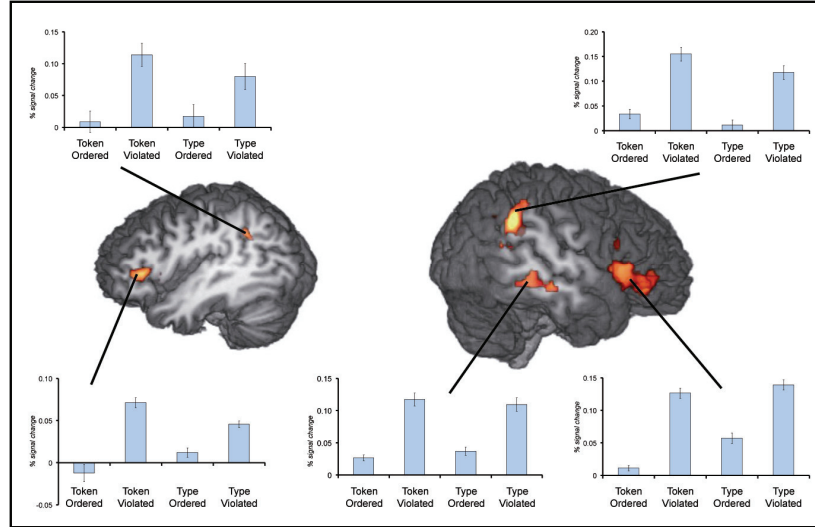


Figure 6.3: Brain correlates of detecting sequential deviants in token SPT (Violated vs. Ordered token sequence). From left to right: left hemisphere from parasagittal section ($x=-40$) and right hemisphere from parasagittal section ($x=55$). The time-courses for the regions of maximal z-score (listed in Table 6.1) are also presented.

6.3 Discussion

The present experiment explored the process of deviant detection in two classes of object sequences which differed in the specificity of expectations which could be formed in each trial. While in the token SPT such expectations were very specific and pertained to the identity of the individual stimulus, in the type SPT these were restricted to the level of stimulus category. These categorical representations require an abstraction of more general stimulus properties and may not capture very specific stimulus features in great detail (Kosslyn et al., 1989).

Introducing deviant events in these two classes of sequences evoked activations from mid- and inferior portions of the lateral prefrontal cortex as well as the inferior parietal regions. The involvement of parietal regions replicates the findings from *Experiment 3* within which prefrontal contributions to detecting object deviants were not identified. In contrast, the prefrontal activation triggered by the presence of deviants in the present experiment can be compared to the one identified in *Experiment 1*. The activation of a wide portion of the inferior frontal gyrus

(IFG) was especially present in the token SPT while the deviants within the type SPT elicited a more restricted activation within the BA 44 of the IFG and a small portion of the middle frontal gyrus (MFG), encompassing the inferior frontal junction (IFJ), a region located at the crossing of the inferior frontal and precentral sulcus (Derrfuss, Brass, von Cramon, Lohmann, & Amunts, 2009). This area has previously been implicated in tasks requiring increased cognitive control (Bunge, Kahn, Wallis, Miller, & Wagner, 2003; Derrfuss, Brass, Neumann, & von Cramon, 2005). In the present context an activation of this area may reflect the fact that type sequences required processing of more abstract rules defining category memberships which were relevant for categorizing a certain event as a deviant.

In contrast, the widespread, mainly ventral prefrontal activation in detecting token deviants may, similar as in *Experiment 1*, reflect controlled retrieval of sequencing structure needed for the verification of sequence regularity. This suggestion would be in line with findings showing the involvement of this area in active selection, comparison and judgement of memorized information (Petrides, 2005). Within the ordered token sequences prediction of incoming stimuli could have been done at a very specific level and every stimulus was informative by itself, requiring no additional processing. Introducing a violation into this context triggered a strong response from prefrontal regions because cognitive control demands were highly increased in comparison to the “baseline” ordered trials. In contrast, in type sequences even ordered trials required constant monitoring of stimuli in order to verify their respective categories, so the additional requirements as induced by the presentation of the deviant were not as big as in the token context. Therefore, in the type SPT the relative increase in prefrontal involvement elicited by sequential deviants was not as strong as compared to the token SPT, which is reflected in a more focused prefrontal activation as identified in this task. This suggestion is in line with the time-courses within the regions which were identified in processing deviants within token SPT. Although they (except for right IPL) were not identified as relevant in processing deviants introduced into the type SPT, time-course analysis within these regions shows that deviants presented in this context also elicited an increase in their respective activities. However, the relative differences between violated and ordered trials were smaller and these areas were therefore not identified in the calculated fMRI contrasts.

On a more general level, in the token task where the expectations were formulated on the specific level of stimulus identity, an overall stronger pattern of acti-

vation was identified when comparing violated to ordered sequence trials. As previously mentioned, this can be related to the smaller relative differences between ordered and violated trials. However, one alternative or complementary explanation might suggest that bigger prediction errors or violations of very specific expectations are processed more elaborately in contrast to less specific ones (Friston et al., 2006). This would suggest that deviant stimuli do not just generally trigger more elaborate processing in contrast to attenuated standards (Blake-more, Wolpert et al., 1998; Corbetta & Shulman, 2002), but that the level of such processing is related to the type and strength of the encountered deviance. If correct, this hypothesis would most probably be relevant to the subset of regions involved in deviant detection and could not uniformly explain the effects across all levels of processing. The present experiment was not designed to directly test this possibility, as this would require a somewhat different experimental design as well as more systematic investigations of all regions involved in deviant detection. However, the present data does not contradict this hypothesis either. It will be important to further address this issue in the future, as it opens interesting questions about potential sources of differences which might lead to the suggested pattern of results. Specifically, it is not clear whether violating expectations of different specificity differs in terms of processing or its final output. The first alternative, suggesting mutually different processing, may propose that comparing expectations of higher specificity to the incoming stimuli is more demanding, as it includes more features which need to be taken into account and mutually compared. Therefore, processing sequential deviants within the token SPT would simply be more demanding and therefore elicit more activations. Alternatively, the source of difference could be related to the outcome of such comparison. In this case, the comparison itself would be computationally equivalent (although not based on exactly the same features), but the mismatch resulting from violating more specific expectations would elicit a higher prediction error. In other words, violating specific predictions might simply be more surprising for the brain, thus leading to the more pronounced activation pattern underlying the detection of such deviants.

7 General discussion

The goal of the experiments conducted within the present thesis was to explore the process of detecting sequential deviants within the context of perceptual sequence processing as investigated using the serial prediction task (SPT). Sequential deviants are encountered in situations in which the sequential structure of a learned stimulus pattern determined by the order of stimulus presentation is violated. A short summary of the results obtained across all experiments is presented below.

7.1 Summary of the obtained results

Experiment 1 aimed at determining the degree to which detecting sequential deviants depends on the brain network previously identified in supporting regular sequence processing in comparison to the degree to which it elicits engagement of additional brain areas initially not involved in perceptual sequencing. The process of detecting sequential deviants was compared to the process of detecting feature (non-sequential) deviants, namely stimuli differing from the majority of other (standard) events in a predefined physical feature, thus violating expectations based on the overall task context. The obtained results indicated a dissociation between the two processes. Specifically, detection of sequential deviants triggered an increase of activity in lateral and medial premotor cortex (PMC) typically also engaged in regular sequence processing. This pattern of activity was suggested to reflect the detection of a mismatch between the expected and presented stimuli and the updating of the underlying sequence representation, i.e., forward model. Presented sequential violations additionally triggered activations in lateral prefrontal areas initially not involved in sequence processing, reflecting the subsequent elaboration of the violation. In contrast, detecting feature deviants triggered primarily bilateral activations within parietal and temporal areas with an additional, but more restricted involvement of prefrontal cortices, reflecting an increase in perceptual and attentional processing evoked by the feature deviant.

In *Experiment 2* a very similar experimental paradigm was used in order to explore the temporal dynamics of detecting sequential and feature deviants. An EEG study was conducted in which event-related potentials elicited by the presence of these two types of deviants were compared. The obtained results indicate that attended sequential and feature deviants both elicited a negative component peaking around 250-350 msec followed by a later positive component which peaked between 500-600 msec. Based on their topography and the fact that they were elicited by attended deviant events (Patel & Azzam, 2005), these components were identified as N2b and P3b, respectively. While N2b has been interpreted as indexing the process of matching the stimuli to a mentally-stored template of the expected events (Patel & Azzam, 2005), the P3b is suggested to reflect updating of the underlying model of the sequence (Polich, 2007) or the post-categorization decision-related processing (Nieuwenhuis et al., 2005). In addition, the obtained results also indicated significant differences in identifying sequential and feature deviants across several processing stages. First of all, feature, but not sequential deviants elicited the enhancement of an early negative component (N1), suggesting a very early registration of the feature change. Furthermore, different latencies and topographies of the N2b and P3b event-related components indicated that deviant detection in the two task contexts differs both in relation to their temporal dynamics and the underlying brain networks supporting these processes. In addition, the present study went beyond exploring only attended sequence processing as induced by standard SPT and addressed the importance of participants' attentional involvement in learning the presented sequential patterns and identifying occasionally introduced violations. This was done by investigating the process of detecting non-attended sequential deviants in contrast to those which are attended and task-relevant, as explored in all other conducted experiments. The obtained results confirmed previous claims about the relevance of attention in learning perceptual sequences. Specifically, only participants who were initially informed about the presence of the ordered sequential structure showed a N2 response to the presented deviants while those who were initially naïve failed to register these events. Although non-naïve participants extracted the sequential structure to a certain degree even when they were later not attending to it, this process was not identical to the one occurring when attention was directed to the order of presented stimuli.

Experiment 3 used fMRI in order to compare the process of detecting sequential deviants within different classes of perceptual sequences organized at a more abstract level of stimulus features. Three stimulus features, namely object identity, spatial position and temporal duration (rhythm), were used for defining a

sequential structure within three different versions of SPT. The obtained results showed that introducing deviants in the context of position and rhythm SPT triggered activations within the parietal, premotor and mostly caudal prefrontal regions. Dissociation between these tasks was also found: activations within the position SPT were distributed more dorsally in contrast to those in the rhythm SPT which were located more ventrally. The involvement of brain regions in detecting position and rhythm sequential deviants corresponds to a certain degree to the mapping which was previously identified in processing regular sequences defined by spatial or rhythmical properties of presented stimuli. Specifically, it was previously shown that predictions based on spatial stimulus properties activate the dorsal part of the PMC in contrast to those based on rhythm properties which activate the inferior portion of the ventral PMC (Schubotz & von Cramon, 2001a; Wolfensteller et al., 2007). Detecting violations within the object SPT showed a unique pattern of parieto-temporal activation which was not accompanied by additional frontal areas.

Experiment 4 used fMRI in order to further explore the process of detecting relational deviants within perceptual sequences defined by object identity. Two different classes of sequences were used, differing in the level of specificity or strength of expectations which could be formed regarding the incoming stimuli. More specifically, the process of detecting violations pertaining to specific (token) and categorical (type) expectations was explored by using two versions of the SPT: in the token SPT the repetitions following the presentation of the original sequence included the exact stimuli of the previously presented stimuli while in the type SPT these repetitions entailed different exemplars from the same category of the original sequence. The obtained results indicate a strong contribution of parieto-temporal areas in token sequences, similar to the object sequences from *Experiment 3*, which were primarily accompanied by ventral lateral prefrontal regions. The detection of violations in the more abstract type SPT triggered a less pronounced overall response which was dominated by lateral prefrontal activation.

7.2 Comparison across experiments

The results obtained in all experiments suggest a partly overlapping, but not fully uniform pattern of activations triggered by the detection of deviants introduced within the context of perceptual sequences defined by different stimulus features and on differing levels of specificity. Overall, this suggests that specific factors defining the sequential structure strongly influence which brain regions become

engaged in processing violations introduced in such sequences. Before exploring these in more detail, a short comparison between *Experiments 1* and *2* will be given.

In *Experiments 1* and *2* the process of detecting sequential deviants was compared to those introduced by feature deviants which violated the overall, global context of the trial. The results from these two experiments complement each other with respect to the type of information they provide and are therefore important to compare. Generally, a high degree of correspondence can be identified between *Experiments 1* and *2* as they both indicate a dissociation in processing two types of deviants. The results from *Experiment 2* suggest that, although the initial registration of sequential deviants was faster than that of the feature ones, the final decision regarding the status of sequential deviants was somewhat delayed. This can be attributed to rather non-uniform strategies employed by the participants for solving this task as some of them used the information from more than one stimulus (although one was sufficient to indicate violation) in order to verify their decision after the violation was first registered. Deciding on the deviance of stimuli differing in one physical feature from individual stimuli required less elaboration, as indicated by the shorter latency as well as sharper on- and offset of the P3b component elicited in this context. A more elaborate decision making process in case of sequential deviants was also suggested by the stronger prefrontal activation elicited by these events in *Experiment 1*. In comparing the first two experiments it is, however, also important to keep in mind that these also partly differed in relation to the used paradigm. Most importantly, the number or sequence repetitions following the presentation of the original pattern was higher in *Experiment 2*, which could suggest that making a decision in this context was somewhat easier, given that more repetitions of the sequential structure might result in the stronger memory trace of the sequence. The importance of the number of sequence repetitions for learning sequential patterns and detecting violations presented within them was, however, not directly addressed in any of the present experiments and would need to be pursued systematically in future studies.

When comparing the results from individual fMRI experiments, a somewhat more complex picture emerges. Violating predictions within sequences in which the order of stimuli was specified by stimulus features of different type and specificity triggered activation patterns which were only partly overlapping. As previously described, activations triggered by sequential deviants in *Experiment 1* were dominated by the lateral dorsal and ventral prefrontal areas, a pattern which

was partially replicated in the context of token sequences in *Experiment 4*. Deviants presented in the context of token sequences triggered a rather pronounced activation in ventral lateral prefrontal regions which was suggested to primarily reflect the retrieval of information required for comparison of the expected and presented stimuli accompanied by an activation of the inferior parietal lobule. Similarity in these two contexts was also expected given the similarity between the two types of sequences used in these experiments. Unlike in sequences from *Experiment 3* or type sequences in *Experiment 4*, which required a certain degree of abstraction in order to match the stimuli from the original and later sequence repetitions, in these sequences the second part of the trial always included exact repetitions of the original stimuli. Therefore, in case of the ordered sequence trials, prediction of incoming stimuli was very specific and the presence of violations could be detected based on the degree of direct physical matching of the presented and expected stimuli. Such matching was potentially perceptually easier in *Experiment 1* where stimulus size served as the only feature distinguishing the two compared stimuli. In contrast, stimuli within the token sequences of *Experiment 4* were perceptually more complex as the forms of two constituting elements needed to be registered and remembered. On the other hand, the number of sequence repetitions in *Experiment 1* was smaller in comparison to the one in token sequences. This made the decision process within *Experiment 4* somewhat easier which is visible in ceiling accuracy rates which were lower within *Experiment 1*. Therefore, the discrepancies between the activations identified within these two contexts can be interpreted as reflecting exactly these factors: the differences in decision difficulty and the need for differently elaborated perceptual processing in the two contexts. The first factor would be reflected in more pronounced activation within the dorsal lateral prefrontal regions subserving manipulation and reorganization of sequences in *Experiment 1*, while the second is visible in the stronger parietal activation identified in token sequences within *Experiment 4*.

In contrast to these sequence contexts which allowed the formation of very specific expectations during sequence repetitions, in all versions of the SPT used in *Experiment 3* as well as in the type SPT in *Experiment 4* these repetitions included stimuli equivalent in the task-relevant, but differing in other stimulus features. As discussed in more detail within the Discussion of *Experiment 3*, sequences defined by the spatial and temporal (rhythmic) stimulus elicited rather comparable activations in the premotor, caudal prefrontal and parietal areas. This pattern was similar to the one identified in the context of ordered serial processing in which sequences are defined by these properties (Schubotz et al., 2008).

However, detecting deviants in these sequences triggered activations of more anterior prefrontal regions in contrast to those involved in regular sequence processing. Since deciding on the presence of a deviant required more elaborate processing in contrast to processing expected stimuli, such involvement could be in line with suggestions regarding the hierarchical organisation of the lateral prefrontal cortex incorporating more abstract processing along the posterior-anterior dimension (Badre, 2008; Koechlin & Summerfield, 2007).

In contrast to this, violations embedded within sequences defined by the object properties in *Experiment 3* triggered a rather unique activation pattern comprising only inferior parietal and temporal activations which was comparable to that identified in both classes of object sequences, namely token and type ones, in *Experiment 4*. This raises a more general question of the potential special status of perceptual sequences defined by object properties as compared to other sequence classes. As previously described, the activation of premotor cortex in processing predictable, dynamic perceptual events is suggested to reflect the extraction of sequential structure and thereby to enable prediction. Although not action specific, this involvement can in certain contexts lead to action: in a way, the premotor-parietal network constantly provides options for such actions and the mapping of different stimulus properties onto different portions of the premotor cortex reflect the transformations afforded by the presented stimuli. For example, rotation as one type of such transformation activates the dorsal premotor cortex which is involved in actions in space (e.g., reaching or saccade shifts) while continuous change in loudness engages the ventral PMC typically involved in articulation. Sequences which were defined by spatial and temporal features in *Experiment 3* as well as size in *Experiment 1* offer such smooth transformations: change of position in the virtual circle represents rotation while size changes may introduce an impression of pulsating motion. But, this can not be done with object sequences defined by a rather arbitrary combination of color and form in which both of these simultaneously change from one stimulus to the next. A certain discontinuity is present in this context because the information is structured in a rule-based fashion reflecting such an arbitrary color-form combination. An increase in such load may lead to the higher engagement of frontal regions even in ordered sequences which, in turn, leads to the decrease in relative contributions from posterior frontal regions in deviant detection. An increase in prefrontal contribution in deviant detection also occurs in cases where sequence repetitions entail repetitions of all stimulus features (meaning that all available stimulus information need to be selected for prediction). This pattern of activation may, on first sight, appear somewhat contradictory to the common understanding that

prefrontal regions should be more active in more demanding tasks were the selection requirements are higher. However, the current findings do not challenge this view, because the identified activations are based on fMRI contrasts which are by definition relative. The lack of prefrontal activations in more demanding selection contexts in sequencing can indicate that in both violated and ordered sequences a certain degree of prefrontal involvement is needed, as premotor-parietal loops may not be able to support less smooth transformations required in these contexts. Therefore, the relative difference in ordered and violated sequences is not so high. In addition, this contribution may also be modulated by the difficulty of the decision as influenced by the number of repetitions of the original sequence within the trial.

7.3 Implications of the obtained findings and future directions

In interpreting the obtained results within the experiments conducted in the present thesis, the internal model account has been repeatedly referred to, as it represents the wider framework in which the used experimental paradigms were developed and the experimental questions posed. Similar frameworks have previously been suggested for the motor domain in which an internal (forward) model is used to predict the sensory consequences of movements based on the motor command (Wolpert & Miall, 1996). However, in line with the suggestion that there is “no theoretical reason to drag a conceptual distinction between anticipating a perceptual event or planning an action” (Hommel et al., 2001, p. 860) it was suggested that the prediction of temporally structured events is equivalently organized regardless whether these occur in the perceptual or the motor domain (Schubotz, 2007). Although this was not discussed in the main part of the thesis, all of the experiments conducted within the present thesis have confirmed the involvement of the premotor systems in dealing with dynamic perceptual events (see Appendices A, B, C). This is in line with previous suggestions stating that PMC would provide a perfect candidate for prospective processing in the seconds-range as required in this context (Schubotz, 2004). Such proposal can be paralleled to the suggestions implicating the motor system in constant prediction of future states required for compensating for the delays in processing sensory (often feedback) information relevant for preparing, evaluating and correcting motor actions (Wolpert & Flanagan, 2001). Such predictive computations implemented within the premotor cortex can be compared to more reactive processing implemented in the parietal areas (Dafotakis, Sparing, Eickhoff, Fink, & Nowak,

2008). Moreover, results from *Experiment 2* confirmed the previously suggested importance of active and attentive involvement of the participant in learning such sequences.

In the present work, a special case in processing perceptual sequences was explored, namely the detection of sequential deviants. These events signal a mismatch which occurs while evaluating the correctness of formulated predictions, which is achieved by comparing the formulated expectations with the incoming bottom-up information about the stimuli which have been presented. Understanding this process is important as the situations in which a difference between predicted and actual information is encountered may signal that the information used for predictions are wrong, leading to a change within the model used for generating those predictions. Therefore, a mismatch (signalling a prediction error) may serve as a feedback teaching signal, communicating a need to update and restructure the internal model. In a comparable manner, Näätänen (1992) has shown that auditory memory incorporates the mechanism which automatically recognizes the auditory input, includes it into the model of auditory environment and derives predictions about upcoming stimuli. Furthermore, such a model may subsequently be revised in situations in which such predictions are violated (Winkler & Czigler, 1998). In the context of perceptual sequencing, a similar updating of the forward model based on which predictions are formed could be triggered after the presentation of a sequential deviant. This was suggested by the results of *Experiment 1* and would need to be further tested within future experiments. In this context, it would be of interest to compare situations in which an equivalent sequential deviant could be interpreted in different ways: first, when it reflects an error in the underlying model; second, when the model is correct but noise in the environment causes a similar effect; third, when the certainty of predictions is lower, as would be the case in probabilistic sequences. In addition, it would be important to study whether the suggested updating of the underlying internal model occurs automatically or only in contexts in which it is beneficial, e.g., when the violation reflects restructuring (change in the sequence) and needs to be used for updating the model and further predicting the incoming stimuli based on the changed sequential pattern.

Furthermore, it would be of interest to explore specific contributions of factors which had an impact on results obtained in the experiments of the present thesis more systematically. First of all, the activations triggered by sequential deviants introduced into object SPT were rather unique when compared to those triggered by deviants in sequences defined by other stimulus features. This may

not only indicate a special status of these deviants, but also of object sequences in general which should be further explored in the context of ordered sequence processing. In addition, exploring the processing of ordered and violated sequences of different specificity would also be of interest, especially if these are defined by stimulus features affording more smooth transformations, such as size or position. Systematic investigation of all of these factors would be important not just for understanding their individual influences, but also because it may allow a more precise, operational definition of the term “strength of expectations”. In the present thesis this term was used and it was suggested that it could reflect or be influenced by e.g., specificity of expectations or number of sequence repetitions. Related to this, it would be of importance to further investigate the rate of learning perceptual sequences and the influence of the number of sequential repetitions for the strength of the formed memory trace and formulated expectations. Another important direction for future research may include addressing the role of attention in learning perceptual sequences. In *Experiment 2* it was not possible to extract sequential structure in unattended sequences, unless the participants were previously familiarized with the existence of the underlying sequential regularity. However, once this initial knowledge was present, some level of sequence learning still occurred even when the sequential structure itself was no longer attended. It is of importance to pursue this issue further and compare the learning process in the two contexts. Importantly, based on the results from this experiment, it is not possible to speculate whether the same system (premotor-parietal) would be involved in processing both types of learning and subsequent prediction. Therefore, exploring this issue would be beneficial not only for better understanding the sequential processing itself, but also further specifying the computations of the premotor cortex. Finally, it would also be important to explore the detection of sequential deviants in other modalities, primarily the auditory one. Overall, pursuing all of these potential directions would be of interest for understanding both the effects of sequential violations as well as the process of regular sequence processing itself.

As previously mentioned, the patterns of activations identified across individual fMRI experiments show overlap, but also reveal some non-uniformities. In a way, this is a non-ideal situation because it is difficult to clearly interpret the obtained results, especially in situations where more than one factor could have influenced them. However, this pattern is also telling. For example, the dissociation along the dorsal-ventral axis in processing spatial and ventral deviants speaks in favor of the suggestion that the functional role of different portions of the prefrontal cortex reflects the type of processed (e.g., spatial or object) information

(Goldman-Rakic, 1995), and not only the type of cognitive process itself (Petrides, 1996). In addition, it also indicates that suggestions according to which detection of relational deviants (also termed associatively novel events) is strictly dependent on hippocampal processing (Kumaran & Maguire, 2006, 2007) may not hold for all contexts. Although the studies investigating the latter issue employed a paradigm which differed from the SPT in terms of temporal structure of the trial, as well the task and participants' attentional involvement, sequential deviations as explored in the present thesis could nevertheless be considered as one type of such (associative or relational) novelty. However, in the present experiments, presentation of such deviants did not elicit the involvement of the hippocampus. This does not invalidate the claims about the importance of this structure in either regular or novel associative processing, but it poses additional questions about whether this can be generalized across different contexts, types of stimuli and temporal scales of stimulus presentation.

As mentioned before, the perceptual sequencing explored in this thesis concerns very short time scales (seconds-range) which are appropriate for the motor system. As it has previously been suggested that exactly this dimension of stimulus organization could be crucial in engaging the different regions and networks (Kiebel, Daunizeau, & Friston, 2008), it is possible to suggest that similar types of processes could be supported by different areas when occurring at different temporal scales. Similar modulations could also be triggered by changes in stimulus features, sensory modalities or other experimental factors. In addition, it is also plausible that detecting deviants occurring at same stimuli, but violating different types of expectations would recruit different brain regions. If one assumes that different networks are involved in formulating predictions which eventually get violated, there should also exist differences in neural correlates of detecting deviants in such contexts, even if these occur on perceptually identical stimuli. As an illustration, previous studies have also shown the differentiation in processing deviants violating different properties of the same context, e.g., rule, category restriction or double deviants in visual sequences (Koester & Prinz, 2007) or higher-level errors pertaining to goals or lower-level motor errors in motor control (Krigolson & Holroyd, 2007). Each of these deviants violated the expectations of different origin and they thus elicited a different pattern of activations. The present thesis once again confirms the crucial dependence of neural correlates of deviant detection on the nature of expectations being violated.

Appendix A: Effects of serial prediction in Experiment 1

Table A.1: Effects of serial prediction in Experiment 1: Anatomical brain area, hemisphere location, Talairach coordinates (x,y,z), maximal z-score and size of significant activations. For abbreviations of activated regions, see List of Abbreviations.

Anatomy	Hem	Talairach Coordinates			z-score	mm ³
		x	y	z		
SPT vs. Control						
PMd	R	31	12	48	4.76	2754
	L	-23	-6	54	3.99	2997
IFG (6 / 44)	L	-50	6	15	4.08	2376
PCU (7)	R	7	-69	57	3.87	3672
	L	-8	-57	51	3.67	
SPL / IPL (39 / 40)	R	43	-45	51	3.80	3132
IPL (39 / 40)	L	-50	-36	48	4.40	6291
IPL / STS (40 / 22)	L	-59	-39	27	3.70	

Appendix B: Effects of serial prediction in Experiment 3

Table B.1: Effects of serial prediction in SPT-O of the Experiment 3: Anatomical brain area, hemisphere location, Talairach coordinates (x,y,z), maximal z-score and size of significant activations. For abbreviations of activated regions, see List of Abbreviations.

Anatomy	Hem	Talairach Coordinates			z-score	mm ³
		x	y	z		
SPT Object vs. Control						
PMd	R	25	1	54	6.02	32454
MFG (6 / 8)	R	43	7	21	4.69	
MFG (8 / 9)	R	43	28	27	5.67	
MFG (10)	R	31	55	12	3.85	
pre-SMA	L	-5	4	54	5.65	9369
PMd	L	-29	1	51	5.94	26568
MFG (8 / 9)	L	-44	28	27	5.39	
FOP	L	-29	22	0	4.69	9828
IPL (39 / 40)	L	-44	-35	39	7.02	140697
SPL (7)	L	-26	-74	39	5.26	
PCU (7)	R	7	-68	48	4.55	
SPL / IPL (7 / 40)	R	34	-53	51	5.75	
THA / BG	R	13	-11	12	4.71	6993
	R	4	-32	-3	4.10	3618

Table B.2: Effects of serial prediction in SPT-P of the Experiment 3: Anatomical brain area, hemisphere location, Talairach coordinates (x,y,z), maximal z-score and size of significant activations. For abbreviations of activated regions, see List of Abbreviations.

Anatomy	Hem	Talairach Coordinates			z-score	mm ³
		x	y	z		
SPT Position vs. Control						
PMv	R	52	-5	39	4.07	13284
IFG (6 / 44)	R	52	7	18	5.84	
SMA	L	-5	-2	60	4.59	14850
PMd	L	-29	-5	54	5.11	
IFG (6 / 44)	L	-50	7	18	5.21	30861
SPL (7)	R	13	-68	51	5.33	
	R	37	-35	48	5.73	2133
MTG (37)	R	40	-53	6	4.24	
LG (18)	R	10	-86	-3	5.37	7938
SPL (7)	L	-17	-68	51	4.77	17091
IPL (40)	L	-38	-41	42	5.71	
CE	R	25	-65	-21	4.40	8046
CE	L	-8	-80	-27	5.08	
BG (PUT)	L	-20	4	9	4.97	1404
BG (PUT)	R	22	-2	9	4.52	1431

Table B.3: Effects of serial prediction in SPT-R of the Experiment 3: Anatomical brain area, hemisphere location, Talairach coordinates (x,y,z), maximal z-score and size of significant activations. For abbreviations of activated regions, see List of Abbreviations.

Anatomy	Hem	Talairach Coordinates			z-score	mm ³
		x	y	z		
<i>SPT Rhythm vs. Control</i>						
PMd	L	-2	4	54	5.82	7965
IFG (6 / 44)	L	-50	7	15	5.41	22032
BG (PUT)	L	-20	4	12	5.45	
MFG (9)	L	-41	31	27	3.90	1458
PMd	R	22	-2	51	4.38	28215
IFG (44)	R	52	10	12	6.08	
IPL (40)	R	43	-35	45	6.19	19683
PCU (7)	R	10	-62	57	4.91	
IPL (40)	L	-41	-35	36	4.42	10125
SPL (7)	L	-14	-68	54	4.23	
CU (18)	R	13	-95	12	4.43	1215
CE	L	-32	-62	-24	4.96	13635
CE	R	25	-65	-18	5.75	5346

Table B.4: Brain activations more engaged in supporting object in comparison to other types of sequences: Anatomical brain area, hemisphere location, Talairach coordinates (x,y,z), maximal z-score and size of significant activations. For abbreviations of activated regions, see List of Abbreviations.

Anatomy	Hem	Talairach Coordinates			z-score	mm ³
		x	y	z		
Object vs. Position / Rhythm SPT						
pre-SMA	L	-2	13	45	4.52	2349
PMC / MFG (6 / 8 / 9)	L	-41	4	30	5.92	10746
MFG (8 / 9)	R	37	28	33	4.47	2511
IFG (11)	R	25	43	-3	4.41	3456
IFG (10)	L	-32	55	15	3.82	3726
SPL / PCU (7)	L	-29	-65	42	6.48	37773
FG (19 / 37)	L	-35	-65	-15	5.32	
	R	37	-65	-15	5.32	30726
THA	L	-8	-11	6	4.36	1890
CE	R	7	-71	-21	5.16	3915

Appendix C: Effects of serial prediction in Experiment 4

Table C.1: Effects of serial prediction in token SPT of the Experiment 4: Anatomical brain area, hemisphere location, Talairach coordinates (x,y,z), maximal z-score and size of significant activations. For abbreviations of activated regions, see List of Abbreviations.

Anatomy	Hem	Talairach Coordinates			z-score	mm ³
		x	y	z		
Token SPT vs. Control						
PMd	R	25	-5	51	5.77	
SMA	R	4	-2	54	4.22	44577
PMd	L	-29	-8	51	5.29	
MFG (8 / 9)	L	-41	28	27	4.13	1593
MFG (10)	R	31	49	6	3.85	1728
IPL (39 / 40)	L	-44	-44	54	7.30	
SPL (7)	L	-23	-56	57	5.11	85995
SPL (7)	R	23	-53	60	5.65	
CE	L	-29	-59	-24	5.30	16281
CE	R	25	-62	-48	6.04	13473
BG	R	19	4	6	4.32	3267
	L	-17	1	12	4.68	4293

Table C.2: Effects of serial prediction in type SPT of the Experiment 4: Anatomical brain area, hemisphere location, Talairach coordinates (x,y,z), maximal z-score and size of significant activations. For abbreviations of activated regions, see List of Abbreviations.

Anatomy	Hem	Talairach Coordinates			z-score	mm ³
		x	y	z		
Type SPT vs. Control						
PMd	R	25	-5	51	5.62	21168
PMd	L	-23	-2	48	5.27	17982
SMA	L	-5	-5	51	4.93	
SPL / OGs (7 / 19)	R	31	-77	36	5.89	84726
SPL / IPL (7 / 40)	R	37	-44	45	5.14	
PCU (7)	L	-11	-59	51	5.02	
IPL (40)	L	-50	-23	27	4.33	
MTG (19 / 37)	L	-47	-59	-15	4.26	
CE	L	-26	-62	-24	5.22	48789
BG	L	-8	-20	-9	4.58	15093

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- 3.2 A: Brain correlates of detecting sequential deviants (Violated vs. Ordered sequence). From left to right: right hemisphere from parasagittal sections ($x=52$, $x=4$); axial section ($z=49$). B: Brain correlates of detecting feature deviants (Target trial vs. No-target trial). From left to right: left hemisphere from parasagittal section ($x=-51$); right hemisphere from parasagittal section ($x=50$); axial section ($z=58$). A and B: Group-averaged statistical maps ($N=14$) are superimposed onto an individual brain which was chosen for being the most similar to the average brain of all subjects participating in the experiment and scaled to the standard Talairach brain size (Talairach & Tournoux, 1988).
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List of Abbreviations

μV	Microvolt
ACC	Anterior cingulate cortex
Ag/AgCl	Silver/silver-chloride
ANOVA	Analysis of variance
BA	Brodmann area
BG	Basal ganglia
BOLD	Blood oxygen level dependent
CU	Cuneus
dIPFC	Dorsolateral prefrontal cortex
EEG	Electroencephalogram
ELAN	Early left anterior negativity
EPI	Echo planar imaging
ERAN	Early right anterior negativity
ERD	Event-related desynchronization
ERN	Error-related negativity
ERP	Event-related potentials
FG	Fusiform gyrus
fMRI	Functional magnetic resonance imaging
FOP	Frontal operculum
FOV	Field of view
FWHM	Full width at half maximum
Hz	Hertz
GLM	General linear model
HG	Hippocampal gyrus

HRF	Hemodynamic response function
IFG	Inferior frontal gyrus
IFJ	Inferior frontal junction
IPL	Inferior parietal lobule
IPS	Intraparietal sulcus
ITG	Inferior temporal gyrus
LG	Lingual gyrus
MDEFT	Modified driven equilibrium Fourier transform
MFG	Middle frontal gyrus
mm	Millimeter
msec	Millisecond
MTG	Middle temporal gyrus
OGs	Superior occipital gyrus
pCG	Posterior cingulate gyrus
PCU	Precuneus
PMC	Premotor cortex
PMd	Dorsal premotor cortex
PMv	Ventral premotor cortex
PrCG	Precentral gyrus
PrCS	Precentral sulcus
pre-SMA	Pre-supplementary motor area
PUT	Putamen
SFG	Superior frontal gyrus
STG	Superior temporal gyrus
SMA	Supplementary motor area
SPL	Superior parietal lobule
SPT	Serial prediction task
SRTT	Serial reaction time task
THA	Thalamus
TPJ	Temporo-parietal junction

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Violation of expectations in sequence processing

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Dissertation

144 pages, 285 references, 16 figures, 10 tables

The goal of the present thesis was to explore the process of detecting a certain category of deviant events, namely sequential deviants presented within the context of predictive perceptual processing as explored using sequences of visual stimuli. These events violate expectations formulated within perceptual sequences whose structure is defined by the order of stimulus presentation. In the first two experiments conducted within the present thesis, the detection of such sequential deviants was compared to the detection of feature deviants which violated the expectations formulated based on perceptual features of individual stimuli. The results from both experiments indicated a dissociation between the processing of these two types of deviants. This was shown both on the level of temporal dynamics as well as the brain areas engaged in processing feature and sequential deviants. Following this, the processing of sequential deviants was additionally investigated within perceptual sequences defined by different stimulus features and on differing levels of specificity. The obtained findings indicate a partly overlapping, but not uniform pattern of activations supporting the detection of sequential deviants. This suggests that specific factors defining the sequential structure strongly influence which brain regions become engaged in processing violations introduced in such sequences. The most important of these factors is the stimulus property defining the sequence and the characteristics of sensorimotor transformations it affords. In addition, the specificity of expectations which can be formulated within the sequence also influences the engagement of brain regions in detecting sequential deviants. Finally, although not explicitly explored, the influence of other sequence properties, e.g., number of sequence repetitions within the trial, might also modulate the involvement of the identified brain networks in detecting such events. In conclusion, detection of sequential deviants does not represent a uniform process, but is highly dependent on the properties of regular sequences which determine the nature of expectations being formulated and consequently violated by the presentation of such events.

Summary

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Introduction

The importance of predictive processing within the motor system was recognized already in the 17th century and pursued first by Descartes, then Helmholtz and later by von Holst, Mittelstaedt and Sperry who in the 1950s provided first experimental evidence demonstrating the importance of motor-to-sensory feedback in controlling behavior (Bays & Wolpert, 2008; Wolpert & Flanagan, 2001). More than half a century later, the internal model framework can be considered a prevailing, widely accepted view within the motor domain. In recent years this notion has been further developed and applied to different phenomena well beyond this domain (Miall & Wolpert, 1996; Wolpert & Kawato, 1998). For example, it has been suggested that the forward model account could provide a general framework for understanding prediction in a wide range of high level cognitive functions including action observation, imitation, mental practice, social interaction and theory of mind (Wolpert et al., 2003). In the same spirit, Schubotz and von Cramon (2003) have shown that the computations and mechanisms underlying a certain class of perceptual phenomena could be considered equivalent to those within the motor domain. Specifically, it has been shown that processing of predictable, dynamic perceptual events or structured patterns of perceptual stimuli relies primarily on the premotor and connected parietal areas (Schubotz & von Cramon, 2002a, b, c; 2003). Furthermore, the involvement of these areas is primarily dependent on participants' active involvement in extracting and predicting the structure of such sequences (Schubotz & von Cramon, 2002b). Thus, motivated by findings implicating the motor system in some forms of perceptual processing, a joint framework unifying the perceptual and motor domain, i.e., the sensorimotor forward model account which is grounded in the predictive nature of the motor system (cf. Schubotz, 2007), was suggested.

The main questions underlying the present thesis as well as the main paradigm used in all experiments stem from this framework.

The main goal of the experiments conducted within the present thesis was to explore the process of detecting deviant events in such a dynamic and predictable perceptual context which is represented through internal models. In order to achieve this goal, the process of detecting sequential deviants, namely events which violate the sequential structure defined by the order of stimuli within the trial, was investigated. Exploring this particular deviant class is important not only for understanding the process of deviant detection, but also for gaining important insights about the dynamics and neural correlates of predictive perceptual processing. In order to explore this issue, the serial prediction task (SPT, Schubotz, 1999) was used as the principal experimental paradigm in all of the conducted studies. This task was developed as a perceptual counterpart to the serial reaction time task (SRTT; Nissen & Bullemer, 1987) in order to investigate sequence processing in an experimental setting with minimum motor requirements. Since the SPT requires participants to extract and predict repetitive sensory patterns within sequentially presented stimuli, this task is also occasionally referred to as the (perceptual) sequencing task. The only response required in this task is delayed until the end of the trial when the participant needs to indicate whether a violation of the learned pattern occurred in the last part of the trial or not. Within each individual study the SPT is presented together with a control, non-sequencing task equivalent in attentional, perceptual and motor demands. Most important features of the SPT include the fact that this task provides continuous stimulation requiring anticipatory processing which is dependent on sensorimotor transformations provided by the premotor cortex. In all of the conducted experiments, the order of three successively presented stimuli defined a sequence which was then repeated within the SPT. The violated pattern which was occasionally presented always included presentation of correct stimuli appearing in wrong order, such that two stimuli exchanged their positions within the sequence (sequential deviant). All experiments explored the neural correlates of detecting these deviating events. Since it was previously shown that the type of processing as evoked by the serial prediction task is by nature predictive (cf., Schubotz, 2007), the process of detecting sequential deviants is considered as a case of violating perceptual expectations or predictions.

Conducted experiments

Experiment 1 explored the process of detecting sequential deviations in short perceptual sequences in which stimulus patterns were defined by the order of stimulus sizes. The goal of this fMRI experiment was to determine the degree to which detecting sequential devi-

ants depends on the brain network previously identified in supporting regular aspects of sequence processing, primarily the medial and lateral premotor regions and the connected parietal areas (cf., Schubotz & von Cramon, 2003) in contrast to the degree to which it elicits additional engagement of brain regions initially not involved in sequence processing. The process of detecting sequential deviants was compared to detecting feature (non-sequential) deviants in a target detection task. These constituted stimuli which differed in their perceptual features from the standard stimuli and were therefore violating expectations based on the overall task context. The obtained results showed a dissociation between the two processes. Sequential deviants triggered an increase of activity in lateral and medial premotor and cerebellar areas which were initially supporting regular sequence processing. This pattern of activity is suggested to reflect detection of a mismatch between the expected and presented stimuli and updating of the underlying sequence representation (i.e., forward model). Presented sequential violations additionally triggered activations in prefrontal areas initially not involved in sequence processing, reflecting the subsequent elaboration of the violation. In contrast, detecting feature deviants triggered primarily bilateral activations within parietal and posterior temporal areas with a more restricted involvement of prefrontal cortices, reflecting an increase in perceptual and attentional processing evoked by these deviant events.

In *Experiment 2* a slightly modified version of the paradigm from the previous experiment was used in order to explore the temporal dynamics of detecting sequential and feature deviants. An EEG study was conducted in order to investigate and compare event-related potentials evoked by the presence of the two previously described types of deviants. Furthermore, this study went beyond exploring only attended sequence processing as investigated using the standard SPT and addressed the importance of participants' attentional involvement in learning perceptual sequences and identifying sequential deviants. The obtained results indicate that both attended sequential and feature deviants elicited a negative component peaking around 250-350 msec followed by a later positive component which peaked between 500-600 msec. Based on their topography and the fact that they were elicited by attended deviant events (Patel & Azzam, 2005), these components were identified as N2b and P3b, respectively. While N2b has been interpreted as indexing the process of matching the stimuli to a mentally-stored template of expected events (Patel & Azzam, 2005), the P3b is suggested to reflect updating of the underlying model of the sequence (Polich, 2007) or the post-categorization decision-related processing (Nieuwenhuis et al., 2005). In addition, the obtained results indicated a dissociation in detecting sequential and feature deviants across all stages of processing. First, only feature deviants elicited N1, an early negative event-related component which suggests a very early regis-

tration of a feature change. Furthermore, different latencies and topographies of the N2b and P3b components indicated substantial differences in both the temporal dynamics and brain networks supporting deviant detection in the two contexts. In contrast to attended sequential deviants, presentation of the unattended ones only elicited a N2 component in a subset of participants which were initially familiarized with the existence of a sequential structure within the trial. Thus, the obtained results indicate the importance of participants' attentional involvement for learning perceptual sequences and detecting violations presented within them.

Experiment 3 used fMRI in order to compare the process of detecting sequential deviants within different classes of perceptual sequences organized at a somewhat more abstract level of stimulus features. Three different stimulus features were used within three different versions of SPT: object identity, spatial position and temporal duration (rhythm). Sequential deviants introduced into sequences defined by spatial and rhythm properties triggered activations within the parietal, premotor and mostly posterior prefrontal regions. Dissociation between these tasks was also found: the activations within the position SPT were distributed more dorsally in contrast to those from the rhythm SPT which were located more ventrally. The involvement of brain regions in detecting sequential deviants within position and rhythm SPT corresponds to a certain degree to the mapping which was previously identified in processing regular sequences defined by spatial or rhythmical properties of presented stimuli. Specifically, it was previously shown that predictions based on spatial stimulus properties activate the dorsal part of the premotor cortex in contrast to those based on rhythm properties which activate the inferiormost portion of the ventral premotor cortex (Schubotz et al., 2008; Wolfensteller, Schubotz, & von Cramon, 2007). Detecting violations within the object SPT showed a unique pattern of parieto-temporal activation which was not accompanied by additional frontal areas. This type of the deviant was further investigated in the last experiment.

Experiment 4 used fMRI in order to further explore the process of detecting sequential deviants introduced into perceptual sequences defined by object identity. Two classes of such sequences were used, differing in the level of specificity or strength of expectations which could be formed regarding the incoming stimuli. This was accomplished by using two versions of a serial prediction task: in the 'token SPT' the repetitions following the presentation of the original sequence included the exact stimuli of the previously presented stimuli while in the 'type SPT' these repetitions entailed different exemplars from the same category of the original sequence. Therefore, in this experiment the effects of sequential violations pertaining to specific (token) and categorical (type) expectations were compared. The obtained results indicate a strong contribution of parieto-temporal areas in to-

ken sequences, similar to the object sequences from *Experiment 3* which were additionally accompanied by lateral prefrontal regions. A partially overlapping involvement of the right inferior parietal cortex was also identified in processing deviants within the context of type sequences which was accompanied by a lateral prefrontal activation. A more pronounced overall response to sequential deviants identified within the context of token in comparison to type deviants was suggested to reflect a larger mismatch resulting from the comparison of the presented stimuli and the more specific expectations as formulated within token sequences.

Conclusion

The goal of the present thesis was to explore the process of detecting sequential deviants within the context of predictive perceptual processing as explored using sequences of visual stimuli. These events violate expectations formulated within such perceptual sequences whose structure is defined by the order of stimulus presentation. In the first two experiments, the detection of such sequential deviants was compared to the detection of feature deviants which violated the expectations formulated based on perceptual features of individual stimuli. The results from both experiments indicated a dissociation between the processing of these two types of deviants. This was shown both on the level of temporal dynamics as well as the brain areas engaged in processing feature and sequential deviants. Following this, the processing of sequential deviants was additionally investigated within perceptual sequences defined by different stimulus features and on differing levels of specificity. Comparison of results obtained across all fMRI experiments indicates a partly overlapping, but not uniform pattern of activations supporting the detection of sequential deviants. Such findings suggest that specific factors defining the sequential structure strongly influence which brain regions become engaged in processing violations introduced in such sequences. The most important of these factors includes the stimulus property defining the sequence and the characteristics of sensorimotor transformations it affords. In addition, the specificity of expectations which can be formulated within the sequence also influences the engagement of brain regions in detecting sequential deviants. Finally, although not explicitly explored, the influence of other sequence properties, e.g., number of sequence repetitions within the trial, might also modulate the involvement of the identified brain networks in detecting such events. In conclusion, detection of sequential deviants does not represent a uniform process, but is highly dependent on the properties of regular sequences which determine the nature of expectations being formulated and consequently violated by the presentation of such events.

Zusammenfassung

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Einleitung

Die Bedeutsamkeit prädiktiver Verarbeitung innerhalb des motorischen Systems wurde bereits im 17. Jahrhundert erkannt und zuerst von Descartes, Helmholtz und später von von Holst, Mittelstaedt und Sperry untersucht, die in den 1950er Jahren erste experimentelle Belege für die Bedeutung von sensomotorischem Feedback zur Bewegungskontrolle lieferten (Bays & Wolpert, 2008; Wolpert & Flanagan, 2001). Mehr als ein halbes Jahrhundert später kann man den theoretischen Rahmen des ‚internen Modells‘ (internal model) im Bereich der Bewegungssteuerung als die vorherrschende und weithin akzeptierte Sichtweise bezeichnen. In den letzten Jahren ist dieses Konzept weiterentwickelt und auch auf verschiedene Phänomene weit außerhalb dieses Bereichs angewandt worden (Miall & Wolpert, 1996; Wolpert & Kawato, 1998). So ist das Konzept des ‚Vorwärtsmodells‘ (forward model), welches der Klasse interner Modelle angehört, als ein allgemeiner theoretischer Rahmen zum Verständnis prädiktiver Prozesse in einem breiten Spektrum höherer kognitiver Funktionen, wie Handlungsbeobachtung, Imitation, mentaler Übung, sozialer Interaktion und ‚Theory of mind‘-Prozessen vorgeschlagen worden (Wolpert et al., 2003). In ähnlicher Weise haben Schubotz und von Cramon (2003) gezeigt, dass die Berechnungen und Mechanismen, die einer bestimmten Klasse perzeptueller Phänomene unterliegen, äquivalent sein könnten mit den Berechnungen und Mechanismen, die im motorischen Bereich erfolgen. Insbesondere ist gezeigt worden, dass die Verarbeitung vorhersagbarer, dynamischer perzeptueller Ereignisse, bzw. strukturierter Muster perzeptueller Stimuli auf cerebraler Ebene primär in prämotorischen Arealen und den mit diesen verbundenen parietalen Arealen abläuft (Schubotz & von Cramon, 2002a, b, c; 2003). Wichtig ist hierbei weiterhin, dass die Beteiligung dieser Areale in erster Linie davon ab-

hängt, dass die Probanden die Struktur einer präsentierten Sequenz aktiv extrahieren und vorhersagen (Schubotz & von Cramon, 2002b). Auf der Grundlage dieser Befunde, die eine Beteiligung des motorischen Systems an einigen Arten perzeptueller Verarbeitung nahe legen, wurde das Konzept des ‚sensomotorischen Vorwärtsmodells‘ vorgeschlagen (Schubotz, 2007). Dieses Konzept versteht sich als theoretischer Rahmen, der den perzeptuellen und den motorischen Bereich eint, und auf der prädiktiven Beschaffenheit des motorischen Systems gründet. Die Kernfragen der vorliegenden Arbeit sowie die Paradigmen, die in den einzelnen Experimenten zur Anwendung kamen, sind aus diesem theoretischen Modell abgeleitet.

Das Hauptziel der Experimente der vorliegenden Arbeit war es, den Prozess der Devianzdetektion in dynamischen und vorhersagbaren perzeptuellen Kontexten zu erforschen, die eine Repräsentation durch interne Modelle erlauben. Zu diesem Zweck wurde die Detektion von sogenannten sequenziellen Devianten untersucht. Ein sequentieller Devianter wird als ein Ereignis verstanden, das die durch die Reihenfolge der Stimuli bestimmte sequentielle Struktur eines Trials verletzt. Die Untersuchung dieses Deviantentyps ist nicht nur für das Verständnis des Prozesses der Devianzdetektion wichtig, sondern ermöglicht es auch, bedeutsame Erkenntnisse über die Dynamik und die cerebralen Korrelate prädiktiver Wahrnehmungsprozesse zu gewinnen. Zur Untersuchung dieser Fragestellung wurde als experimentelles Paradigma in allen hier vorgestellten Experimenten die serielle Prädiktionsaufgabe (serial prediction task, SPT, Schubotz, 1999) verwendet. Diese Aufgabe wurde ursprünglich als perzeptuelles Pendant zur seriellen Reaktionszeitaufgabe (serial reaction time task, SRTT, Nissen & Bullemer, 1987) entwickelt, um Sequenzierungsprozesse mit minimalen motorischen Anforderungen experimentell zu untersuchen. Die SPT-Aufgabe erfordert die Extraktion und Prädiktion sich wiederholender sensorischer Muster in sequentiell präsentierten Stimuli und wird daher gelegentlich auch als (perzeptuelle) Sequenzierungsaufgabe bezeichnet. Im Rahmen dieser Aufgabe ist lediglich eine einzige motorische Reaktion nötig, und zwar erst am Ende des Trials, wenn die Probanden angeben müssen, ob im letzten Teil des Trials eine Verletzung des gelernten Musters stattgefunden hat oder nicht. Im Rahmen jedes einzelnen Experiments der vorliegenden Arbeit wurde zusätzlich zur SPT-Aufgabe eine nicht sequentielle Kontrollaufgabe implementiert, die hinsichtlich attentionaler, perzeptueller und motorischer Anforderungen äquivalent zur SPT-Aufgabe war. Eines der wichtigen Merkmale der SPT-Aufgabe ist die kontinuierliche Stimulation, die eine antizipative Verarbeitung erfordert, welche wiederum auf sensomotorischen Transformationen beruht, wie sie vom prämotorischen Kortex ermöglicht werden. In allen durchgeführten Experimenten wurde eine Sequenz durch die Reihenfolge von drei aufeinanderfolgenden Stimuli definiert, und im Laufe eines Trials mehrmals

wiederholt. Das verletzte Muster, das nur gelegentlich auftrat, beinhaltete immer drei korrekte Stimuli, allerdings traten diese in der falschen Reihenfolge auf, so dass zwei der Stimuli ihre sequentielle Positionen tauschten, was als sequenzieller Devianter bezeichnet wird. In allen Experimenten wurden die cerebralen Korrelate der Detektion dieser devianten Ereignisse untersucht. In früheren Studien ist gezeigt worden, dass die Art der Verarbeitung, die durch die serielle Prädiktionsaufgabe induziert wird von Natur aus prädiktiv ist (zum Vergleich, Schubotz, 2007). Daher ist der Prozess der Detektion sequentieller Devianter als eine Form der Verletzung perzeptueller Erwartungen oder Vorhersagen zu betrachten.

Experimente der vorliegenden Arbeit

In *Experiment 1* wurde der Prozess der Detektion sequentieller Devianter in kurzen perzeptuellen Sequenzen, deren Muster durch die Reihenfolge verschieden großer Stimuli definiert wurde, untersucht. Das Ziel dieser fMRT-Studie war es herauszufinden, in welchem Ausmaß die Detektion sequentieller Devianter von dem cerebralen Netzwerk abhängt, das sich in früheren Studien für die Verarbeitung von regulären Sequenzen als relevant erwiesen hat. Dieses Netzwerk umfasst primär die medialen und lateralen Regionen des prämotorischen Kortex und die mit diesen verbundenen Regionen im parietalen Kortex (siehe auch Schubotz & von Cramon, 2003). Darüber hinaus sollte untersucht werden, in welchem Ausmaß die Detektion sequentieller Devianter zusätzliche Hirnregionen aktiviert, die nicht an der regulären Sequenzverarbeitung beteiligt sind. Der Prozess der Detektion von sequentiellen Devianten wurde mit der Detektion von sogenannten Feature-Devianten (nicht-sequentiellen Devianten) in einer Target-Detektionsaufgabe verglichen. Diese Feature-Devianten wichen bezüglich ihrer perzeptuellen Eigenschaften (wie zum Beispiel, ihrer Farbe) von den Standardreizen ab und verletzten auf diese Weise Erwartungen, die auf dem allgemeinen Aufgabenkontext beruhten. Die Ergebnisse von *Experiment 1* zeigen eine Dissoziation der beiden Prozesse. Sequentielle Deviante gingen mit einem Aktivierungsanstieg in lateralen und medialen prämotorischen Arealen, sowie cerebellären Arealen einher, die auch bei der Verarbeitung regulärer Sequenzen beteiligt waren. Es wird vorgeschlagen, dass dieses Aktivierungsmuster die Detektion einer Nichtpassung zwischen erwarteten und tatsächlich präsentierten Stimuli anzeigt und eine dementsprechende Aktualisierung der Sequenzrepräsentation (d.h., des Vorwärtsmodells) widerspiegelt, das der generierten Erwartung zugrunde liegt. Zusätzlich dazu gingen die sequentiellen Devianten mit Aktivierungen in frontalen Arealen einher, die initial nicht an der Sequenzverarbeitung beteiligt waren. Dieser Befund wird im Sinne einer nachfolgenden Elaboration der Verletzung interpretiert. Im Gegensatz dazu ging die Detektion der nicht-sequentiellen Devianten

mit primär bilateralen Aktivierungen in parietalen und posterior temporalen Arealen einher, während die Aktivierung im präfrontalen Kortex sich auf ein kleineres Gebiet beschränkte. Dieses Aktivierungsmuster reflektiert die durch den nicht-sequentiellen Devianten ausgelöste Steigerung der perzeptuellen und attentionalen Verarbeitung.

In *Experiment 2* wurde eine leicht modifizierte Version des Paradigmas aus dem vorigen Experiment verwendet, um die zeitliche Dynamik der Detektion von sequentiellen und nicht-sequentiellen Devianten zu untersuchen. *Experiment 2* war eine EEG-Studie, in der die ereigniskorrelierten Potentiale, die durch die beiden zuvor beschriebenen Deviantentypen ausgelöst werden, untersucht und verglichen werden sollten. Weiterhin ging diese Studie über die Untersuchung aufmerksamer Sequenzverarbeitung, wie es durch die Standard-SPT-Aufgabe induziert wird, hinaus. Dieser zusätzliche Aspekt betraf die Bedeutung der attentionalen Beteiligung der Probanden beim Lernen perzeptueller Sequenzen und der Identifikation von sequentiellen Devianten. Die Ergebnisse zeigen sowohl für beachtete sequentielle Deviante als auch für Feature-Deviante eine negative Komponente mit einem Maximum um 250-300 ms, die von einer späteren positiven Komponente mit einem Maximum um 500-600 ms gefolgt wurde. Aufgrund ihrer Topographie und der Tatsache, dass sie von beachteten devianten Ereignissen (Patel & Azzam, 2005) ausgelöst wurden, wurden die Komponenten als N2b und als P3b klassifiziert. Die N2b wird bislang als ein Indikator für einen Vergleichsprozess zwischen einem Stimulus und einem mental gespeicherten Template des erwarteten Ereignisses angesehen (Patel & Azzam, 2005), wohingegen die P3b sowohl als Indikator für die Aktualisierung des zugrundeliegenden Sequenzmodells (Polich, 2007) als auch für die entscheidungsbezogene Verarbeitung nach der Kategorisierung interpretiert wurde (Nieuwenhuis et al., 2005). Zusätzlich legen die Ergebnisse von *Experiment 2* eine Dissoziation der Detektion von sequentiellen Devianten und Feature-Devianten über alle Phasen der Verarbeitung nahe. Zunächst lösen nur Feature-Deviante eine N1, also eine frühe negative Komponente aus, was eine sehr frühe Registrierung der Feature-Veränderung nahe legt. Weiterhin deuten die unterschiedlichen Latenzen und Topographien der N2b und P3b-Komponenten auf substantielle Unterschiede sowohl in der zeitlichen Dynamik als auch hinsichtlich der cerebralen Netzwerke, die die Deviantendetektion in den beiden Kontexten unterstützen, hin. Im Vergleich zu beachteten sequentiellen Devianten lösten nicht beachtete Deviante nur in einer Subgruppe von Probanden, die zuvor über die sequentielle Struktur innerhalb des Trials informiert worden waren, eine N2-Komponente aus. Dieser Befund unterstreicht die Bedeutung der attentionalen Beteiligung der Probanden für das Lernen perzeptueller Sequenzen und die Detektion von Abweichungen.

In *Experiment 3* wurde der Prozess der Detektion von sequentiellen Devianten in verschiedenen Arten perzeptueller Sequenzen mittels fMRT untersucht. Die Sequenzarten unterschieden sich auf der abstrakteren Ebene der Stimuluseigenschaften, welche die sequentielle Struktur definierten. In drei verschiedenen Versionen der SPT-Aufgabe wurden drei verschiedene Stimuluseigenschaften verwendet: Objekt-Identität, räumliche Position und zeitliche Dauer (Rhythmus). Sequentielle Deviante in Sequenzen, die durch räumliche oder rhythmische Eigenschaften definiert waren, gingen mit Aktivierungen in parietalen, prämotorischen und überwiegend posterioren präfrontalen Arealen einher. Es gab allerdings auch Dissoziationen zwischen diesen beiden Aufgaben: die Aktivierungen in der Positions-SPT-Aufgabe lagen weiter dorsal im Vergleich zu den Aktivierungen in der Rhythmus-SPT-Aufgabe, die weiter ventral lokalisiert waren. Die Hirnregionen, die an der Detektion von sequentiellen Positions- und Rhythmus-Devianten beteiligt waren, entsprechen zu einem gewissen Grad denen, die in früheren Studien für die Verarbeitung regulärer Positions- und Rhythmussequenzen identifiziert wurden. So ist gezeigt worden, dass Prädiktionen, die auf räumlichen Stimuluseigenschaften basieren, mit Aktivierungen im dorsalen Teil des prämotorischen Kortex einhergehen, im Vergleich zu Sequenzen, die auf rhythmischen Stimuluseigenschaften basieren, welche wiederum mit Aktivierungen im inferioren Teil des ventralen prämotorischen Kortex einhergehen (Schubotz et al., 2008; Wolfensteller, Schubotz, & von Cramon, 2007). Im vorliegenden *Experiment 3* war die Detektion von Verletzungen in den Objekt-Sequenzen mit einem speziellen Muster parieto-temporalen Aktivierungen verbunden, ohne eine zusätzliche Beteiligung frontaler Areale. Dieser daher als speziell anzusehende Devianz-Typ wurde im Anschluss im letzten Experiment genauer untersucht.

In *Experiment 4*, einem weiteren fMRT-Experiment, wurde der Prozess der Detektion sequentieller Devianten in perzeptuellen Sequenzen, die durch die Objekt-Identität der Stimuli definiert wurden, detaillierter untersucht. Zu diesem Zweck wurden zwei verschiedene Sequenz-Typen generiert, die sich hinsichtlich der Spezifität bzw. der Stärke der Erwartungen unterschieden, welche bezüglich der präsentierten Stimuli generiert werden konnten. In der sogenannten ‚Token-SPT-Aufgabe‘ bestanden die Wiederholungen der Originalsequenz aus exakt denselben Stimulusexemplaren, die in der Originalsequenz präsentiert worden waren. In der sogenannten ‚Typ-SPT-Aufgabe‘ hingegen wurden für die Wiederholungen Stimulusexemplare verwendet, die zwar derselben Kategorie angehörten wie die in der Originalsequenz präsentierten, aber nicht mit diesen identisch waren. Mithin wurden in *Experiment 4* die Effekte sequentieller Verletzungen von spezifischen (Token) und kategorialen (Typ) Erwartungen verglichen. Die Ergebnisse legen, ähnlich den Objekt-Sequenzen in *Experiment 3*, eine starke Beteiligung parieto-temporalen Areale

für die Token-Sequenzen nahe, welche hier zusätzlich von Aktivierungen in lateralen präfrontalen Arealen begleitet wurden. Für die Detektion sequentieller Devianten in Typ-Sequenzen wurde eine teilweise mit diesen Regionen überlappende Aktivierung im rechten inferioren Parietalcortex gefunden, wiederum begleitet von Aktivierungen im lateralen präfrontalen Kortex. Die Aktivierung auf sequentielle Deviante hin war in der Token-SPT-Aufgabe generell ausgeprägter als in der Typ-SPT-Aufgabe. Dies lässt sich im Sinne der stärkeren Nicht-Passung interpretieren, die sich aus dem Vergleich der präsentierten Stimuli mit den spezifischeren Erwartungen ergeben, die im Rahmen der Token-Sequenzen formuliert werden konnten.

Zusammenfassung

Das Ziel der vorliegenden Arbeit war die Untersuchung der Detektion sequentieller Devianter im Kontext prädiktiver perzeptueller Verarbeitung, unter Verwendung von Sequenzen visueller Stimuli. Durch die devianten Ereignisse werden Erwartungen innerhalb perzeptueller Sequenzen verletzt, deren Struktur durch die Reihenfolge der präsentierten Stimuli definiert ist. In den ersten beiden Experimenten wurde die Detektion derartiger sequentieller Devianter mit der Detektion von Feature-Devianten verglichen, welche globale Erwartungen verletzen, die auf den perzeptuellen Features der einzelnen Stimuli basieren. Die Ergebnisse beider Experimente legen eine Dissoziation der Verarbeitung dieser beiden Devianz-Typen sowohl auf der Ebene der zeitlichen Dynamik als auch auf der Ebene der beteiligten Hirnareale nahe. Im Anschluss daran wurde die Verarbeitung sequentieller Devianter im Rahmen verschiedener perzeptueller Sequenzen genauer untersucht, die durch verschiedene Stimuluseigenschaften definiert waren oder sich durch unterschiedliche Spezifität (der formulierbaren Erwartungen) auszeichneten. Wenn man die Ergebnisse der drei fMRT-Experimente der vorliegenden Arbeit vergleicht, ergibt sich für die Detektion sequentieller Devianter ein teilweise überlappendes, aber nicht einheitliches Muster cerebraler Aktivierungen. Diese Befunde legen nahe, dass die spezifischen Faktoren, welche die sequentielle Struktur definieren, einen starken Einfluss darauf haben welche Hirnregionen an der Detektion von Verletzungen der verschiedenen Sequenzen beteiligt sind. Insbesondere zwei Faktoren haben sich als besonders wichtig herausgestellt. Der erste wichtige Faktor ist die sequenzdefinierende Stimuluseigenschaft, welche auch die Charakteristik der sensomotorischen Transformation bestimmt, die sie erfordert. Der zweite wichtige Faktor ist die Spezifität der Erwartungen, die ein bestimmter Sequenztyp überhaupt ermöglicht. Schließlich könnten weitere, hier nicht explizit untersuchte Sequenzeigenschaften, wie z.B. die Anzahl der Sequenzwiederholungen, die Beteiligung der hier identifizierten cerebralen Netzwerke bei der Detektion devianter Ereignisse modulieren. Zu-

sammenfassend ist festzuhalten, dass die Detektion sequentieller Devianter keineswegs einen einheitlichen Prozess darstellt, sondern vielmehr hochgradig von denjenigen Eigenschaften einer Sequenz abhängt, welche die Art der formulierbaren und durch deviante Ereignisse verletzbaren Erwartungen bestimmen.

Selbständigkeitserklärung

Hiermit erkläre ich, daß die vorliegende Arbeit ohne unzulässige Hilfe und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt wurde und daß die aus fremden Quellen direkt oder indirekt übernommenen Gedanken in der Arbeit als solche kenntlich gemacht worden sind.

Andreja Bubić

Leipzig, den 24. März 2009

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