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Learning from errors: Genetic evidence for a central role of dopamine in human performance monitoring

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1 Introduction

Living in a constantly changing environment requires continuous updating of performance plans. This is necessary to receive maximal positive outcome from one's actions. A particular brain system monitors ongoing human performance and signals the need for adaptation whenever the outcome of an action is at risk or worse than expected. If a person is confronted with the same situation again, s/he remembers this situation and behaves in an appropriate manner. Performance monitoring needs to interact with learning to provide the organism with tools to face future challenges. Different areas in the brain are potentially involved in this process: the posterior medial frontal cortex (pMFC) is heavily involved in processing of errors and negative feedback – cases in which activity of a performance monitoring system is needed. Holding relevant information online, in order to guide human performance, the lateral prefrontal cortex (PFC) seems a promising target. Finally, to enable long term adaptation of behavior also learning-related brain areas have to be considered, for example the hippocampus.

The neuromodulator dopamine (DA) is thought to play a major role within the process of performance monitoring and learning from action outcomes. Phasic changes in DA concentration signal the valence of the outcome of an action: whenever the outcome of an action is better than expected there is a phasic increase in dopaminergic activity, whereas when the outcome of an action is worse than expected, a phasic decrease in dopaminergic activity can be observed. This dopaminergic signal is conveyed for example to the pMFC, where in case of negative action outcomes remedial actions can be triggered. Another major target of dopaminergic projections from the midbrain are the basal ganglia (BG), a structure involved in habit learning. They presumably use phasic dopaminergic signals to learn only actions that are associated with a positive outcome. In contrast to this slowly-acting process of habit formation in the BG another system is monitoring action outcomes within a more restricted time range: the PFC is thought to be the "home" of working memory, an ability of holding information online over a given time period.

Under standard conditions BG and PFC work in parallel. DA is the neuromodulator which ties these two systems together: DA is also highly relevant for processes like working memory. The processes outlined above rely on the functional integrity of the DA system. Dopaminergic signaling can be challenged in many ways – over the last years it turned out that not only pathological processes or drugs of abuse are potent modulators of dopaminergic function. Also the genetic makeup of a person can contribute to subtle alterations in dopaminergic neurotransmission.

In the present work we show that human performance monitoring is dependent on the neurotransmitter DA. A genetic polymorphism modulating the DA D2 receptor density in the striatum can influence how the performance monitoring system responds to negative feedback. Furthermore, we show how this negative feedback is used to enable long term adaptations of performance, i.e. learning. Timing of the experimental paradigm should have an influence on the performance in the task. Related to this there should be differential interactions between the genotype and the timing influence. The role of DA in triggering performance-monitoring-related activity in the pMFC will be discussed as well as genotype-dependent differences in learning. The latter differences are discussed in terms of habit learning vs. working memory processes. Differential influences of a lower or normal1 D2 receptor density on these two systems of action guidance are also covered.

After a short introduction into the theoretical background of performance monitoring and the brain areas involved in this process we will turn to the role of DA in this process. We will show how dopaminergic signaling can be influenced by genetic polymorphisms within the dopaminergic system. We will present evidence from functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) showing that alterations in dopaminergic signaling lead to corresponding alterations in the processing of negative feedback and related to this, to alterations in the use of negative feedback for feedback-guided learning. Implications of these findings will be shortly discussed. A general discussion will be provided which includes also an outlook to future research topics.

[1] "Normal" refers to the fact that 70% of the population have this receptor density – therefore normality is meant in terms of frequency.

2 Theoretical Background

2.1 Performance Monitoring

How does the human brain realize that an error occurred in the continuous stream of performance? Either the brain signals that something in the performance was suboptimal or the person receives negative feedback from the environment. There is evidence from electrophysiological and fMRI studies that these two modalities of signaling erroneous performance are processed in similar regions of the human brain (Ullsperger & von Cramon, 2003; Miltner et al., 1997).

Reason (1990) distinguished three error types:

- Mistakes: errors in planning an action
- Lapses: failures in the storage phase, i.e. between planning and executing the action
- Action Slips: failures in the execution of an action, i.e. the correct response is known, but the incorrect response is executed

Mistakes are hard to detect because of the large temporal offset between the time of error commission and the consequence of the error. Action slips are very easy to detect. Considering the option of endogenous error detection the question arises how the brain "knows" which answer would have been the correct one and subsequently how the process of error detection and error signaling is implemented in the brain. Alternative theories dealing with this question have one property in common: They require representations of the correct and the actually executed action. This is necessary for a comparison of or a conflict between these two actions. This comparison is taking place either at the stage of preparation/execution of the action (Response Conflict Model) or the stage of evaluation of the executed action (Mismatch Hypothesis and Reinforcement Learning Hypothesis). Another common feature of these theories is that error detection is used to enable adaptive behavior in an unstable environment. These adaptations can

take place on different timescales: Probably the fastest reaction to an error is the immediate error correction. This is execution of the correct response (Rabbitt, 1966a, 1966b). A further quick adaptation after an error is slowing down in the trial following an error. This so-called post-error-slowing was first discovered by Rabbitt (1966b) and interpreted as a hint for a more cautious response strategy after an error. Ridderinkhof (2002) proposed the so-called post-error-reduction in interference. That means that after an error had occurred more cognitive control is employed in order to improve subsequent behavior. If now the trial after an error is a trial with interference between competing response alternatives, this interference is more easily resolved because of the higher amount of cognitive control in this trial. In the long run, errors serve as teaching signals enabling learning. As errors are rather rare events they carry more information about how to perform than correct responses do. Therefore, errors are often highly valuable for learning. Error-driven learning may be the consequence of an error with the longest temporal impact. Assuming learning from errors requires a functional relationship between performance monitoring and learning-related areas in the brain.

2.2 Correlates of Performance Monitoring

2.2.1 Electrophysiological Correlates of Performance Monitoring

In 1990, Falkenstein and colleagues reported a sharp negative deflection with a fronto-central scalp distribution in the human electroencephalogram (EEG) after subjects had committed an error. Falkenstein and colleagues called this peak error-negativity (Falkenstein et al., 1990; Ne, also referred to as error-related-negativity, ERN Gehring et al., 1993). It occurs between 50-100 ms after the onset of the erroneous action. It is often followed by a positive deflection at about 300 ms post-error with a more parietal scalp distribution, the so-called error-positivity (Pe). The functional significance of the ERN can be described as being an electrophysiological correlate of error detection or conflict monitoring. The role of the Pe is much less clear. A recent review by Overbeek and colleagues (2005) found weak support for the assumption that the Pe is related to the emotional reaction to an error. Others describe the Pe as being a correlate of error-awareness (Nieuwenhuis et al., 2001; Endrass et al., 2005).

The ERN can be triggered by errors committed with different effectors: hand (Fiehler et al., 2005), foot (Holroyd et al., 1998), voice (Masaki et al., 2001) or

eye movements (Nieuwenhuis et al., 2001; Van`t Ent & Apkarian, 1999). In situations in which subjects do not have enough information to decide whether or not an action was erroneous, an ERN-like negativity can be triggered by negative performance feedback (Miltner et al., 1997). The so-called feedback-ERN or feedback-related negativity (FRN) is similar in topography to the response ERN (medial frontal distribution) and is supposed to be generated by the same brain regions as the response ERN (Gehring & Willoughby, 2002; Nieuwenhuis et al., 2004). According to Holroyd and Coles (2002) the amplitude of the FRN varies with the degree of experience/knowledge the subject has about the task. At the beginning of a new task subjects do not know which response to perform. Therefore, performance monitoring must rely on external feedback. With increasing knowledge about the nature of the task the information value of the feedback decreases as does the amplitude of the FRN.

Source localization and fMRI studies (Dehaene et al., 1994; Gehring et al., 2000; Ullsperger & von Cramon, 2003) constantly point to a region within the pMFC as being the source of the ERN and the FRN: the rostral cingulate zone (RCZ; Ullsperger & von Cramon, 2004).

2.2.2 Hemodynamic Correlates of Performance Monitoring

There is good evidence for the RCZ being a key player in performance monitoring. In case of an error, increase in RCZ activity can be observed (Ullsperger & von Cramon, 2001, 2003; Klein et al., 2007a). This error-related activity can be triggered by self-generated errors (Ullsperger & von Cramon, 2001) or by external error feedback (Holroyd et al., 2004).

A recent metaanalysis combining results from various fMRI studies on error processing (red triangles), pre-response conflict (blue dots), decision uncertainty (green circles) and negative feedback (yellow triangles; Ridderinkhof et al., 2004, see figure 2-1) gives further support to the notion of a central role for RCZ in performance monitoring.

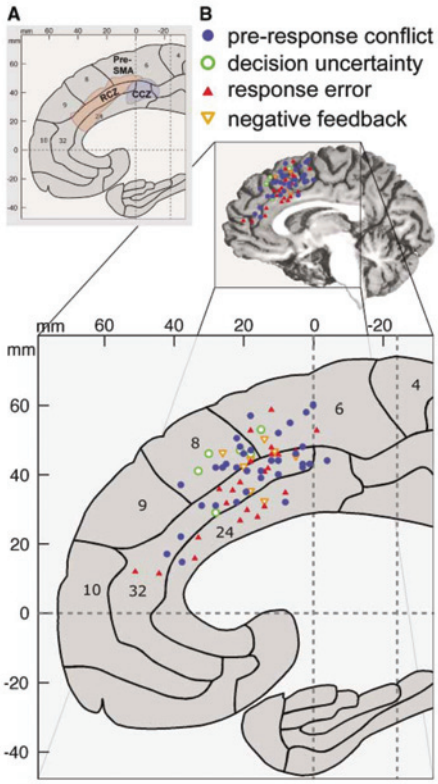


Figure 2-1 Metaanalysis on Performance Monitoring (taken from Ridderinkhof et al., 2004)

As can be seen from fig. 2-1 performance monitoring related processes cluster within the RCZ. From an anatomical (see section 2.4) and functional perspective this brain area seems to be well suited to play a central role in performance monitoring and subsequent behavioral adaptations.

DA is assigned a central role in current theories of cognitive control. A dip in dopaminergic activity following negative performance outcome/performance feedback is thought to trigger RCZ activity with the goal of optimizing future behavior (Holroyd & Coles, 2002).

2.3 Models of Error Detection

Different models have been developed to explain how the brain detects an error. They vary in terms of the signal that serves as the error correlate or in terms of the potential consequences of an error. In the following section three main theories will be briefly introduced: the mismatch hypothesis, the response conflict model and the reinforcement learning model.

2.3.1 Mismatch Hypothesis

The mismatch hypothesis assumes that a comparison process in the brain reveals a mismatch between the intended and the actually performed action when an error was made (Falkenstein et al., 1990, 2000; Gehring et al., 1993, Coles et al., 2001, Falkenstein, 2004). While the stimulus is still processed and the representation/implementation of the correct response is built up, a second, in this case incorrect response is being executed. After execution of the incorrect response an efference copy of this response is compared to the now available representation of the correct response. If a mismatch is detected an error signal is generated which in turn leads to measurable correlates of error detection.

2.3.2 Response Conflict Model

The response conflict model assumes that the measurable correlates of error processing are not due to error detection. They are assumed to be a direct expression of conflict between competing response alternatives (Botvinick et al., 2001, 2004). Two types of conflict can be distinguished by their time of appearance in human performance: If two response tendencies are triggered at the same time and these two tendencies compete, a pre-response conflict occurs. On the other hand, if a premature response has been given and the tendency for the correct response evolves later, a post-response conflict is assumed.

2.3.3 Reinforcement Learning Model

Holroyd and Coles (2002) proposed a model of performance monitoring that combines error processing with mechanisms of reward signaling. The reinforcement learning model stresses the importance of errors for improvements in subsequent task performance implementing principles of reinforcement learning (Holroyd & Coles, 2002). The model holds strong assumptions with respect to brain areas involved in error processing. The theory describes a central role for the

neurotransmitter DA in performance monitoring. This is done by incorporating findings from the animal literature showing that dopaminergic neurons in the midbrain signal the value of the outcome of an action. If an unexpected reward is presented, a phasic increase in activity of midbrain dopamine neurons can be observed. Whenever the outcome of an action is worse than expected an "error in reward prediction" is detected by the BG and signaled via a phasic dip in dopaminergic activity (Schultz, 2000, 2002). This phasic DA dip is thought to disinhibit apical dendrites of layer V neurons in the RCZ. RCZ activity in turn can be used to improve the performance of the task or to trigger subsequent adaptations in performance. According to Holroyd & Coles (2002) the BG learn to predict the outcome of an action and therefore to detect a discrepancy between an expected and the actual outcome. This learning improves over time enabling BG to play the role of an adaptive critic in performance monitoring.

Given the important role ascribed to the medial frontal cortex anatomical and functional details of this brain region should be introduced.

2.4 Anatomy of the Medial Frontal Cortex

Based on cytoarchitectonic maps Brodmann (1909) divided the cortex into 43 cortical regions, so-called Brodmann Areas (BA). Regions most interesting for performance monitoring within the frontomedian wall are BA 6 (premotor isocortex), BA 8 (prefrontal isocortex), BA 32 (paralimbic dysgranular cortex) and BA 24 ("limbic" agranular cortex).

2.4.1 Performance Monitoring Related Areas of the Medial Frontal Cortex

In the following, performance monitoring related areas will be described in more detail.

- BA 6 can be divided into two areas based on functional and connectivity criteria: the pre-supplementary motor area (pre-SMA) and the supplementary motor area (SMA; Picard & Strick, 2001). Based on cytoarchitectonic and histochemical monkey data, Matelli and colleagues (1985) suggested that monkey F6 (in monkeys, frontal cortex is subdivided into areas from F1 to F7) corresponds to the human pre-SMA, whereas monkey F3 is corresponding to the human SMA (see also Luppino & Rizzolatti, 2000). In humans the level of the anterior commissure (VCA line) constitutes the

border between SMA and pre-SMA (Picard & Strick, 2001). Vorobiev et al. (1998) further subdivided the SMA based on architectonic features into the caudal SMA and rostral SMA. The SMA is more closely related to motor functions as it projects directly to the primary motor cortex and the spinal cord. The pre-SMA on the other hand is interconnected with the prefrontal cortex (Bates & Goldman-Rakic, 1993) thus functionally related to selection and preparation of movement as well as controlling of movements in terms of when to start the movement triggered by external contingencies or motivation (Luppino & Rizzolatti, 2000).

- BA 8, superior to BA 32 and anterior to pre-SMA, covers the posterior part of the superior and middle frontal gyri and extends medially to the paracingulate sulcus (Petrides & Pandya, 1999).
- BA 32 is located between the cingulate sulcus and the paracingulate sulcus (if existent) and forms a belt around BA 24 (Petrides & Pandya, 1999). The width of this transition cortex in humans is currently under debate.
- BA 24 is constituted by the anterior cingulate cortex (ACC). The ACC is located on the anterior portion of the cingulate gyrus. Superiorly the ACC is bordered by the sulcus cinguli, inferiorly the border of the ACC is marked by the sulcus corporis callosi. The role of dorsal ACC, i.e., the part located superior to the corpus callosum, in behavioral control is highlighted by three key features: projections to the motor cortex and the spinal cord (role in motor control); reciprocal connections between ACC and the lateral prefrontal cortex (role in cognition); extensive afferents from midline thalamus and brainstem monoamine nuclei (ACC function influenced by arousal/drive states (Paus, 2001)).

2.4.2 The Rostral Cingulate Zone

In the primate brain the cingulate sulcus contains three different motor areas (Picard & Strick, 2001):

1. the rostral cingulate motor area (CMAr)
2. the caudal cingulate motor area located in the ventral bank of the sulcus (CMAv)
3. the caudal cingulate motor area located in the dorsal bank of the sulcus (CMAd).

Picard and Strick (2001) proposed that corresponding areas exist in the human brain. They distinguish a rostral cingulate zone (RCZ with two subdivisions: anterior RCZ (RCZa) & posterior RCZ (RCZp)) and a caudal cingulate zone (CCZ; see fig. 2-2). The CCZ is activated in relation to movement execution and seems to be comparable to the monkey CMAd. Based on functional data the CCZ seems clearly distinct from the SMA despite their close proximity.

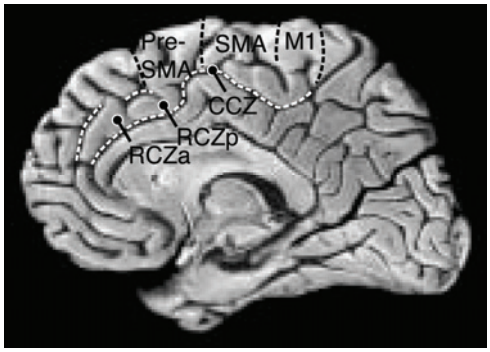


Figure 2-2 Medial frontal cortex (taken from Picard & Strick, 2001)

Motor and cognitive functions may both be represented within the RCZ: movement-related activations (rostral to VCA line) as well as activations related to a word generation task (in or near cingulate or paracingulate sulci; Crosson et al., 1999) can be found within this area. Two major views have been proposed to describe the overall function of the RCZ: performance monitoring (evaluative function of RCZ) and attention/selection for action (motor function of RCZ). According to Picard and Strick (2001) these two views relate to different subdivisions of RCZ: Performance monitoring is proposed to be located in RCZa (potentially corresponding to monkey CMAr) whereas selection for action is correlated to RCZp (potentially corresponding to monkey CMAv) function. While an earlier review of neuroimaging studies suggested evidence for this separation in humans (Picard & Strick, 2001), more recent metaanalyses demonstrated that performance-monitoring-related activity increases can be found in the entire RCZ (Ridderinkhof et al., 2004; figure 2-1).

Holroyd & Coles (2002) proposed the reinforcement learning model of error detection/processing (see section 2.3.3). Within this theoretical framework a central role in triggering performance monitoring related activity in the frontomedian

wall is proposed for the mesocortical DA system. Therefore the anatomy as well as the functionality of the human dopaminergic system will be described in the following sections.

2.5 Dopamine and Dopaminergic Neurotransmission in the Brain

2.5.1 Midbrain Dopamine Neurons and the Striato-Nigro-Striatal Network

Midbrain Dopamine Neurons

Roughly 50 years ago the neurotransmitter DA was first discovered in the human brain (Carlsson et al., 1958). In the meantime DA has become a well-known actor in different brain functions. Besides playing a central role in many major illnesses like Parkinson's disease, schizophrenia, attention deficit hyperactivity disorder (ADHD) or drug addiction, DA has become a major target for research questions in cognitive neuroscience as well. DA is thought to play a role in different cognitive functions such as reinforcement learning, motivation (thereby linking cognition and action), working memory, attention and goal directed behaviors. Classically, midbrain DA neurons are divided into two tiers (Haber, 2003) based on cellular as well as on neurochemical features and on different patterns of connectivity (Bentivoglio & Morelli, 2005):

1. dorsal tier containing
   - ventral tegmental area (VTA)
   - dorsal substantia nigra, pars compacta (dorsal SNc)
   - retrorubral cell groups
2. ventral tier containing most of the SNc (a densocellular group and the cell columns).

Figure 2-3 shows a coronal section through the human midbrain displaying some key structures of the human dopaminergic system.

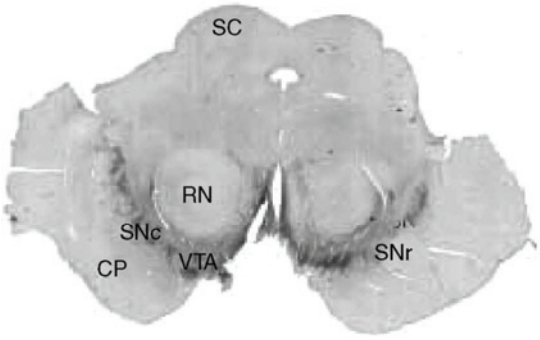


Figure 2-3 Photomicrograph of a tyrosine hydroxylase positive-stained coronal section through the human midbrain (taken from Haber, 2003) showing the distribution of dopaminergic cells in the substantia nigra and the nearby ventral tegmental area. SC = superior colliculus; RN = red nucleus; SNc = substantia nigra pars compacta; CP = cerebral peduncle; VTA = ventral tegmental area; SNr = substantia nigra pars reticularis

The dorsal tier is relatively low on DA transporter (DAT) and D2 Receptor messenger-RNA (mRNA), whereas the ventral tier shows a high expression of DAT and D2 receptor mRNA. The ventral tier is especially vulnerable to neurodegeneration whereas the dorsal tier is not (Haber et al., 1995).

Striato-Nigro-Striatal Network

The midbrain striatal projections are oriented in an inverse dorsal-ventral topographic organization. Dorsal and medial DA cells send projections to ventral and medial parts of the striatum whereas ventral and lateral cells project to dorsal and lateral parts of the striatum (Haber, 2003). The most limited input from the midbrain, primarily derived from the VTA, is going into the ventral striatum. The rest of the ventral striatum is innervated by the entire dorsal tier (most medial and dorsal part of the densocellular group). Central striatal areas receive input from the densocellular group. The ventral tier projects to the dorsolateral striatum (cell columns projecting exclusively there). Projections from the striatum to the midbrain are also inversely dorsally-ventrally arranged. Dorsal aspects of the striatum project to the ventral regions of the midbrain whereas ventral areas of the striatum project dorsally (Haber, 2003).

Mesocortical Projections

Besides projections to the striatum, axons of DA neurons project topographically to most areas of the neocortex with most prominent projections to the prefrontal cortex. Projections to the prefrontal cortex are not as strictly organized in terms of topography as projections to the striatum. They mostly arise from VTA.

Projections to anterior cingulate cortex instead arise from cells of the lateral portion of the VTA and of the medial portion of the SNc. Dopaminergic axons in the cortex branch, thus reaching more than one cortical area. Neurons from the medial portion of the SNc are sending collaterals to the frontal cortex as well as to subcortical targets (striatum and septum; Bentivoglio & Morelli, 2005).

Three major pathways from midbrain DA neurons have been identified corresponding to distinct functional roles (Iversen & Iversen, 2007):

1. To the dorsal striatum: central role in coordinating loops linking the midbrain, the BG, the thalamus and the cortex thereby orchestrating motor behavior (Haber , 2003)
2. To the ventral striatum (including nucleus accumbens): implicated in motivation, thereby providing a link between affect and action. Also highly relevant for reward-based learning of goal directed behavior (Iversen & Iversen, 2007)
3. To the lateral and medial frontal cortex: DA release in prefrontal cortex, mainly acting through D1 receptors, is thought to influence spatial working memory (Sawaguchi & Goldmann-Rakic, 1991; Wang et al., 2004).

2.5.2 The Striatum

The striatum is one of the major projection areas of midbrain DA neurons and represents the main input structure into the BG. Neurons within the striatum receive large inputs from all areas of the cortex and the thalamus which underlines the important computational role of the striatum especially in the acquisition of motor and cognitive action sequences (Calabresi et al., 2007). Inputs from the cortex converge on GABA-ergic medium spiny neurons (90-95% of all striatal neurons are medium spiny neurons (MSNs); projection cells to the BG output structures) and exert a strong glutamatergic excitatory influence on these neurons. Dopaminergic signals from the substantia nigra pars compacta converge with these cortical inputs enabling the striatum to play a key role in processing of re-

ward signals. Thereby associations of DA mediated transmission and sensory cue processing from cortical areas are established.

Functional subregions of the striatum are defined on the basis of the organization of the corticostriatal input. Motor and premotor cortex project to the dorsolateral striatum and to parts of the central and caudal putamen. The ventromedial striatum (nucleus accumbens, rostral, ventral nucleus caudatus and putamen) receives input from the medial frontal cortex, which is involved for example in the development of reward-guided behavior. The region between the dorsolateral and the ventromedial striatum receives input from the dorsolateral prefrontal cortex, an area involved for example in working memory.

The Corticostriato-Thalamocortical Loop – Classical View

The striatum projects to the pallidal complex and the substantia nigra pars reticulata (SNr; Haber & Gdowski, 2004) via two main pathways (Frank, 2005). The output from the globus pallidus internal segment (GPi) and the SNr goes to the thalamus and from there to the cortex, thereby forming the basic cortico-basalganglia loop, referred to as direct pathway. In addition an indirect pathway is also assumed, connecting the striatum via the globus pallidus external segment (GPe), subthalamic nucleus to the GPi, thalamus and cortex. The two pathways appear to differ with respect to their response to dopamine (see below).

These two organizational schemes most likely work together. This allows coordinated behavior to be maintained but also to be modified by appropriate external and internal stimuli. The direct pathway is thought of as facilitating a response, the indirect pathway inhibits responses. Cells in the direct pathway project from the striatum and if firing, inhibit the GPi. As the GPi is tonically inhibiting the thalamus, inhibition of the GPi results in disinhibition of the thalamus. This disinhibition allows the thalamus to get excited by other excitatory projections. Cells in the indirect pathway instead inhibit the external segment of the globus pallidus (GPe), which tonically inhibits the GPi. The effect of excitation of indirect cells is increasing the inhibition of the thalamus. If now striatal cells in the direct pathway disinhibit the thalamus, the activity of the motor command that is currently present in the motor cortex is enhanced thereby facilitating the execution of this response (“Go” signal). Activity in the indirect pathway suppresses a response thereby sending a “No-Go” signal.

Challenges for the Classical View

The idea of a movement releasing direct pathway and a movement inhibiting indirect pathway has recently been challenged by Ann Graybiel (Graybiel, 2005). The most relevant challenges concerning our work should briefly be mentioned:

1. *Target nuclei of the direct and indirect pathway*: In monkeys the direct and indirect pathway have collaterals that target all nuclei of the BG (GPe, GPi and SNr). The conventionally accepted segregation into direct pathway (GPi, SNr) and indirect pathway (GPe) thus seems to be challenged.
2. *Inhibition by pallido-thalamic pathway*: Taking into account rebound excitation of thalamic neurons caused by GABAergic inputs, the view is challenged that BG output to the thalamus is always inhibitory in nature.
3. *Unique role of DA*: Recent evidence suggests that DA neurons of the VTA produce fast excitations of the ventral striatum by releasing glutamate (Chuhma et al., 2004). This glutamate release is thought to push striatal neurons into an upstate with DA determining how long the neurons will stay in this state.
4. *The same cortical input into both pathways*: The classical view that the motor cortex sends the same cortical information to striatal projection neurons in either the direct or the indirect pathway has been challenged recently. Lei and colleagues (2004) showed that collaterals of pyramidal tract neurons project to indirect pathway in the sensorimotor striatum. Neurons in the direct pathway on the other hand receive input from distributed terminals of non-pyramidal-tract neurons having intratelencephalic projections.

Thus the question is not whether or not the BG play a central role in integration of reinforcement and action-related signaling. Rather existing models will have to be extended in order to integrate recent findings, thus making models of BG function more comprehensive.

As the classical model of BG loop activity is offering the opportunity to derive testable hypotheses about the differential role of D1 and D2 receptors, this model will be the basis for our investigations – keeping in mind that modifications may be necessary.

A Model of Dopamine Influencing Basal Ganglia Loop Activity

The activity within the BG loops is strongly influenced by phasic changes in DA. The DA D1 receptor family is mainly excitatory whereas receptors from the D2 family are mainly inhibitory in nature. D1 receptors are mainly expressed in striatal cells of the direct pathway whereas D2 receptors can be mainly found in the indirect pathway (Frank, 2005). Figure 2-4 illustrates this in more detail.

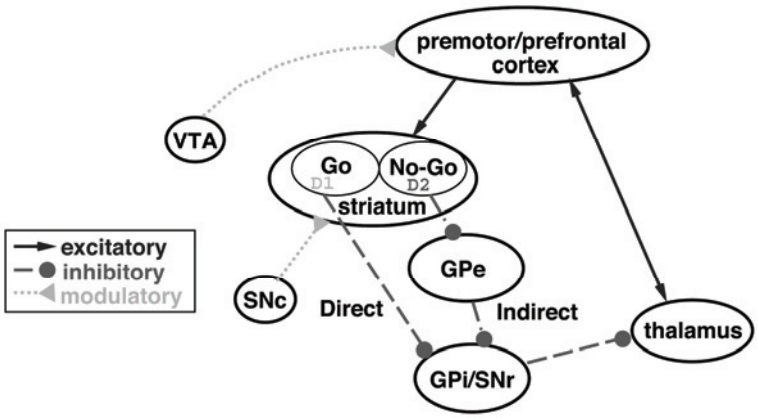


Figure 2-4 The corticostriato-thalamocortical loops (VTA = ventral tegmental area; SNc = substantia nigra pars compacta; SNr = substantia nigra pars reticularis; GPi = Globus pallidus internal segment; GPe = Globus pallidus external segment; taken from Frank, 2005)

As mentioned above, cells in the striatum can be divided into two subclasses (based on biochemistry and projections). The "Go" cells project through the GPi disinhibiting the thalamus. They facilitate execution of an action represented in the cortex. The "No-Go" cells on the other hand are integrated in the indirect pathway therefore having an opposing effect: suppression of a response (Frank, 2005). In case of an increase in DA, e.g. following reward, due to the asymmetry in receptor density (D1 vs. D2 receptors in the direct and indirect pathway, resp.) the direct pathway is getting active whereas the indirect pathway is suppressed. DA depletion, for example following a response error, in turn has the opposite effect, triggering the indirect pathway to be more influential.

A basic principle in learning theory holds that more active cells undergo long-term potentiation (LTP) whereas less active ones show long-term depression (LTD). Due to the phasic modulation of DA in response to an action outcome one would expect in case of a positive action outcome more DA driven "Go" learning.

This should in turn lead to a higher probability of a re-execution of this rewarded action (LTP on “Go” cells, LTD on “No-Go” cells) because cells are much more active following a “Go” signal. If the outcome of an action is worse than expected “No-Go” learning should be increased to prevent the erroneous action from being re-executed (LTP on “No-Go” cells, LTD on “Go” cells; Calabresi et al., 1997). A fundamental property of DA in the human cortex is that it can exert its influence in two different ways: through tonic and phasic signaling (Grace, 1991). All the theories mentioned above heavily rely on phasic changes in dopaminergic activity. The following section will describe these implications in some more detail.

2.6 Dopamine and Reward

It is not (non-)reward per se that is coded by the activity of midbrain dopaminergic neurons, it is the so-called “prediction error” or “error in reward prediction”. This means that the expectation of receiving a reward is violated by the actually experienced action outcome. By definition this prediction error can have two signs: On the one hand, an agent can get more than expected (positive error in reward prediction), on the other hand, the outcome of an action can be worse than expected (negative error in reward prediction). The DA response can therefore be formalized in the following equation (Schultz, 2007):

DA response = prediction error = reward occurred – reward predicted

The dopaminergic response resembles the principle learning term of the Rescorla-Wagner Model (Rescorla & Wagner, 1972) and other models using temporal difference learning (Sutton & Barto, 1981). Learning only takes place if the organism encounters a difference between an expected and an actual action outcome. In order to contribute to learning a reinforcer must be unpredicted by the organism. Reinforcers that turn out to be better than expected trigger learning, reinforcers that are fully predicted do not contribute to learning, and reinforcers that turn out to be worse than expected lead to extinction of previously learned behavior. In terms of firing rates of dopaminergic neurons in the ventral tegmental area (VTA), this can be visualized as follows:

In the upper panel of figure 2-5 the reaction of dopaminergic cells confronted with an unexpected reward (R) is depicted. A phasic increase in firing rate can be observed. After several trials of conditioning a conditioned stimulus (CS) that is reliably followed by reward can elicit a “reward-response”. When the real reward is presented no further change in the firing rate can be observed (middle panel).

Finally (bottom panel), when a CS predicts a reward, but no reward occurs, a phasic decrease in the activity of the dopaminergic neurons can be observed (Schultz et al., 1997). There is evidence that these outcome-dependent changes in extracellular DA level are critical for learning. In animals, D1 receptor stimulation leads to LTP, on the other hand, D2 receptor stimulation restricts LTP (Nishi et al., 1997).

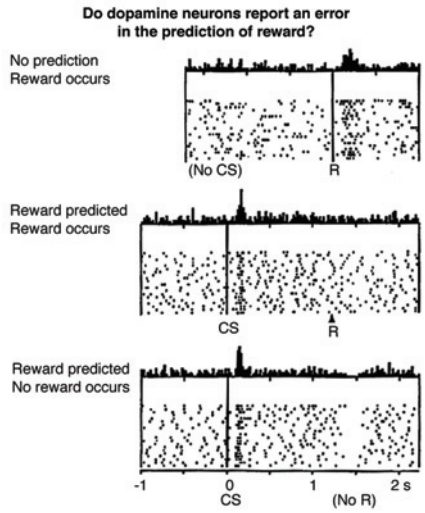


Figure 2-5 Phasic changes in dopaminergic firing (taken from Schultz et al., 1997)

Associative learning may be enhanced by the presence of DA. Thus, DA may act as a teaching signal (Schultz, 2002). Associative learning could be realized by converging input of cortical and DA afferents on a medium spiny neuron in the striatum (see figure 2-6). The cortical afferent delivers specific aspects of the reward-related event (for example sensory modality) using glutamatergic signaling. The occurrence of a positive or negative error in reward prediction leads to a global, spatially unspecific change in DA concentration. Only synapses that are activated at the same postsynaptic spine will be influenced by this dopaminergic teaching signal.

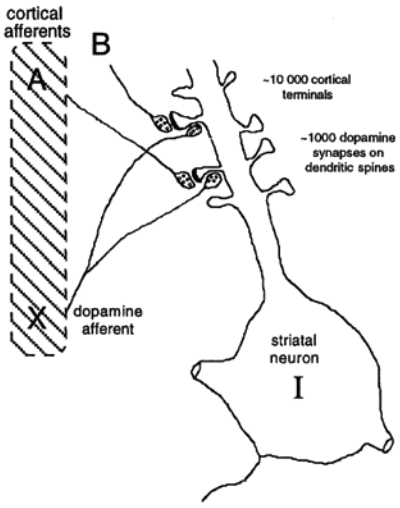


Figure 2-6 Medium spiny neuron of the striatum: inputs from cortex and dopaminergic cells (taken from Schultz, 2002)

2.7 Dopamine and Working Memory

The PFC also receives strong dopaminergic input which influences information processing in this area. An interesting example is the dose-dependent effect of DA on working memory function. Following the work of Patricia Goldman-Rakic and colleagues (e.g. Goldman-Rakic, 1995) only an optimal level of DA guarantees a proper working memory function. Either too much or too little of DA is detrimental for working memory performance (e.g. Vijayraghavan et al., 2007). This dose-dependent effect of DA can be illustrated as an inverted U curve (see figure 2-7), showing optimal performance only on medium levels of DA.

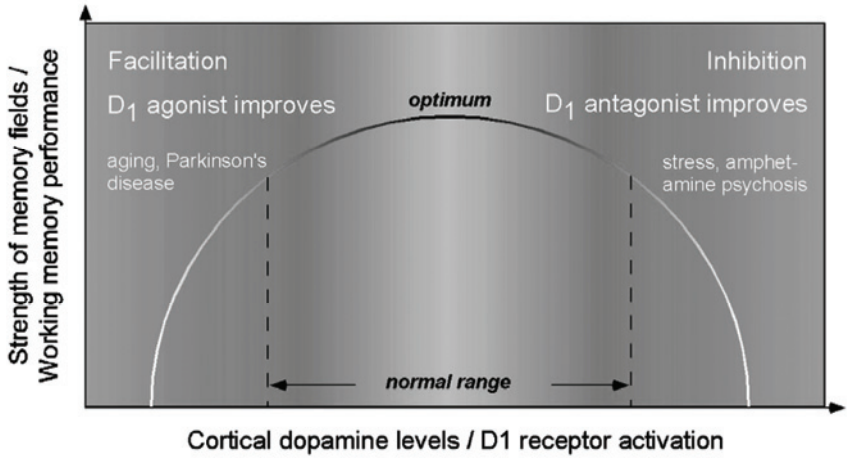


Figure 2-7 Dose-dependent effect of a selective D1 agonist on activity of a prefrontal neuron (taken from Goldman-Rakic et al., 2000)

Taken together these notions imply that DA could be the chain binding together performance monitoring and memory formation to enable long-term adaptations of performance. The following section will cover this topic in more detail.

2.8 Interactions of Performance Monitoring and Memory Systems

Recent theories and empirical findings highlight the role of pMFC in learning based on the results of performance monitoring. The reinforcement learning theory of performance monitoring suggests a close interaction of the midbrain DA system, the striatum, and the pMFC (Holroyd & Coles, 2002). Phasic DA signals indicate that the action outcome is worse or better than expected. These signals are conveyed to the pMFC, where they are used to improve task performance in accordance with the principles of reinforcement learning. Electrophysiological findings on the response and feedback error-related negativity (Holroyd & Coles, 2002; Nieuwenhuis et al., 2002) and fMRI data (Mars et al., 2005) on the dynamics of error-related activity support the view that the pMFC is important for optimizing behavior by rule learning based on previous experience. Lesion data in monkeys provide further support that the pMFC is critical for learning of action-outcome history (Kennerley et al., 2006).

The hippocampus has been shown to be involved in associative learning, particularly in early acquisition (Toni et al., 2001). In the task underlying the empirical part of this work (see section 3.4), participants had to learn the association of different symbols with reward probabilities by "trial and error". To adjust rule representations, i.e. associations between symbols and rewards, on unexpected outcomes (Ridderinkhof et al., 2004) pMFC needs to interact with memory-related structures such as the hippocampus. To enable information exchange between these two brain systems, fiber connections lead from the dorsal cingulate cortex in the pMFC to the hippocampus via the cingulate bundle (Morris et al., 1999; van Hoesen et al., 1993).

A recent study by Hester and colleagues (2007) provides evidence pointing to a close interaction between performance monitoring and learning-related areas. Using an associative learning task they showed that activity within the pMFC was significantly greater for errors that were corrected in the subsequent trial as compared to repeated errors. The error-related pMFC activity during the recall phase of the experiment predicted future responses (correct vs. incorrect). Interestingly, also activity in the hippocampus predicted future performance and was correlated with error-driven pMFC activity.

2.8.1 Action-Outcome vs. Habit Learning

Two learning mechanisms may work in parallel during acquisition of a new task. A fast subsystem allowing work with very recent information (working memory or goal-directed learning) and a learning system with a broader temporal perspective that is capable of integrating rewards over time thereby building up a reward history (stimulus-response or habit learning). The first process is often referred to as action-outcome learning. Actions in this framework are goal-directed, that is, they are performed with the aim of obtaining a goal. Within the second learning process, instrumental behavior is acquired through the coupling of responses and stimuli. Formation of stimulus-response associations is reflected in this process. Reward primarily serves the function of strengthening the stimulus-response association. The reward itself is not encoded as a goal (Everitt & Robbins, 2005). This latter system would be able to signal which action led to positive feedback more often in a given period of time. For the neural implementation of this mechanism the BG, especially the striatum, seem to be a promising candidate region because of massive dopaminergic input from the substantia nigra and the ventral tegmental area (Ashby & Spiering, 2004; Graybiel, 1998; Packard &

Knowlton, 2002). The faster memory system might be represented in the PFC (see also section 4.6).

Evidence from animal research suggests that there are two distinct processes that contribute to instrumental conditioning, i.e. learning to perform a particular action in response to a stimulus in order to obtain reward (Valentin et al., 2007). It is assumed that there is a goal-directed component in learning which involves establishing an association between a response and the respective incentive value of the response. A second system is habit learning which is involved in stimulus-response learning. At least in animals, researchers suggest that there are distinct neurobiological systems subserving these two processes. The prefrontal cortex and the dorsomedial striatum are proposed to be involved in goal-directed learning, whereas the dorsolateral striatum is involved in habit learning. In humans the neostriatum (caudate and putamen) is assumed to play a central role in habit learning (Knowlton et al., 1996).

Concerning the interplay of the two systems in instrumental responding it is assumed that both forms of learning are active in parallel (Killcross & Coutureau, 2003). Alternatively, it is possible that one system dominates behavioral control at a particular point in time. Habit learning is thought to develop much slower and more gradually. It is thought to start dominating responses when action guidance via goal directed learning declines (Killcross & Coutureau, 2003).

Related to this, a model built on monkey data by Fusi et al. (2007) suggests that there are two learning components involved in a conditional sensorimotor learning task: fast and slow components. The fast components might be responsible for choosing the response operated in PFC while the slow components are more responsible for controlling these choices, operated by circuits in the BG. If, for example, the task is to learn that a balloon (see fig. 2-8) has to be responded to by a left saccadic eye movement (see Fusi et al., 2007), the fast component captures the last instance of the respective stimulus and the adequate answer (due to rapid decay in memory). The slow component captures more than the last instance of a stimulus-response presentation. It is therefore able to span over more than one experimental block.

The example given in figure 2-8 shows that the slow component conveys information about a particular stimulus being associated with a right saccadic movement in one block of the experiment, whereas in the other block a left saccadic movement was the required with the same stimulus. Thus the slow component represents the reward history that is the overall probability that a certain response is rewarded given a certain situation.

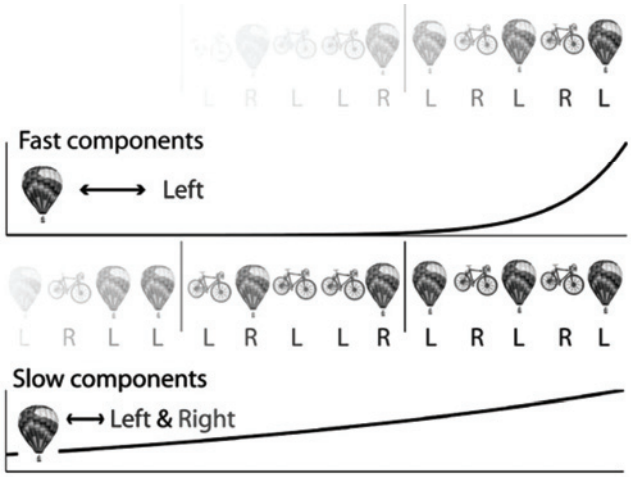


Figure 2-8 Fast and slow components in learning (taken from Fusi et al., 2007)

Consistent with this, other authors assume that the BG are specialized in slowly integrating positive and negative action outcomes over many trials. This finally results in establishing a motor habit (Frank & Claus, 2006; Jog et al., 1999; Knowlton et al., 1996). PFC in contrast is assumed to actively maintain information in working memory via persistent neural firing (Goldman-Rakic, 1995). This information can have a biasing effect on guiding behavior in a top-down manner (Miller & Cohen, 2001). This very recent information from working memory can complement as well as compete with more habitual representations, at least during early stages of a task where no habit has evolved yet.

2.8.2 Dopamine in the PFC: State 1 vs. State 2

An agent encountering a new situation may be faced with multiple elements all potentially relevant for actions within this situation. In order to find the best suited action, the agent needs to keep track of all different elements in the situation. This requires holding multiple items in working memory. According to a model of Seamans and colleagues (2001; see fig. 2-9) this is achieved by the so-called state 1 of dopaminergic effect on frontal information processing (D2 dominated). After a certain time of exposure it might be adaptive to develop one dominant representation that is used to guide performance. This is called state 2 and is mainly dominated by D1 receptors.

- State 1: D2 modulation predominates which leads to a net reduction in inhibition. This reduction in inhibition causes a loss of robustness of the system. This may be caused by D2 receptor activation reducing $GABA_A$ and NMDA currents (Trantham-Davidson et al., 2004; Seamans & Yang, 2004). Thus, multiple inputs have access to working memory buffer. This allows building up multiple representations. Hence, the working memory network shows less stimulus specific tuning because many items are represented simultaneously within the system. None of these items is represented strongly enough to become a dominant representation.
- State 2: D1 modulation predominates, leading to a net increase in inhibition. Inputs therefore have difficulties getting into PFC networks. If one representation gets into working memory buffer, it can produce very long lasting and stable network activations. Via activation of D1 receptors, DA enhances response-related firing over background activity. Thus, complimentary influences on task-related neural activity are exerted. One way by which DA may cause such a differential influence is to increase the excitability of local interneurons and GABAergic conductance. The tuning of pyramidal cells is thereby sharpened and activity is focused on task-relevant items (Seamans et al., 2001). Especially GABAergic activity is thought to sharpen the memory field of pyramidal neurons thereby tuning PFC mechanisms to the task at hand.

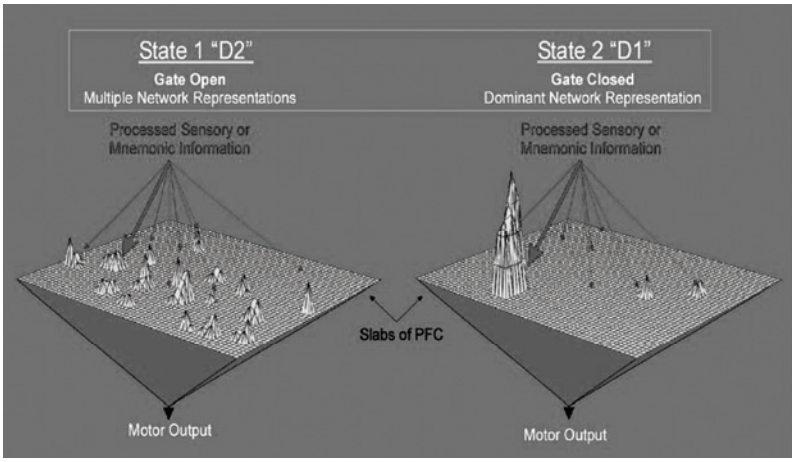


Figure 2-9 Two-state model of DA action in PFC (taken from Seamans & Yang, 2004)

DA at low concentrations seems to act via D1 receptors, whereas at high concentrations DA is acting via D2 receptors (Seamans et al., 2001). High micromolar DA levels are needed to stimulate D2 receptors in PFC. D1 receptors are mainly located extrasynaptically. Thus, high intrasynaptic DA concentrations would first stimulate synaptically located D2 receptors. Before DA diffuses into the extrasynaptic space this D2 activation causes a transient state 1 dynamic. Subsequent activation of D1 receptors leads to a re-establishment of state 2 dynamics. The function of the transient state 1 dynamic could be to reset cortical networks allowing new information to be processed in working memory. Thus, new goal state representations may be established. These representations would then be maintained by a subsequent D1-mediated state 2 dynamic (Seamans & Yang, 2004; Seamans et al., 2001).

Dopamine, acting on structures in the pMFC, the PFC and potentially the hippocampus, appears to play a major role in outcome-dependent learning and optimization of behavior. Influences on dopaminergic signaling are manifold: Exogenous influences such as drugs of abuse and endogenous influences like Parkinson's disease can be differentiated. They influence the level of DA available for tonic or phasic signaling. In recent years a further endogenous influence came into focus of DA research: Genetics, especially genetic polymorphisms affecting different parts of the dopaminergic system. One of these polymor-

phisms, the DRD2 TAQ IA was taken into account as a modulator of dopaminergic neurotransmission in the empirical part of this work.

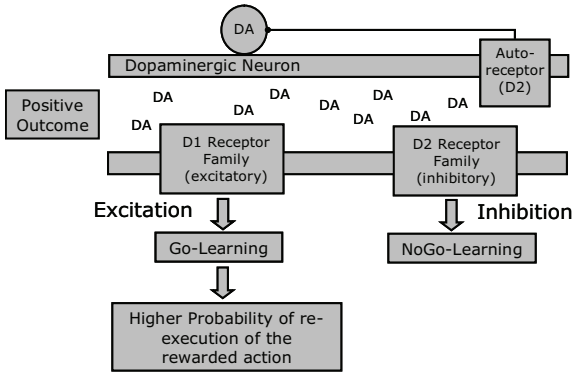
2.9 The DRD2 TAQ IA Polymorphism as a Mediator of Dopaminergic Signaling

The DRD2 TAQ IA polymorphism is a restriction fragment polymorphism on chromosome 11 at q22-q23 which is caused by a single nucleotide mutation (single nucleotide polymorphism; SNP). A SNP is a variation in the DNA sequence occurring when a single nucleotide in the genome differs between members of a species or between paired chromosomes in an individual. To be called a SNP, a variation must occur in at least 1% of the population. In case of the DRD2 TAQ IA the prevalence of the mutated A1 allele is 28% and that of the homozygous A1A1 genotype is roughly 3% in the population. Because of the small prevalence of the A1A1 genotype, A1 allele carriers are often contrasted with non A1 allele carriers. Therefore, the homozygous A1A1 allele carriers are collapsed with the heterozygous A1A2 allele carriers forming the A1+ group. The homozygous A2A2 allele carriers on the other hand are commonly referred to as A1- group. Individuals carrying the A1 allele have an up to 30% reduction in DA D2 receptor density compared to individuals that are homozygous for the A2 allele (Thompson et al., 1997; Pohjalainen et al., 1998; Jönsson et al., 1999; Ritchie & Noble, 2003).

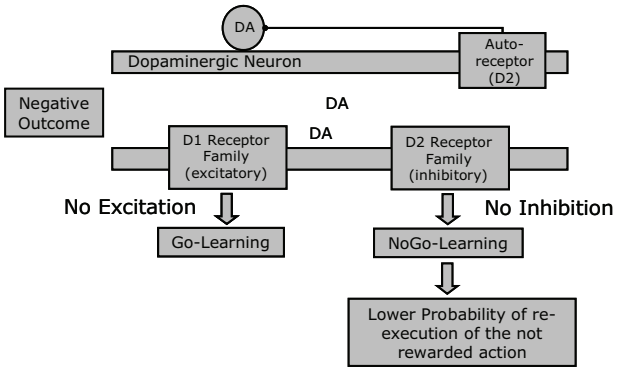
Although the polymorphism is located in the 3´-untranslated region of the DRD2 gene, it has functional consequences, possibly due to linkage disequilibrium with another functional relevant D2 variant. A recent study by Zhang and colleagues (2007) showed functional relevance for two frequent intronic SNPs (rs2283265 & rs1076560) which decrease expression of the DRD2 short splice variant (which is expressed mainly presynaptically) as compared to the DRD2 long splice variant (which is expressed mainly postsynaptically). These two SNPs are in strong linkage disequilibrium with each other. The DRD2 TAQ IA polymorphism we investigated in our sample is also in linkage disequilibrium with these two SNPs (SNPs 17/19: D´ = .855; Zhang et al., 2007). This linkage might provide a mechanistic basis for functional/clinical associations observed with the DRD2 TAQ IA polymorphism.

2.10 Consequences of an Altered Dopamine D2 Receptor Density

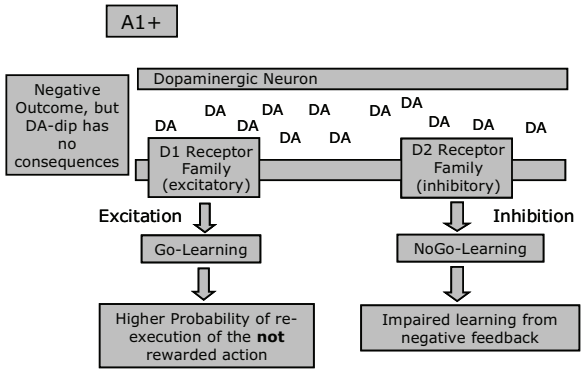
Given the important role of DA in performance monitoring, it seems very likely that genetic polymorphisms acting on the D2 receptor density should influence performance monitoring. Two mechanisms are possible: On the one hand a reduction in receptors can lead to a disruption of dopaminergic transmission, especially of the part of transmission that is relying on the D2 receptors. On the other hand, D2 receptors are the main DA autoreceptors. This could mean that a reduction in these autoreceptors automatically leads to a tonically higher DA level. This tonically higher level in DA should interact with phasic dopaminergic signalling. For example, a dip in dopaminergic function after a negative action outcome should be much less pronounced when the dopaminergic system is tonically very high on DA. These relationships are schematically drawn in figure 2-10, pointing especially to the influence of the A1 allele.



Positive action outcome: Increase in DA, “Go” learning is stimulated. DA concentration regulated by presynaptic D2 Autoreceptors



Negative action outcome: Dip in DA, "No-Go" learning is stimulated because D2 receptors can not cause an inhibitory influence any more



A1+ subjects: Potentially missing D2 autoreceptors lead to high tonic DA, dip due to negative action outcome has less consequences resulting in "Go" learning of the not rewarded action

Figure 2-10 Schematic of modulatory dopaminergic influences on "Go" and "No-Go" learning with genetic influences on D2 receptors.

Figure 2-10 illustrates the principles of DA action in "Go" and "No-Go" learning (see also section 2.5.2). If DA level raises following a reward, the "Go" pathway gets activated. The "No-Go" pathway is being inhibited by activation of inhibitory D2 receptors. Thus, learning following the principles of reinforcement learning can take place. A dip in dopaminergic activity has the opposite effect. Excitatory D1 receptors get not activated and no "Go" learning is triggered. D2

receptors are also not activated, so no inhibition is exerted on the "No-Go" pathway therefore "No-Go" learning can take place. This in turn leads to learning to avoid not rewarded actions. Reduced D2 receptor density could mean that the DA level is tonically elevated due to missing D2 autoreceptors. Therefore, a dip in DA can not exert its full influence. As a result "Go" learning for non-rewarded actions can take place.

2.11 Outline of the Present Studies

Dopaminergic neurons in the midbrain are assumed to signal whether or not an action was successful in terms of receiving reward. Thus, alterations in dopaminergic transmission caused by genetic influences should interfere with performance monitoring and subsequent performance adaptation. If the reinforcement learning model (Holroyd & Coles, 2002) holds true, dips in dopaminergic activity should lead to activity in the performance monitoring area. This error-related activity should in turn lead to performance adaptations like learning. This implies that also learning-related brain areas should be activated to enable long term adaptation of performance.

Functional integrity of DA system is not always given. Alterations in dopaminergic signaling can occur due to illness (e.g. Parkinson's disease or schizophrenia), drug addiction (e.g. alcohol or cocaine) or pharmacological intervention (e.g. DA agonists/antagonists). As described in the previous section, genetic influences can also interfere with dopaminergic transmission. In our empirical studies described in chapter 4 we investigated how a single nucleotide polymorphism (SNP) interacts with processing of negative feedback and subsequent learning from this negative feedback. The SNP we investigated (DRD2 TAQ IA) is known to modulate the striatal DA D2 receptor density thereby dividing subjects in two groups: one group with an unaffected receptor density, the other one with an up to 30% reduction of DA D2 receptors. First of all, this reduction in DA receptors could interfere with error processing in the pMFC as error processing is assumed to be highly dependent on dopaminergic signaling (Holroyd & Coles, 2002). Furthermore the reduction of D2 receptors could interfere with "No-Go"-Learning either by reducing the amount of (postsynaptic) D2 receptors, or by reducing the density of presynaptic D2 autoreceptors leading to a higher tonic DA level. This elevated tonic DA should interfere with phasic dopaminergic signaling triggered by the midbrain DA neurons.

If activity in learning-related areas is indeed coupled to performance monitoring – which seems plausible given the importance of long term behavioral adaptation to optimize future action outcomes – changing interactions between monitoring and learning related brain areas due to variations in D2 receptor density could be expected. Finally as DA also affects prefrontal functioning, genetically driven working memory differences could be expected, too.

In chapter 4 we will report an fMRI study (Klein et al., 2007b) and an EEG study employing a probabilistic learning task. By using subjects invited with respect to their genetic configuration we tried to capture genetically driven differences in performance and/or brain activity associated with the respective genotype. Our results show a central role of the neurotransmitter DA in human performance monitoring and outcome-dependent learning.

3 Methods

In the following the reader should be familiarized with methods employed in our set of empirical studies. We will briefly introduce functional magnetic resonance imaging (fMRI), electroencephalography (EEG), genotyping, the probabilistic learning task we used and computational modeling.

3.1 Functional Magnetic Resonance Imaging

This section should provide a short introduction into functional magnetic resonance imaging (fMRI). After giving the physical and physiological background, we will briefly explain the statistical analysis of fMRI data. For a more detailed introduction into fMRI see Buxton (2002) or Jezzard et al. (2002).

3.1.1 Basic principles of fMRI: Physics

Nuclear Magnetic Resonance

Atoms with an odd number of protons built the basis for magnetic resonance imaging. Protons in an atom nucleus spin about themselves (therefore they are often referred to as spins). This rotation or spin causes an angular momentum. If now the number of protons is uneven, this property results in a magnetic moment (which can be described as a vector). In biological tissue like the human body, hydrogen nuclei are a perfect candidate for magnetic resonance imaging (MRI) mainly for three reasons:

1. They only have a single proton.
2. High concentration in the human body
3. High magnetic susceptibility (resulting in a large nuclear magnetic resonance (NMR) signal)

If no external magnetic field is applied to the tissue, magnetic vectors are oriented randomly. As soon as a hydrogen nucleus is moved into a strong external magnetic field (B_0), its magnetic moment aligns with the direction of this external field. As slightly more neurons will align (parallel direction; low-energy-state of the neurons) rather than counter-align (anti-parallel direction; high-energy-state of the neurons) with this external field B_0, the net magnetic vector will point to the direction of the magnetic field. It is only this small surplus of spins oriented with the external magnetic field that can be used for imaging. The orientation in the direction of the magnetic field is not the only consequence of placing the spins in an external magnetic field. The field forces the magnetic moment to preccess around the direction of the field. The precession frequency is known as "Lamor" frequency and is proportional to the strength of the magnetic field.

Excitation and Relaxation

As only magnetization perpendicular to the magnetic field can be used for magnetic resonance imaging, the nuclei have to be transferred from an aligned to a counter-aligned orientation. This is done using a radio frequency (RF) pulse. The pulse causes the net magnetic vector to be tilted towards the plane perpendicular to the external magnetic field. This is achieved by energy absorption of the protons from the radio frequency enabling the protons to switch to the high-energy-state of anti-parallel orientation. Therefore the process is called excitation. There is a second effect of this RF pulse: The precession of the spins is synchronized, i.e. they preccess in phase.

If the radio frequency is switched off two independent processes start:

1. Protons start to turn back into their original orientation (T_1-relaxation).
2. Due to random interactions of the spins with each other the phase coherence between the spins decays over time (T_2-relaxation).

Not only random interactions between nuclei (spin-spin interactions) but also inhomogeneities in the magnetic field cause nuclei to preccess with different frequencies. The effect of rephasing caused by local field inhomogeneities plus the decay due to spin-spin interactions is referred to as time constant T_2*. As the role of the local field inhomogeneities is especially important for functional magnetic resonance imaging this phenomenon will be explained in some more detail in the section about the physiological basis of fMRI.

Spatial Encoding

The signal per se does not say anything about the place of its origin – therefore additional magnetic field gradients have to be superimposed over the original external magnetic field. A slice within the volume is selected by applying an excitation pulse (with the proper frequency). Therefore only spins from this slice contribute to the signal that is measured. For the remaining dimensions two more gradients are employed. One of these gradients is used for changing the precession frequency (frequency encoding) of the spins the other one is used for phase encoding. The signal finally measured is not made out of a single frequency but a frequency spectrum in which all information necessary for spatial encoding in all three dimensions is included.

3.1.2 Basic Principles of fMRI: Physiology

Because T_1 and T_2 are depending on the tissue, it is possible to distinguish between different tissue types by looking at differences between T_1 and T_2 generated signals. The signal that is most relevant for fMRI is T_2*, because this constant is, as mentioned before, also depending on local field inhomogeneities and not just on spin-spin interactions. Such inhomogeneities can be caused by the level of blood oxygenation. This is the link between magnetic resonance imaging and "function" of the brain (Ogawa et al., 1990, 1993). Oxygen in the blood is coupled to hemoglobin molecules. Oxygenation causes the hemoglobin to become diamagnetic, whereas hemoglobin without oxygen becomes paramagnetic. This paramagnetic effect causes small local field inhomogeneities in the magnetic field. This in turn leads to faster dephasing of the spins after being brought in phase by a RF pulse. The opposite is true for oxygenated hemoglobin: If the blood primarily contains oxygenated hemoglobin, the phase coherence is evident for much longer time. Applied to the T_2* time constant, this means that T_2* is shorter if not much oxygen is around, whereas it is longer in case of high oxygenation. Functional MRI makes use of this phenomenon by measuring this T_2* signal, commonly referred to as blood-oxygen-level-dependent (BOLD) signal, which represents changes in blood oxygenation over time.

Nevertheless the physiological basis of the fMRI signal is not fully understood. The hemodynamic response to neuronal activity is a complex interplay between cerebral blood flow, cerebral blood volume and local oxygen uptake near active neurons. Neuronal activity is followed by an increase in local oxygen uptake, a large increase in cerebral blood flow and a small increase in cerebral blood volume. This means that compared to the oxygen uptake at the active neu-

ronal site the increase in oxygenated blood is disproportional high, leading to corresponding changes in T_2*-sensitive signals (the signal decay is much slower). This overflow of oxygenated blood at active neuronal site leads to an increase of T_2*-relaxation time which is in turn interpreted as being an index of (neuronal) activation at this particular brain area.

3.1.3 Processing and Statistical Analysis of fMRI Data

Preprocessing

Aim of the processing steps in the analysis of fMRI data is to detect with a high spatial resolution changes in the BOLD response which are related to the experimental design. Before entering the statistical analysis, a number of pre-processing steps have to be performed to clean the data from artifacts and make different datasets from different subjects comparable across time and space. First step of pre-processing is the slicetime correction. This is necessary because not all slices in the brain are acquired simultaneously but with a certain temporal displacement. This is usually done using a linear or sinc-interpolation (Lohmann et al., 2001). A further potential source of noise in fMRI data is motion of the subjects during image acquisition. Motion can be corrected using a matching metric based on linear correlation for geometrical alignment. This means that the 2D images are rotated and shifted until they match a reference scan. A final step is removing slow signal drifts over the course of the experiment for example by applying a high-pass filter.

To determine the anatomical localization of brain activity and to perform statistical analysis over groups of subjects the functional datasets have to be aligned with anatomical data and have to be transferred into a standardized coordinate system. This registration is performed by shifting and rotating the 2D functional slices so that they fit with a high-resolution 3D anatomical dataset, which is usually acquired before the functional scan. This dataset is commonly provided within a standardized coordinate system, as for example the Talairach system (Talairach & Tournoux, 1988). To allow comparisons between subjects the registered datasets have to be normalized, that is, they are scaled to match in size. This scaling can be done either in linear or in non-linear fashion.

Statistical Analysis

Once the data is free of artifacts and aligned in the same reference space, statistical analysis can start. Aim of performing fMRI studies is to detect brain areas that significantly co-vary in activity with a given experimental design. This can be achieved by applying a General Linear Model (GLM; Friston, 1994; Worsley & Friston, 1995) to the data. The key assumption in this model is that the observed data can be explained by a linear combination of explanatory variables and an error term. Aim of applying GLM to the data is to obtain statistical parametric maps (SPMs) or contrast images. SPMs give the statistical significance of each voxel being activated by a certain experimental condition. A contrast image first shows the differential activity between two experimental conditions, expressed as the difference between two or more model parameters, the so-called beta-values. These beta-values represent an estimate of signal change in the BOLD time course in relation to the experimental stimulation. SPMs are then obtained by means of a Student's t-test. The resulting t-values are transformed into z-scores which finally results in an individual SPM{z}. The z-scores indicate whether the conditions of interest differ on a voxel-wise basis. This step is referred to as first-level analysis. In the analysis of an entire group of subjects, the t-test is applied to model parameters of all subjects (second-level analysis). In yet further analysis steps one can test for example for group differences (higher-level analysis) by means of a two-sample t-test. Alternatively, on the second or higher levels of analysis, beta-values can be subjected to Bayesian statistics (e.g. Neumann & Lohmann, 2003) to gain probabilistic values for differences between conditions or groups.

Psychophysiological Interaction Analysis (PPI)

As we employed a Psychophysiological Interaction Analysis (PPI) for our fMRI data this method should be briefly explained. The idea of PPI is to look for interactions between brain areas which correlate with an external (psychological) variable (Friston et al., 1997). For example looking at changing interactions between brain areas under two experimental conditions: condition 1: attention to the stimuli vs. condition 2: no attention to the stimuli. The external psychological variable in this case would be "attention on/off". A possible result could be that interactions between brain areas are much stronger if the subject is paying attention to the stimuli.

In our study, the external variable was the time the subjects were working on the task. We divided the experiment into three parts of equal length thereby cap-

turing the difference between steep rule acquisition ("learning", first third) at the beginning of the experiment and more stable rule exploitation at the end of the task (last third). We were primarily interested in time-dependent changes in the interplay between performance monitoring and all other brain areas. Therefore, we contrasted the functional connectivity between the rostral cingulate zone (RCZ) and all other brain areas in the first third of the experiment against the functional connectivity in the last third of the experiment.

3.2 Electroencephalography

3.2.1 Measuring Human Electroencephalogram

Attaching a pair of electrodes to the human scalp and connecting them to an amplifier reveals a pattern of variations in voltage over time, called electroencephalogram (EEG). The amplitude of this signal varies between -100 and +100 μV with frequencies of up to 40 Hz or more (Rugg & Coles, 1995). The number of electrodes used for recording the EEG varies with the reason for which the EEG is conducted. In most cases several electrodes are placed over different cortical areas. The system for naming and placing the electrodes is usually the international standardized 10-20 system (Jasper, 1958). Frontal electrodes are labeled with an "F", temporal ones with a "T", central electrodes with a "C", parietal ones with "P" and occipital ones with an "O". The letter "z" refers to electrodes on the midline, electrodes on the left side are numbered odd, and electrodes on the right side have an even number. Electrodes need to be connected to a reference. This could for example be the so-called linked-mastoid reference (electrodes on the left and right mastoid, respectively) or every electrode is referenced against the average electrical activity of all other electrodes (average reference).

The EEG signal is often contaminated by artifacts, caused for example by muscle activity or eye blinks. High frequency muscle activity can be filtered out by applying a low-pass filter. Artifacts with a very low frequency can be removed using a high-pass filter. Eye blinks can be detected by means of an independent-component analysis (Jung et al., 2000). The respective components are then removed from the signal to obtain an eye-blink free EEG. One of the biggest advantages of EEG over fMRI is the high temporal resolution with which ongoing brain activity can be measured. This advantage comes at the cost of a very low spatial resolution. It is not always clear where a potential that is measured on the surface of the scalp is originally generated. Even source localization techniques address-

ing this so-called inverse problem do not provide a highly reliable spatial tracking of underlying sources.

3.2.2 Event-Related Potentials (ERP)

An event taking place while continuous EEG is recorded might cause changes in the ongoing electric activity of the brain. These event-related changes are referred to as event-related potentials (ERP). An event can be any experimental manipulation a researcher is interested in (sounds, pictures, reactions of the subjects etc.). Thus ERPs reflect brain activity that is time-locked to ongoing processing of the particular event. Although the precise localization of the electrical activity is largely unknown, the following aspects of ERP generation seem to be clear (Rugg & Coles, 1995):

1. Activity measured at the surface reflects activity of a sizeable population of neurons.
2. These neurons must be synchronously active and must share a certain geometric configuration: Parallel orientation perpendicular to the cortex, so that a dipolar electric field can evolve.
3. ERP waveforms seem to reflect post-synaptic dendritic potentials.

It has to be pointed out that there is a lot of neural activity present that is not detected by the EEG. The orientation of neurons in the thalamus for example guarantees that recording electrodes are unable to detect their electric activity.

Often the ERP signal is weak compared with the overall electrical activity of the brain. Therefore, the ERP needs to be separated from the background "noise". A popular technique for achieving this is averaging. If the ERP is time-locked to the event but the background activity is random, one should be able to cancel out the random noise by averaging. To obtain a stable and clean ERP several epochs within the EEG containing the event of interest are needed. The waveform resulting from averaging many epochs is characterized by different negative and positive voltage deflections. Naming of these deflections is related to their polarity relative to baseline or the preceding peak (negative deflection (N) and positive deflection (P) in μV) and their latency relative to the event of interest (given in ms). Figure 3-1 gives an example for obtaining an ERP from several epochs of ongoing EEG. The P300 for example is a positive deflection occurring 300 ms after onset of the stimulus.

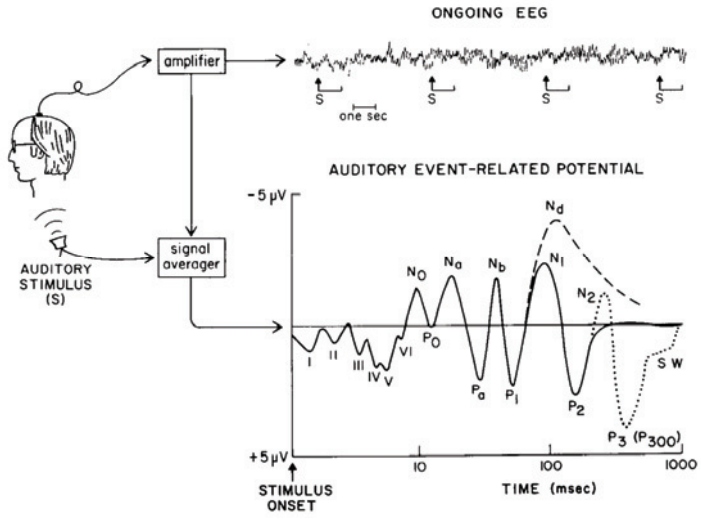


Figure 3-1 Obtaining an ERP: Event-related activity after a stimulus S is obtained by averaging several epochs containing the event of interest (taken from Hillyard & Kutas, 1983)

3.3 Genotyping

3.3.1 Real Time Polymerase Chain Reaction and Melting Curve Analysis

Real Time Polymerase Chain Reaction

Deoxyribonucleic acid (DNA) analysis was performed for our experiments using real time polymerase chain reaction (RT-PCR; Reuter et al., 2005). This technique allows quantification of polymorphic DNA regions and detection of single nucleotide polymorphisms (SNP) in one run. Hybridization probes are used to perform genotyping by melting curve analysis. This hybridization probes are oligonucleotides labeled by a fluorescent dye. For detecting a SNP two probes are necessary: One that covers the DNA strand so that the polymorphic region is covered (sensor hybridization probe) and a second one (anchor probe) that is located in a site of close proximity to the sensor probe. While the sensor probe is labeled by fluorescein, the anchor probe is marked with LC Red 640. During the amplification process the hybridization probes anneal to the amplified DNA. With an

LED the fluorescein of the hybridization probe is exited which in turn emits green light. This green light then excites the LC Red 640 dye which starts emitting red light. The optical unit of the RT-PCR machine is able to measure the intensity of the red light. The more new target DNA sequences are built, the stronger is the light signal. This light signal is a direct measure of DNA copies in a PCR run. In the now following elongation phase the temperature is raised resulting in a displacement of hybridization probes from the DNA.

Melting Curve Analysis

In order to detect point mutations on the DNA strand, a melting curve analysis can be performed. For this the temperature of the probe is slowly raised from 40°C to 75°C. The temperature by which the hybridization probes are melted off the DNA strand is an indicator for the presence or absence of a point mutation. If there is a mismatch between the DNA strand and the hybridization probe in terms of one nucleotide, then the probe melts off at a lower temperature than in case of a perfect fit between DNA and probe. Three characteristic curves can be obtained by the melting curve analysis: a curve with a single early peak (homozygous wild type), a curve with a single late peak (homozygous mutant) and a curve with two peaks (heterozygous genotype).

3.3.2 Detecting the DRD2 TAQ IA Polymorphism

In our study DNA was extracted from buccal cells to avoid selective drop-out of subjects with blood and injection phobia. The samples were purified with a standard commercial extraction kit. Using the Light Cycler System genotyping was performed by real time PCR (RT-PCR) using fluorescence melting curve detection analysis (see above). Single nucleotide polymorphisms (SNP) can hereby be detected without conducting gel electrophoresis and ensuing sequencing after purification. Furthermore, PCR has a high precision with a reliability of 1.0. The following primers and hybridization probes were used:

Forward primer: 5'-CGGCTGGCCAAGTTGTCTAA-3';

Reverse primer: 5'- AGCACCTTCCTGAGTGTCATCA -3';

Anchor hybridization probe: 5'-LCRed640-TGAGGATGGC-TGTGTTGCCCTT-phosphate-3';

Sensor hybridization probe: 5'-CTGCCTCGACCAGCACT-fluorescin-3'

The PCR comprises 55 cycles of denaturation (95°C, 0s, ramp rate 20°C/s), annealing (63°C, 10s, ramp rate 20°C/s) and extension (72°C, 10s, ramp rate 20°C/s). This procedure was followed by an incubation period of 10 min to activate the Fast-Start Taq DNA polymerase of the reaction mix (Light Cycler Fast-Start DNA Master Hybridization Probes). After this amplification time a melting curve was generated. The temperature was held constant at 40°C for 2 min and then slowly heated up to 95°C (ramp rate 0.2°C/s). The fluorescence signal was plotted against the temperature to obtain a melting curve with the respective melting points (T_m). For the DRD2 polymorphism the following melting points can be observed: T_m for the A1 allele is 55°C, for the A2 allele T_m is 64.8°C.

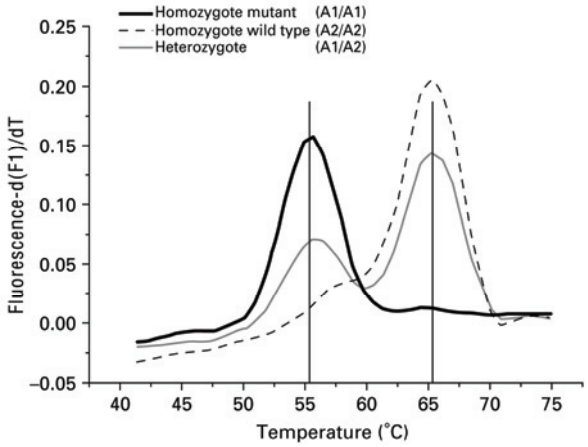


Figure 3-2 Result of the melting curve analysis of the DRD2 TAQ IA polymorphism (taken from Reuter et al., 2005)

In figure 3-2, melting temperature is calculated by taking the first negative derivative of the melting curve. The height of the amplitudes is not informative in this figure. What is of relevance is the temperature of the peak (T_m). A single early peak is indicative of a mutation on both alleles (A1/A1 genotype), whereas a single late peak speaks in favor of the homozygote wild type (A2/A2 genotype). Two peaks are typical for a heterozygote sample (A1/A2 genotype).

3.4 Probabilistic Learning Task

We employed a probabilistic learning task known to be sensitive to dopaminergic manipulations (Frank et al., 2004).

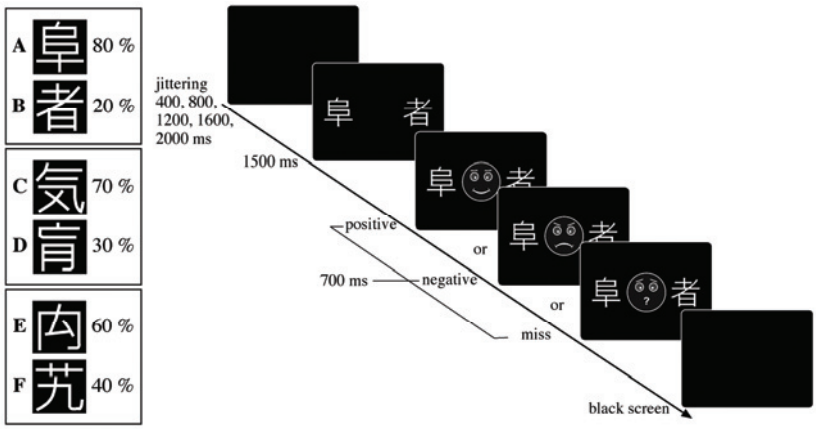


Figure 3-3 Schematic of the probabilistic learning task and the trial timing (fMRI)

Participants were presented on each trial with a pair of symbols that were rewarded using a probabilistic schedule (see fig. 3-3). From each pair the more often rewarded symbol had to be guessed and indicated by a button press. The quality of the choice was immediately signaled by valid feedback after the response. After learning, participants were confronted in a behavioral post-test with the same symbols, now paired with all symbols but the one from the learning phase. In the behavioral post-test data, we determined how often participants chose the most often rewarded symbol "A" in all possible recombinations and how often they avoided the least often rewarded symbol "B", reflecting reinforcement and avoidance learning, respectively.

In more detail the experimental setup looked as follows: Three pairs of symbols were presented: "AB", "CD", and "EF" in random order. In "AB" trials choosing symbol "A" led to positive feedback in 80% and negative feedback in 20% of all trials (vice versa for choosing "B"). Symbol "C" was rewarded in 70% of "CD" trials and "E" was rewarded in 60% of "EF" trials. Over the course of the acquisition phase, subjects learned to choose the "good" symbols "A", "C", and "E" more often than their respective counterparts.

Every pair of symbols was presented 140 times during the course of the experiment. In the fMRI session participants worked on 462 trials, 42 of which were null events used to improve the modeling of the BOLD response. Trial timing was as follows: The onset of the trial was jittered with 400, 800, 1200, 1600 and 2000 ms. During this interval, participants saw a blank screen. They were simultaneously presented with two stimuli for up to 1500 ms. In case of a response, a smiling or grimly looking face was presented for 700 ms, corresponding to positive and negative feedback, respectively. If no response occurred, participants saw a face with a question mark instead of the mouth. After the feedback, the screen went black again until the next trial started. Trial duration was 5 seconds. Trials appeared in random order, and the presentation of the symbols was balanced between the right and left side of the screen. The winning symbol was randomly determined within the before mentioned probabilistic schedule.

After this learning session, participants were confronted in a behavioral post-test with the same symbols, now paired with all symbols but the one from the learning phase ("AC", "AD", "AE", "AF", "BC", "BD", "BE", "BF", "CE", "DF", 12 times per new pair, i.e. each symbol was presented equally often). Again, subjects had to choose one symbol, now without receiving feedback. The choice behavior was analyzed as follows: The portion of "A" choices in pairs containing "A" reflects preference (learning from reinforcement); the portion of non-"B" choices in pairs containing "B" reflects avoidance (learning from errors). The post-test took place outside the scanner. We also added completely new symbols to the post-test, so participants were also confronted with "AX", "BY", "CT", "DU", "EV", and "FW" (presented 24 times each). In these latter combinations, however, subjects employed some kind of recognition heuristic and only chose the known symbols. Therefore, these trials were excluded from analysis of preference resp. avoidance of A and B.

3.5 Computational Modeling

For our experiments, subjects' behavior and responses were modeled in a modified Rescorla-Wagner model adapted from Rodriguez et al. (2006). Rescorla-Wagner models capture the core principle that learning of stimulus-reward associations is based on the difference between a prediction and an actual outcome of an action (O'Reilly et al., 2007). With the extension of the delta learning rule by a parameter that forces the model to make the same choice as the subject, we mimicked each subject's behavior during learning on a trial-by-trial basis, which is

required in order to relate the subject's behavior and model predictions to the measured fMRI signal.

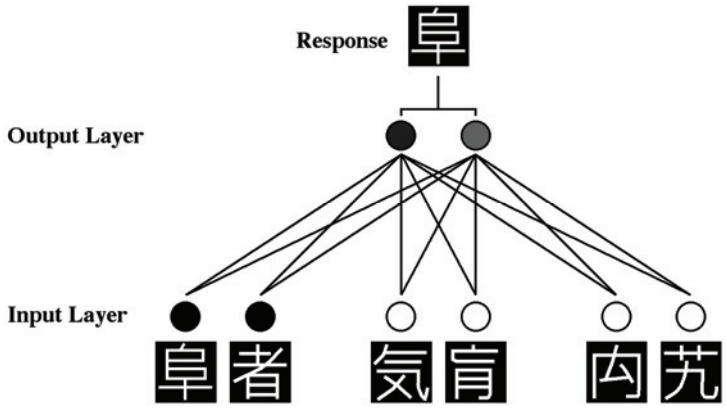


Figure 3-4 Schematic of the computational model

The model consisted of six input nodes I_j, j = 1...6 (see figure 3-4), corresponding to the six possible input symbols, with weighted connections to two output nodes O_1 and O_2. Activity of the output nodes was computed on each trial as

$$O_j = \Sigma_i V_{ij} I_i,$$

where V_{ij} is the weight of the connection from input node I_i to output node O_j. Weights were updated on each trial by

$$\Delta V_{ij} = \lambda S_i (E_i - O_i) I_j,$$

where E_i is the target value of the ith output node according to the probabilistic schedule described earlier (section 3.4). S_i is the symbol that was actually chosen by the subject, which was included to make the model simulate the behavior of the individual subject. The learning rate λ was determined for each subject individually such that over all valid trials the sum of the squared difference between the model's output and the subject's response was minimized:

$$\Sigma_{ik}(S_{ik} - O_{ik})^2 \rightarrow \min,$$

where i = 1...2, and k is the number of valid trials.

Such computational models facilitate the extraction of parameters that can not directly be measured and their inclusion in the subsequent fMRI data analysis. In

our application, the parameter "certainty of the given response" was derived from the model for each trial as the absolute value of the difference in the two output neurons that represented the presented pair of symbols:

$$\text{certainty-of-response} = | O_1 - O_2 |.$$

Before learning, the difference is zero reflecting a complete state of uncertainty. During the learning process, the difference between the output neurons generally increases (as a general tendency, not for any particular trial). However, this increase differs between different symbol combinations in a probabilistic learning task, depending on the difference of reward probability between different stimuli (see section 3.4). Thus, the "certainty of the response" captures how well the subject is learning over time and in addition the probabilistic schedule of the task which, of course, strongly influences the certainty about the expected reward in a particular trial.

4 Empirical Studies

4.1 fMRI Study

4.1.1 Rationale

"You learn from your mistakes", people say. In fact, improving our performance is based on learning about the relation of positive and negative outcomes and the actions carried out under certain conditions. Rewards strengthen associations between contextual stimuli and actions thereby reinforcing and maintaining successful behavior (Thorndike, 1911); whereas punishments induce avoidance of erroneous actions. While we usually learn from both, positive and negative reinforcement, it has been shown that the relative amount of learning from success and errors may vary across individuals (Frank et al., 2004). As errors usually occur at a lower frequency than successful actions, they often carry more information about necessary adaptations of behavior, which renders error processing a major constituent of learning. An important factor in the use of negative and positive feedback for learning seems to be the neurotransmitter DA (Schultz, 1998, 2002; Frank, 2005). The BG, in particular the nucleus accumbens (NAC), have been shown to play a major role in reward-based learning (Cools et al., 2002; Pagnoni et al., 2002). When action outcome – usually a negative feedback or error – calls for adaptations, a performance monitoring system in the posterior medial frontal cortex (pMFC) signals the need for adjustments (Ridderinkhof et al., 2004; Ullsperger & von Cramon, 2003). The rostral cingulate zone (RCZ) located in the pMFC has been suggested to be involved in learning from errors (Mars et al., 2005; Holroyd & Coles, 2002). A neurobiological theory holds that this region receives dopaminergic teaching signals from the midbrain coding whether an event is better or worse than predicted (Holroyd & Coles, 2002). These signals are presumably used for immediate behavioral adjustments as well as learning. The dynamic interaction of the performance monitoring system and brain struc-

tures underlying long-term memory formation, such as the hippocampus, during reinforcement learning is still poorly understood.

Here, we show that a human genetic polymorphism (DRD2 TAQ IA) known to modulate DA D2 receptor density influences rule learning, particularly the use of negative feedback for avoidance learning. Using fMRI we demonstrate that RCZ, NAC, and hippocampal activity as well as their interactions are modulated by the genetically determined dopaminergic transmission. These differential activations and interactions in turn lead to increased or decreased avoidance of actions associated with negative outcomes.

4.1.2 Materials and Methods

We included N = 26 subjects (mean age ± SEM: A1- genotype: 26.9 years ± 1.1, A1+ genotype: 25.3 years ± .68)) in our sample. Only male subjects were included to avoid interactions between the DA level and the menstrual cycle. All subjects were healthy, from Caucasian origin and native speakers of German. Prior to the fMRI measurement subjects gave written informed consent to be informed about incidental pathological findings by an in-house neurologist. All participants gave written informed consent both before genotyping and before fMRI measurement. Subjects were invited with respect to their DRD2 TAQ IA polymorphism configuration from a larger sample which was in Hardy-Weinberg equilibrium. The study was approved by the Research Ethics Committee of the University of Leipzig, Germany. We employed the probabilistic learning task as described in section 3.4.

4.1.3 FMRI Data Acquisition and Processing

The fMRI data was acquired at 3 T. A standard head coil was used. Twenty-six slices were measured (thickness 3.5 mm, 0.7 mm gap) positioned parallel to the anterior commissure-posterior commissure (AC-PC) plane. Before recording of the functional data, a set of 2 dimensional (2D) images was measured for each participant using a modified driven equilibrium Fourier transform (MDEFT) sequence. Functional images were acquired using a single-shot gradient echo-planar imaging (EPI) sequence (Tr = 2000 ms, Te = 30 ms ; 64x64 pixel-matrix, flip angle 90°; field of view = 192 mm). To improve the localization of activation, high resolution brain images (3D reference data) were taken for each participant in a previous session.

We processed the fMRI data using the software package LIPSIA (Lohmann et al., 2001). Low frequency signals were suppressed using a 1/120 Hz highpass filter. For spatial smoothing we applied a Gaussian filter with 5.65 mm full width at half maximum (FWHM). To correct for slice-time acquisition differences, a spline-interpolation algorithm was used. To remove motion artifacts, we corrected functional data using a matching metric based on linear correlation. For coregistration of functional and anatomical data, the anatomical slices (MDEFT) were aligned geometrically with the functional slices (EPI-T1). From these data, rotational and translational parameters were calculated, constituting a transformation matrix that registered the anatomical slices with the 3D reference data set. For standardization, we scaled each transformation matrix to the Talairach standard brain size (Talairach & Tournoux, 1988) by means of linear scaling. Finally, the individual transformation matrices were applied to the functional raw data set of each participant.

The statistical analysis was based on a least-squares estimation using the general linear model for serially autocorrelated observations (Friston et al., 1995; Worsley & Friston, 1995). The design matrix was created with a synthetic hemodynamic response function (Friston et al., 1998) and its first derivative. The model equation, including the observation data, the design matrix and the error term, were convolved with a Gaussian Kernel of dispersion of 4 s FWHM to account for the temporal autocorrelation of the model (Worsley & Friston, 1995). As all functional data sets were aligned to the same reference space, a group analysis was performed.

Group differences were tested using a second-level Bayesian analysis (Neumann & Lohmann, 2003; Friston & Penny, 2003; Friston, 2002; Woolrich et al., 2004), because this technique has been shown to be highly reliable when applied to different groups of subjects (Neumann & Lohmann, 2003). Bayesian analysis compared to null hypothesis significance tests can be more tolerant against outliers as the influence of individual subjects on group statistics is weighted by the within-subject variability. The technique allows to directly assess hypotheses of interest. Specifically, the posterior probability of an effect directly reflects the probability that the effect of interest is true in the light of the observed data.

Furthermore, we calculated a Psychophysiological Interaction Analysis (PPI, see section 3.1.3; Friston et al., 1997; Gitelman et al., 2003) to investigate, whether or not correlation between the RCZ and other brain areas were changing over time. A seed voxel for the correlation was determined for each subject by searching for the individual frontomedian maximum within a search radius of 10

mm around x = 4, y = 24, z = 33. The psychological variable was determined by the time course of the experiment, such that the first third of the study phase was contrasted with the last third.

4.1.4 Behavioral Results

The groups defined by the presence or the absence of the A1 allele (A1- vs. A1+) did not differ in the average frequency of selecting favorable symbols nor in the rate of negative feedback (see table 4-1). However, we found a remarkable group difference in avoidance learning (fig. 4-1).

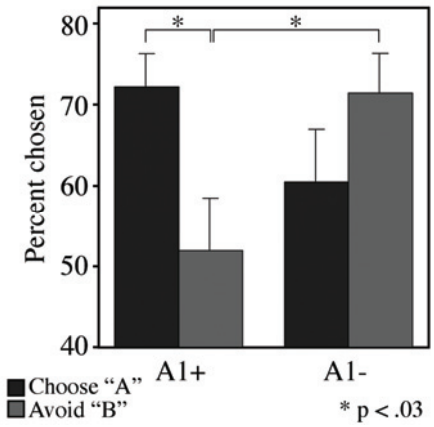


Figure 4-1 Results from the behavioral post-test

In the post-test, A1 allele carriers (A1+ group) avoided the negative symbol "B" significantly less than they chose the positive symbol "A" (p=.03). Moreover, their avoidance of "B" was reduced as compared to the non-A1 allele carriers (A1- group; p=.03), who did not show a significant difference between selecting symbol "A" and avoiding symbol "B" (p = .17; group x selection interaction, p = .009).

Table 4-1 Behavioral results from the learning phase (1) and the behavioral post-test (2) separately for the members of the two genetic groups

	A1+	**A1-**
(1) Behavioral results from the learning phase (given in mean percent chosen ± SEM)		
Choosing symbol "A"	86.2% ± 3.1	84.3% ± 3.6
Choosing symbol "C"	72.8% ± 3.4	71.4% ± 3.8
Choosing symbol "E"	70.8% ± 4.7	75.8% ± 3.9
Percent Negative Feedback	39.2% ± 1.3	40.8% ± 1.4
(2) Behavioral results from the post-test (given in mean percent chosen ± SEM)		
Choosing symbol "A" (A1+ > A1-; t = -1.5, p = .15)	72.9% ± 4.1	60.5% ± 6.5
Avoiding symbol "B" (A1+ < A1-; t = 2.4, p = .03)	52.0% ± 6.5	71.6% ± 4.8

4.1.5 FMRI Results

The behavioral results suggest that subjects from the A1+ group learn less to avoid actions associated with negative feedback than subjects in the A1- group. Consistent with that they also showed reduced negative-feedback-related fMRI signal increases in the RCZ (x = 4, y = 24, z = 33, z-score 3.5, 324 mm^3) compared to the A1- group (see figure 4-2, a; table 4-2 shows a list of additional feedback-related activation maxima).

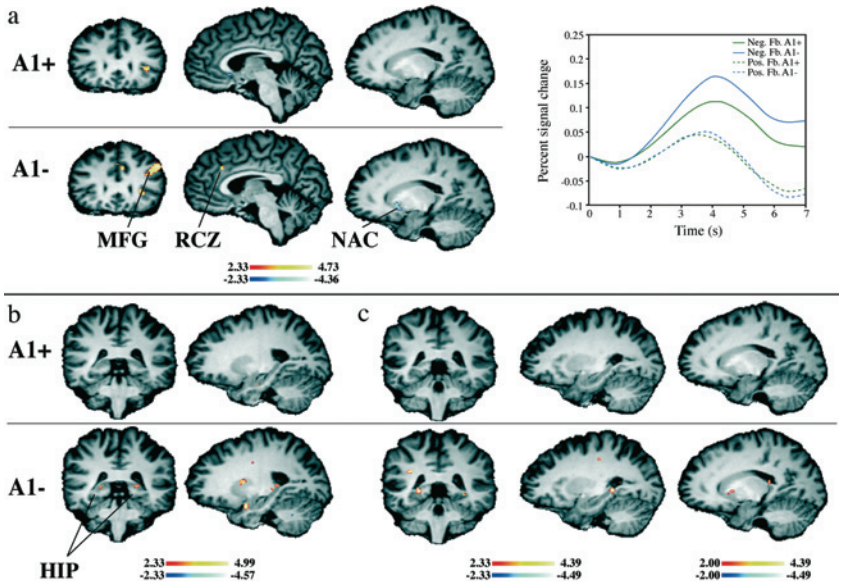


Figure 4-2 Genetic influences on the fMRI results. Only clusters with at least 81 mm³ activated at z >= 3.09 are shown. For visualization the maps are thresholded at z = 2.33 (unless stated differently). (a) Contrast "negative vs. positive Feedback" for the two genetic groups, projected onto a coronal (y = 24), and two sagittal slices (x = 4 and x = 16); negative Feedback > positive Feedback = red, positive Feedback > negative Feedback = blue. Percent signal change for positive (Pos.) and negative (Neg.) feedback (Fb.) taken from RCZ (x = 4, y = 24, z = 33). MFG = middle frontal gyrus, RCZ = rostral cingulate zone, NAC = nucleus accumbens. (b) Parametric within subject fMRI analysis using the certainty of the given response as a regressor, projected onto a coronal (y = -39) and a sagittal (x = 22) slice. HIP = Hippocampus. (c) Psychophysiological Interaction Analysis between RCZ (x = 4, y = 24, z = 33) and other brain areas, projected onto a coronal (y = -42) and two sagittal (x = -26 and x = 16) slices. Red: stronger interaction in the first third than in the last third of the experiment, blue: stronger interaction in the last than in the first third.

In the Bayesian analysis we observed a posterior probability of 95.8% for a group difference in RCZ activity induced by negative feedback, again implying that negative feedback processing was reduced in the A1+ group. This notion is further supported by the finding that only for members of the A1- group, positive correlations of negative-feedback-related RCZ activity and preference of symbol "A" (r = .53, p = .05) and avoidance of symbol "B" (r = .55, p = .04) was found. The correlation between the hemodynamic activity and the performance in the behavioral post-test was calculated for the RCZ coordinate with the highest prob-

ability of a difference between the two groups (x = 4, y = 29, z = 33, 99.24% probability of a difference).

Table 4-2 Additional brain regions, Brodmann areas, and Talairach coordinates (x, y, z) of voxels co-varying significantly with feedback processing. Only clusters with more than 10 voxels activated are reported here.

				Talairach coordinates		
Brain region	**Brodmann area (BA)**	**z-value**	**mm³**	**x**	**y**	**z**
A1+ group						
Negative > Positive						
R anterior Insula	BA 13	4.73	1296	34	20	3
A1- group						
Negative > Positive						
R precentral gyrus	BA 6	3.71	270	40	-1	36
R middle frontal gyrus	BA 9	4.64	2808	49	20	33
R superior temporal gyrus		3.52	270	49	-40	18
R Insula	BA 13	4.05	486	28	26	3
Positive > Negative						
L superior frontal gyrus	BA 8	3.90	270	-11	47	39
R cingulate gyrus	BA 31	3.49	324	4	-31	33
R ventral striatum (nucleus accumbens)		3.96	1323	16	8	-6
R dorsal striatum (putamen)		3.80	*)	19	12	3
L ventral striatum (putamen)		4.37	837	-23	11	-3
anterior fronto-median cortex	BA 10	3.67	324	-5	50	-3
R parahippocampal gyrus	BA 27	4.11	324	25	-28	-6

Note: R/L = right/left; *) this activation is connected with the nucleus accumbens activity such that the volume cannot be determined separately.

A further strong signal increase on negative feedback in the right middle frontal gyrus (x = 40, y = 21, z = 27, z-score = 4.3, MFG) was found only in the A1- group (posterior probability of group difference: 97.1%). As this brain region is commonly found in working memory tasks (Petrides et al., 1993; Petrides, 2005), it may be speculated that A1- participants used a monitoring-within-memory strategy of keeping track with selection-outcome history.

To study learning over the time course of the probabilistic learning task, we modeled subjects' behavior using a modified Rescorla-Wagner reinforcement learning model (Rodriguez et al., 2006; see section 3.5 and fig. 3-4 for details). In this computational model, the difference of activity in the output neurons provides a trial-by-trial estimate of certainty of the given response. Overall, the A1- group reached a significantly higher response certainty in the last third of the experiment (F = 2.7, p = .04). The development of the certainty over the course of the experiment is shown in fig. 4-3.

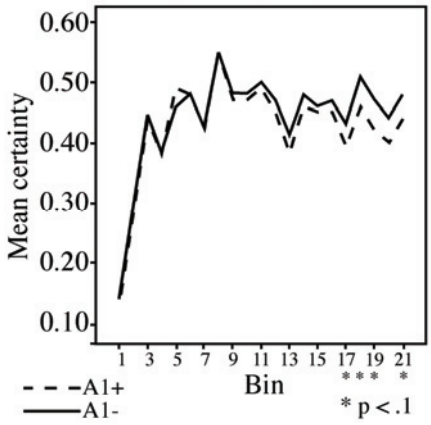


Figure 4-3 Result from computational model: certainty of the given response, binned in bins of 20 consecutive trials each (binning in all following figures showing binned trials performed like that)

In both groups, the curves resemble a logarithmic learning curve with a steep increase in the first third and an asymptotic course at the end of the experiment. After an initial period of about 200 trials, the A1- group develops a higher response certainty than the A1+ group. For both genetic groups response certainty negatively correlated with pMFC activity (see fig. 4-4), thus replicating earlier

reports that demonstrated a role of this region in processing decision (un)certainty (Ridderinkhof et al., 2004; Ullsperger & von Cramon, 2003; Volz et al., 2003).

Interestingly, in the A1-group the time course of certainty showed a positive correlation with activity in the posterior hippocampus bilaterally (x = 22, y = -39, z = 6; z-score = 3.9, 216 mm³ and x = -23, y = -39, z = 3; z-score = 3.5, 81 mm³), whereas no such correlation was found in A1+ participants (Bayesian posterior probability of group difference, right: 94.9%, left: 96.2%; see fig. 4-2, b).

In other words, the hippocampal complex changes its activity over the time course of the experiment, and this change is stronger in A1- subjects who develop higher response certainty and better avoidance of unfavorable selections (for additional correlations see table 4-3).

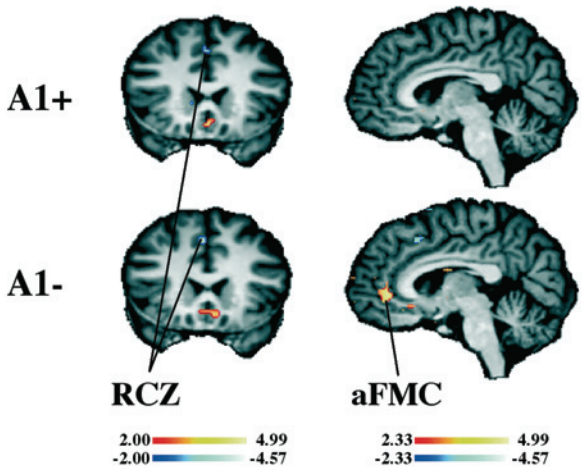


Figure 4-4 Parametric within-subject fMRI analysis using the certainty of the given response as a regressor. Projected onto a coronal (y = 18) and a sagittal (x = -5) slice. Positive correlation = red, negative correlation = blue; RCZ = rostral cingulate zone; aFMC = anterior frontomedian cortex

Table 4-3 Additional brain regions, Brodmann areas, and Talairach coordinates (x, y, z) of voxels co-varying significantly with certainty of the given response. Only clusters with more than 10 voxels activated are reported here.

				Talairach coordinates		
Brain region	**Brodmann area (BA)**	**z-value**	**mm³**	**x**	**y**	**z**
A1+ group						
Positive correlation with response certainty						
anterior frontomedian cortex	BA 10	4.3 4.7	2727	-2 4	42 57	0 18
R retrosplenial cortex	BA 29	4.06	432	10	-49	18
anterior frontomedian cortex	BA 10	3.80	378	7	59	12
R pregenual anterior cingulate cortex	BA 24	3.96	486	10	32	9
Negative correlation with response certainty						
L intraparietal sulcus (ascending branch)	BA 40	3.74	972	-44	-46	51
L intraparietal sulcus (ascending branch)	BA 7	3.62	324	-29	-43	39
L middle frontal gyrus	BA 8	3.95	270	-38	29	39
A1- group						
Positive correlation with response certainty						
R cingulate cortex (caudal cingulate zone)	BA 23	3.92	324	4	-16	33
L Putamen		3.90	540	-23	-10	15
R Putamen		3.76	378	22	-1	12
L posterior insula		3.87	297	-38	-13	3
subcallosal anterior cingulate cortex	BA 24/25	4.02	1080	-8	20	-6
L anterior frontomedian cortex	BA 10	4.84	540	-11	62	-6
L amygdala		3.82	891	-20	-7	-18
R amygdala		4.99	378	22	-1	-18

Negative correlation with response certainty						
L intraparietal sulcus (horizontal branch)	BA 40	3.62	405	-50	-49	48
L inferior frontal junction	BA 9	3.85	513	-44	5	36
L middle occipital gyrus	BA 18	4.57	702	-35	-91	0
R inferior occipital gyrus	BA 18	3.56	405	31	-88	-6
cerebellum (superior posterior fissure)		4.28	459	-35	-64	-21
cerebellum (superior posterior fissure)		3.52	270	34	-55	-27

Note: R/L = right/left.

How does feedback monitoring in the RCZ interact with forming memories in the hippocampus? Anatomically, these areas are connected via the cingulate bundle. To investigate learning-related changes in functional interactions of the RCZ and other brain areas over time, we performed a Psychophysiological Interaction Analysis (PPI; Friston et al., 1997; Gitelman et al., 2003; see section 3.1.3 for details). The experiment was divided into three parts of equal length. We then contrasted the functional connectivity of the RCZ observed in the first third with the connectivity observed in the last third of the learning experiment, thereby capturing the difference between steep rule acquisition in the beginning and more stable rule exploitation at the end. Again, in the A1- group we observed a significant change over time: In the first third of the experiment the functional coupling between RCZ activity and the bilateral hippocampus (left (x = -26, y = -42, z = 3; z-score = 4.4, 459 mm^3) and right (x = 28, y = -42, z = -3; z-score = 3.4, 135 mm^3)) was significantly stronger than in the last third (fig. 4-2, c). The A1+ group showed no such correlation (Bayesian posterior probability of group difference: left hippocampus, 99.98%; right hippocampus, 99.91%). Furthermore, only the A1- group showed a similar change in functional coupling between nucleus accumbens and RCZ over the time course of the experiment (x = 16, y = 9, z = 3; z-score = 3.4, 108 mm^3; Bayesian posterior probability: 99.54%). The nucleus accumbens, another major target of dopaminergic projections, has been implicated in feedback-based decision making as well (Ullsperger & von Cramon, 2003; Knutson et al., 2001; Cools et al., 2004; Heekeren et al., 2007). In accordance

with previous findings, the fMRI signal in the nucleus accumbens on both sides is increased on positive feedback as compared to negative feedback (fig. 4-2, a). This reward-related activity increase is reduced in the A1+ group in the right nucleus accumbens (x = 16, y = 9, z = -6; z-score = -3.96; Bayesian posterior probability of group difference 94.8%; on the left side, posterior probability reaches only 74.1%). This finding is consistent with the findings of lower striatal DA D2 receptor densities associated with this allele (Ritchie & Noble, 2003; Jönsson et al., 1999; Pohjalainen et al., 1998).

In addition, we extracted trial-by-trial prediction errors from the computational model (Pessiglione et al., 2006) and used it as a parametric regressor to analyze the fMRI data (fig. 4-5).

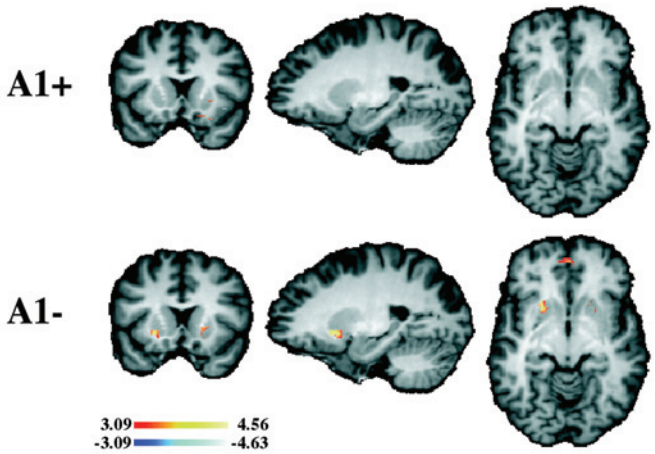


Figure 4-5 Parametric within subject fMRI analysis using the prediction error as a regressor, projected onto a coronal (y = 12), a sagittal (x = -23) and a horizontal slice (z =-3)

As expected from previous research (Pessiglione et al., 2006; Yacubian et al., 2007), activity in the striatum (x = 19, y = 6, z = 0, 783 mm³, z-score = 3.91; x = -23, y = 11, z = -3, 756 mm³, z-score = 4.17) as well as the frontomedian cortex (x = -2 , y = 35, z = 12, 513 mm³, z-score = 3.97; x = 1, y = 47, z = -3, 351 mm³, z-score = 3.64) co-varied with the prediction error in the A1- group. Also in the A1+ group the prediction error co-varied with activity in the striatum. Posterior probabilities are relatively low but speak in favor of a group difference (striatal activations: 64.9% and 77.63%; pMFC: 88.24% and 67.64%).

To test whether the reduction in fMRI signals observed for the A1+ subjects is specific for performance monitoring processes, a contrast of all responses with the right hand against implicit baseline was calculated (positive and negative outcomes collapsed). This contrast focuses on task-related brain activity while excluding the specific difference of processing negative and positive feedback. As can be seen in fig. 4-6, the same set of brain structures (mainly consisting of the dorsal frontoparietal network, visual areas and the cerebellum) is activated. It can be concluded that the effect of genotype on brain activity is highly specific to learning from feedback and does not generalize to other task-related activity.

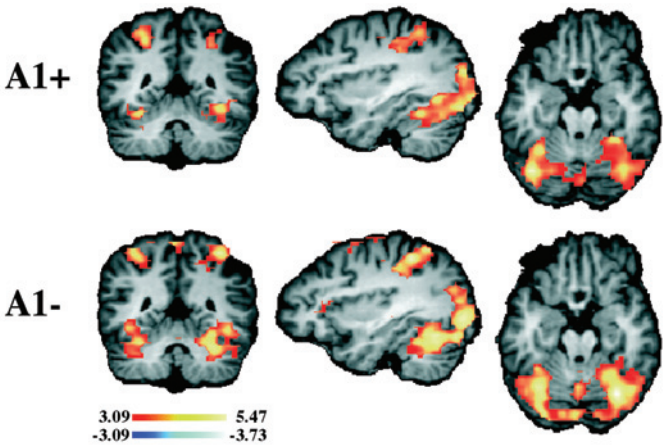


Figure 4-6 Task-related fMRI signal increases independent of the difference between positive and negative feedback processing (baseline contrast of right-handed responses, all outcomes collapsed). In both genotype groups, the same set of brain structures is activated.

4.1.6 Discussion

Our results confirm that DA plays a major role in performance monitoring and behavioral modification for reaching optimal performance levels. Alterations in dopaminergic transmission lead to corresponding alterations in negative feedback processing and related to this, to differences in learning from negative feedback. It appears that reduced DA D2 receptor density is associated with reduced capacity to learn negative characteristics of a stimulus from negative feedback. High receptor density in the A1- group is associated with clear avoidance of the most negative stimulus whereas a reduced receptor density in A1+ subjects is not. Cor-

responding to this, subjects with a reduced receptor density show a weaker BOLD response to negative feedback in the pMFC and the MFG. These genetically driven differences in avoidance learning seem to result from a weaker neuronal response to negative feedback and a reduced interaction of performance monitoring in pMFC and memory-formation in the hippocampus.

At first sight, our findings that subjects with lower D2 receptor densities show reduced avoidance learning may appear to conflict with the results by Frank and colleagues (Frank et al., 2004) who showed that patients with Parkinson's disease on medication, i.e., with enhanced dopaminergic transmission, have problems in learning the negative value of stimuli. However, a recent study revealed a higher rate of DA synthesis in the striatum for subjects with the A1+ configuration compared to A1- subjects (Laakso et al., 2005). This higher level of DA might be caused by a lack of D2 autoreceptors. Missing autoreceptors lead to a higher synthesis rate of DA, which in turn leads to a higher level of DA. This may strengthen transmission via D1 receptors and relatively reduce modulation of post-synaptic D2 activity by phasic changes in DA release. According to the model by Frank and colleagues (Frank et al., 2004; Frank, 2005) this should be associated with a relative decrease in avoidance learning and a shift to learning mainly from positive reinforcement. Parkinson's disease is often treated with tonically acting direct D2 agonists which also reduce phasic modulations at post-synaptic D2 receptors. A phasic decrease in DA, as suggested to occur on negative feedback (Schultz, 2002; Holroyd & Coles, 2002), may thus be less effective in both studies. This dulled D2 mediated dopaminergic signal in turn would finally lead to a weaker hemodynamic response in the RCZ. Further studies are needed to unravel the complex interactions of DA D2 receptor density and dopaminergic transmission in frontal cortex and the striatum.

As stated before, EEG has one major advantage over fMRI: higher temporal resolution. To get an impression of electrophysiological processes underlying negative feedback processing in the probabilistic learning task we repeated the task while concurrently measuring the EEG.

4.2 EEG Study

4.2.1 Rationale

As described in section 2.2.1, the electrophysiological correlate of error-processing is the error-related negativity (ERN; Falkenstein et al., 1990; Gehring et al., 1993). Numerous source localization studies (e.g. Luu & Tucker, 2001) and fMRI studies (Ullsperger & von Cramon, 2001; Debener et al., 2005) have localized the source of the ERN in the pMFC, specifically in the rostral cingulate zone (RCZ). Not only error processing but also negative feedback processing seems to take place in this brain area (Ullsperger & von Cramon, 2003; Holroyd et al., 2004). As mentioned before, outcome coding of an action as better as or worse than expected seems to rely on dopaminergic activity in the midbrain (Schultz, 2002). In the previously described fMRI study (section 4.1 and Klein et al., 2007b) we showed that a genetic polymorphism known to affect DA D2 receptor density in the striatum influences how negative feedback is processed in RCZ and how subsequent learning from negative feedback varies in accordance with D2 receptor density.

With the following study we wanted to address the same question now using the higher temporal resolution of electroencephalography (EEG). We investigated, whether the differences in negative feedback processing can also be found in the feedback-related negativity (FRN; Miltner, Braun & Coles, 1997), a frontomedially distributed component following negative performance feedback sometimes also referred to as medial-frontal negativity (MFN; Gehring & Willoughby, 2002). The FRN can be observed 200-400 ms after the onset of negative feedback and it seems to be generated also in the dorsal ACC (Holroyd et al., 2004). Typically, the potential is larger on negative feedback compared to positive feedback (Gehring & Willoughby, 2002). The FRN also seems to rely on dopaminergic signaling (Holroyd & Coles, 2002). Supporting evidence for this comes from performance monitoring studies with older subjects in whom DA release is reduced (Baeckman et al., 2000): Subjects with higher age show a reduced FRN amplitude (Nieuwenhuis et al., 2002; Eppinger et al., 2007). Therefore, a straightforward prediction is that the FRN should show the same influence of a variation in DA D2 receptor density as it was the case for RCZ activity following performance feedback. A genetically driven reduction in amplitude in response to negative feedback would thus be expected.

Furthermore, we aimed at replicating our findings of a genetically determined learning bias for negative and positive action outcomes. Computational modeling was employed in the same fashion as in the fMRI study.

4.2.2 Materials and Methods

30 people took part in the EEG study, 14 of which belonging to the A1+ group (mean age ± SEM = 25.4; 0.85), the remaining 16 subjects belonging to the A1- group (mean age ± SEM = 24.5; 0.76). We employed the same probabilistic learning task (Frank et al., 2004) as in the fMRI study (for a description of the task see section 3.4) with two differences. First, as EEG is not relying on the BOLD response, we adjusted the trial timing as follows: Participants saw the respective pair of symbols for up to 1500 ms. Immediately after the response the performance feedback was displayed for 700 ms. After this a blank screen was displayed until a total trial duration of 2.8 s was reached. For the reasons mentioned before and for practical reasons we decided to choose this faster trial timing. Second, we employed different characters (Hiragana) as symbols (see table 4-4 for examples of the stimuli we used).

Table 4-4 Stimuli of the probabilistic learning task (fast and slow version). Reward probabilities are given in brackets.

Stimuli of the fast version (EEG)			Stimuli of the slow version (fMRI)		
					
"A" (80%)	"C" (70%)	"E" (60%)	"A" (80%)	"C" (70%)	"E" (60%)
					
"B" (20%)	"D" (30%)	"F" (40%)	"B" (20%)	"D" (30%)	"F" (40%)

Besides these two changes the procedure was the same as in the fMRI measurement, including the behavioral post-test, which also took place in the EEG booth. As no null events had to be included, subjects worked on 420 trials (140 per symbol pair). The same logic to determine the "choose A" and "avoid B" performance in the post-test data was applied as in the fMRI study.

During recording of the EEG, participants sat in a dimly lit, sound-attenuated electrically and acoustically shielded chamber with a monitor in front of them. The EEG was recorded from 64 Ag/Ag-Cl electrodes mounted in an elastic cap (BrainCap – MR 64 Channel, Easy Cap, TM) and named after the international 10-20 system (Jasper, 1958). During measurement all electrodes were referenced against CPz. Offline they were re-referenced against the arithmetic mean of the mastoid electrodes. For controlling eye movement artifacts a bipolar vertical and horizontal electroocculogram (EOG) was recorded. All impedances were kept below 5 kΩ. The data was sampled with 70 Hz and digitized with 250 Hz frequency (16 bit resolution).

Further data processing was done using EEGLAB v5.02 (Swartz Center of Computational Neuroscience, Institute for Neural Computation, University of California, San Diego). First, the data was filtered using a high-pass filter of 2.0 Hz and a low-pass filter of 40 Hz. A manual correction for technical and muscle artifacts was done, followed by a correction for eye movements based on independent component analysis (ICA; Jung et al., 2000). After re-coding of the triggers the response locked signal was averaged for every electrode and every person for trials with positive and trials with negative feedback separately. The mean amplitude between -1000 and -800 relative to the response was used as baseline. Based on existing literature showing a peak for the FRN 200-400 ms after feedback, we decided to take the minimum in a time window of 200-400 ms after the response (as the feedback appeared immediately on the response) as time frame to look for the FRN. Thus, the FRN was defined as the minimum in a time window of 200-400 ms.

4.2.3 Behavioral Results

In the learning phase of the experiment A1+ subjects chose the more often rewarded symbols (“A”, “C”, or “E”) reliably more often than subjects from the A1- group. Table 4-5 summarizes the main behavioral results from the learning phase and from the post-test. A1+ subjects show better overall performance in the task as indexed by central measures of learning and learning success. It should be noted, however, that the performance of the A1- subjects with respect to choosing symbol “A”, “C” or “E” in the learning phase was significantly above chance (p-values < .013).

Table 4-5 Summary of the behavioral results from the probabilistic learning task

	A1+	A1-
(1) Behavioral results from the learning phase (given in mean percent chosen ± SEM)		
Choosing symbol "A" (A1+ > A1-: t = -4.0; p = .000)	81.3% ± 2.2	65.2% ± 3.3
Choosing symbol "C" (A1+ > A1-: t = -2.1; p = .05)	78.4% ± 3.5	67.4% ± 3.9
Choosing symbol "E" (A1+ > A1-: t = -2.1; p = .04)	67.6% ± 4.3	56.9% ± 2.5
Percent Negative Feedback (A1+ < A1-: t = 2.6; p = .01)	41.4% ± 1.1	45.0% ± 0.9
(2) Behavioral results from the post-test (given in mean percent chosen ± SEM)		
Choosing symbol "A" (A1+ > A1-: t = -1.8; p = .09)	65.3% ± 3.9	54.4% ± 4.6
Avoiding symbol "B" (A1+ > A1-: t = -1.7; p = .1)	66.3% ± 5.8	53.1% ± 5.1

Analysis of the development of choosing the good symbol (“A”, or “C”, or “E”; see fig. 4-7) over time reveals that carriers of the A1 allele (A1+ subjects) show a strong tendency to choose the good symbol already in very early stages of the experiment (main effect genotype: F = 16.6; p = .000). Furthermore, subjects from the A1+ group received significantly less negative feedback (t = 2.6; p = .01).

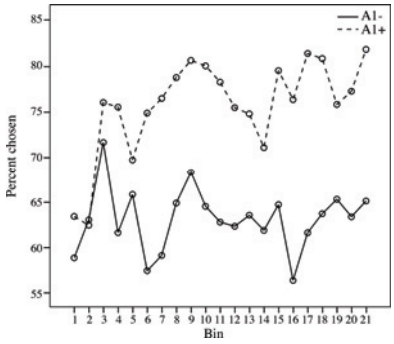


Figure 4-7 Choosing the good symbol ("A", "C" or "E"), binned

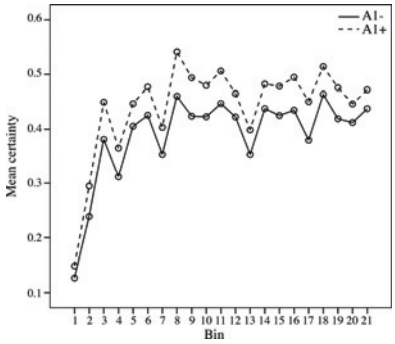


Figure 4-8 Certainty of the given response derived from the computational model, binned

The development of response certainty over time (the same computational model architecture was employed as in the fMRI study, see section 3.5) shows a similar pattern (see fig. 4-8): Subjects from the A1+ group develop a higher response certainty already in very early stages of the experiment (main effect of genotype: $F = 18.7$; $p = .000$).

A remarkable difference between genetic groups is evident from the learning rates of the computational model, i.e. the coefficient by which the weights of the model are updated after having received feedback: A1+ subjects show a higher learning rate, i.e., a stronger updating of their model after feedback ($t = -2.7$; $p = .01$).

In the post-test (see fig. 4-9) A1- subjects show a rather poor performance: They neither showed a strong tendency of choosing symbol "A" (preference learning), nor a strong tendency to avoid symbol "B" (avoidance learning). In fact, both values did not differ significantly from chance (Choose "A": $t = 1$; $p = .4$; Avoid "B": $t = 0.6$; $p = .6$). Subjects from the A1+ showed a choosing behavior significantly above chance level (Choose "A": $t = 3.9$; $p = .002$; Avoid "B": $t = 2.8$; $p = .01$). A significant main effect for genotype ($F = 8.3$; $p = .008$) but no interaction between genotype and choosing behavior in the post-test could be observed ($F = .05$; $p = .8$). Here, genotype did not differentiate between preferring to learn from positive or negative feedback.

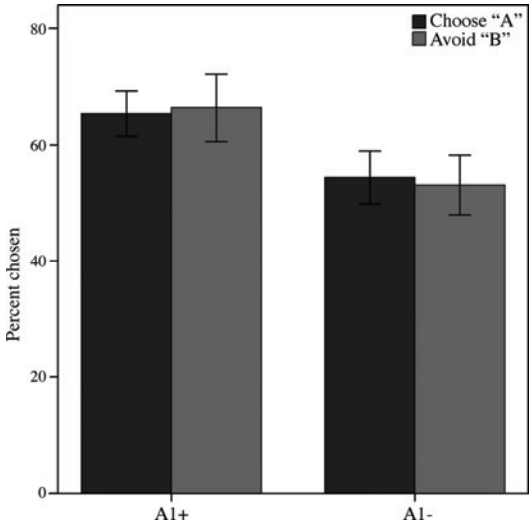


Figure 4-9 Post-test: Choosing the good symbol "A" and avoiding the bad symbol "B"

With respect to response-switching behavior after having received positive feedback, A1+ subjects are less likely to switch responses, i.e. choosing the other symbol ($t = 4.3$, $p = .000$) when compared to A1- subjects. Furthermore, subjects from the A1+ group also switch significantly less after negative feedback ($t = 3.0$, $p = .005$) as compared to A1- subjects.

4.2.4 ERP Results

We extracted the FRN as the minimum in the time-window 200-400 ms after feedback. In fact ERPs were locked to the response as feedback was provided immediately after button press. As the FRN is known to have a centro-medial scalp topography we included the following electrodes for further analysis: F3, F4, Fz, FC3, FCz, FC4, C3, Cz. ERP data were subjected to a repeated measures ANOVA with the within subject factors feedback (negative vs. positive) x anterior-posterior dimension (anterior, middle, posterior) and laterality (left, median, right), and the between subject factor genotype (A1+ or A1- subjects). We revealed no main effect for feedback, but a significant main effect for the anterior posterior dimension ($F = 6.6$, $p = .003$) and the laterality dimension ($F = 39.8$, $p = .000$).

There was a weak trend for an interaction between genotype and feedback (F = 2.8, p = .11). The significant interaction between anterior-posterior dimension and laterality (F = 14.2, p = .000) showed that the FRN was most pronounced at electrode FCz. Figures 4-10 and 4-11 show response locked averages for negative and positive feedback separately for the two genetic groups.

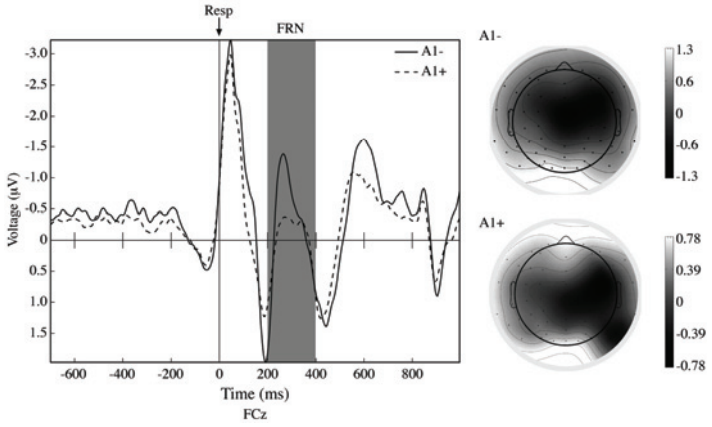


Figure 4-10 ERPs locked to negative feedback; electrode FCz; topographies at 250 ms after response

Following negative feedback the FRN was significantly more pronounced at electrode FCz for A1- subjects (t = -3.2, p = .004; see fig. 4-10) as compared to A1+ subjects. We found no significant difference following positive feedback (t = -1.5, p = .15; see fig. 4-11). Within-group comparisons between positive and negative feedback revealed that A1- subjects showed a significantly more negative FRN for negative as compared to positive feedback (t = 2.1, p = .05). No such difference could be found for the A1+ subjects, in fact their negativity for positive feedback was slightly higher.

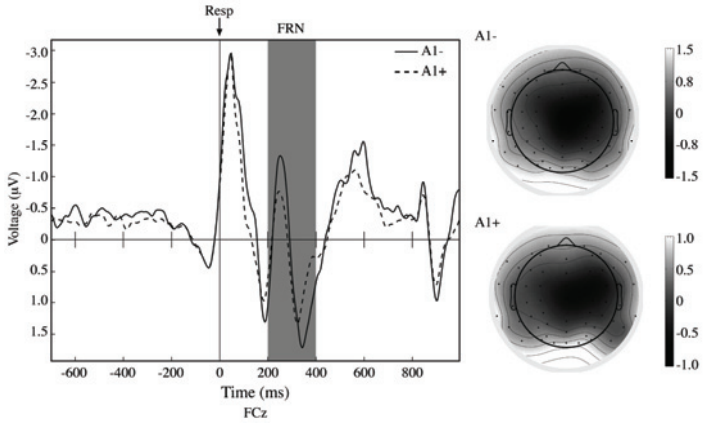


Figure 4-11 ERPs locked to positive feedback; electrode FCz, topographies at 250 ms after response

We observed a correlation between FRN amplitude and choosing behavior in the training phase of the task. A1- subjects showed a negative correlation between the FRN amplitude following negative feedback and choosing of symbol "A" or "C" ($r = -.77$, $p = .000$ and $r = -.6$, $p = .02$, respectively). No such correlation could be found for A1+ subjects.

Furthermore, we observed a significant positive correlation between FRN amplitude following negative feedback (FCz) and the certainty of the given response derived from the computational model for A1+ subjects. Higher certainty was coupled with a smaller (i.e. more positive) FRN amplitude ($r = .73$, $p = .003$). Interestingly, the opposite is true for A1- subjects: Here we found a negative correlation between response certainty and FRN amplitude following negative feedback ($r = -.82$, $p = .000$). Similar to that the FRN amplitude following positive feedback also correlates negatively with certainty in our task ($r = -.56$, $p = .024$), again only for A1- subjects.

4.2.5 Discussion

On the behavioral level this EEG experiment shows a clear main effect of genotype on task performance. A1+ subjects show better learning in the training phase of the task. Results from the computational model point to the same direction: A1+ subjects develop a higher response certainty during the training phase. Looking at the learning rates of the computational model it can be seen that A1+ sub-

jects have a higher learning rate, i.e. their internal rule representation is updated much more by an individual feedback provided on each trial.

For the FRN at electrode FCz it can be seen that subjects with a normal receptor density show a more pronounced negativity in response to negative feedback as compared to subjects with reduced D2 receptor density. For the A1- group the negativity following negative feedback is more pronounced than that following positive feedback. This was not the case for the A1+ group.

In contrast to our previous findings, in the EEG version of the task subjects with a reduced receptor density seem to have some advantages, at least on the behavioral level. They do not react as strongly to negative feedback as A1- subjects do, but they are better in choosing the good symbol and they develop higher response certainty.

Difference in FRN amplitude might have something to do with a developing task-related response certainty. Following Holroyd and Coles (2002) the FRN amplitude decreases with increasing knowledge about which response is appropriate in the given task situation. When subjects start working on a task that is completely unknown, no representation of the correct response is available. In this situation performance feedback conveys a lot of information. With increasing experience the impact of the individual feedback decreases. Following this logic the FRN should decrease in amplitude as the certainty of the subject about how to handle the task increases.

Pointing to this direction we observed a significant positive correlation between FRN amplitude following negative feedback (FCz) and the certainty of the given response for A1+ subjects. Higher certainty was coupled with a more positive FRN. Interestingly, the opposite is true for A1- subjects: Here we found a negative correlation between response certainty and FRN amplitude following negative feedback. A relationship between feedback-related activity and task-certainty as proposed by Holroyd and Coles (2002) could be observed: Smaller certainty was coupled with a higher FRN amplitude. The same relationship can be shown, although weaker but still significant, for the FRN amplitude following positive feedback, suggesting that also positive feedback might contribute to developing certainty in our task.

The negative correlation we found between FRN amplitude and choosing behavior in the training phase of the task also points to a relationship between the FRN and measures of learning success. The more negative the FRN following negative performance feedback, the more choosing of a relatively more often

rewarded symbol (here demonstrated for “A” and “C”) was observed. This relationship only holds true for the A1- subjects, although they do not choose the relatively more often rewarded symbol as often as A1+ subjects. A1- subjects seem to rely more on information provided by the FRN but they are not able to establish stable task rules.

The most prominent difference between the two versions of our task was the different trial timing. In the fMRI study mean trial duration was 5 s, whereas in the EEG study the trial duration was 2.8 s. In the following we will compare the fMRI findings with the EEG results, trying to find an explanation for the trial timing related differences.

4.3 EEG vs. fMRI Results: A Comparison

To get an impression of potential trial timing influences on task performance we considered only version influences (EEG = fast vs. fMRI = slow version) and did not look for genotype x version interactions. Looking at the learning performance displayed as percentage choosing the good symbol (“A”, “C” or “E”, see figure 4-12) it can be seen that subjects in the slow version of our task choose a good symbol more often than in the fast version. Moreover, their learning curve shows a steeper increase. The main effect of version is significant ($F = 8.3$, $p = .006$).

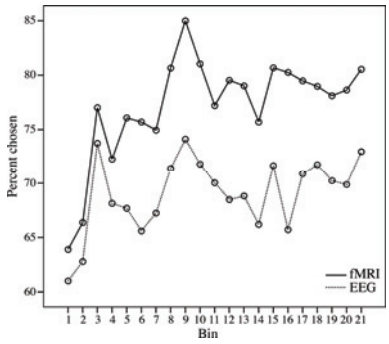


Figure 4-12 Comparison between fast and slow timing: Choosing the good symbol (“A”, “C”, “E”), binned

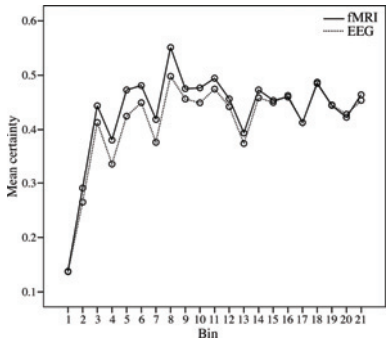


Figure 4-13 Comparison between fast and slow timing: Certainty of the given response, binned

Another index of learning success is response certainty (see figure 4-13). It could be expected that subjects in the slow version show higher response cer-

tainty. Here we found a significant interaction between bin and version ($F = 2.4$, $p = .05$).

The post-test performance of subjects from the two timing conditions was also compared with each other. We wanted to test whether the learning bias (learn from negative or positive feedback) was influenced by trial timing. From figure 4-14 it can be seen that no interaction between experimental version (fast vs. slow) and choosing symbol "A" or avoiding symbol "B" was evident. As a weak trend, subjects in the slow condition seem to learn more than subjects in the fast condition ($F = 1.8$, $p = .19$) indexed by post-test performance. The average learning rates of the computational model revealed no difference between the two conditions.

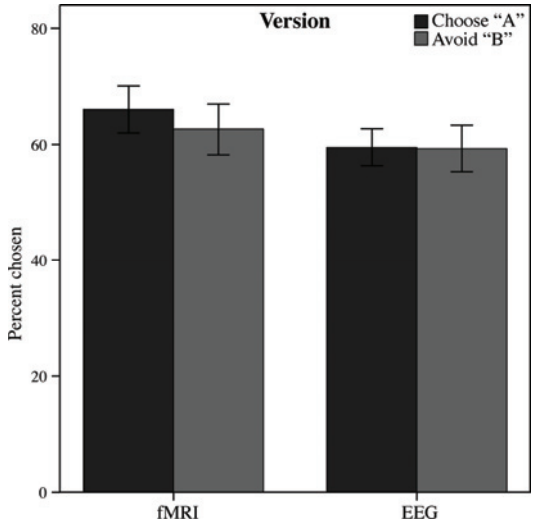


Figure 4-14 Comparison between fast and slow timing: Post-test

Taken together these results suggest that longer trial durations lead to better results in terms of choosing the good symbol, in terms of response certainty and in terms of post-test performance. So far we only looked for timing-related differences. Another interesting question is, whether these timing related influences are dependent on the genotype of our subjects. We took another look at the timing-related influences, now considering also genotype of our subjects as a factor.

4.4 Equal Timing Influence for Genotypes?

The interaction between genotype and version in terms of choosing a good symbol in the training phase was significant (F = 6.6, p = .01). In the fast condition (fig. 4-15) A1+ subjects show a better learning performance, but in the slow condition (fig. 4-16) A1- subjects show a better learning performance.

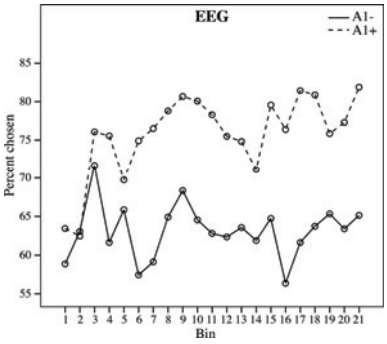


Figure 4-15 Choosing the good symbol ("A", "C", "E"), fast timing, binned

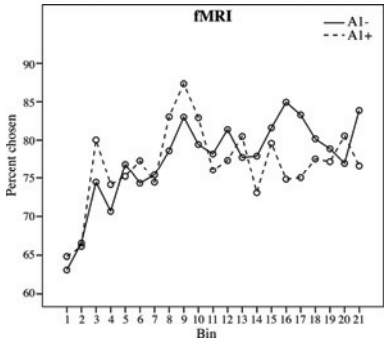


Figure 4-16 Choosing the good symbol ("A", "C", "E"), slow timing, binned

The mean of choosing a good symbol differed significantly between the genotypes in the fast timing condition (t = -4.1, p = .000). The same difference failed to reach significance in the slow condition (t = .15, p = .88).

In case of response certainty the main effect for version and for genotype did not reach significance but the interaction was significant (F = 9.3, p = .004). In the fast condition (fig. 4-17) A1+ subjects reached a higher response certainty. In the slow condition (fig. 4-18) A1- subjects showed a higher response certainty.

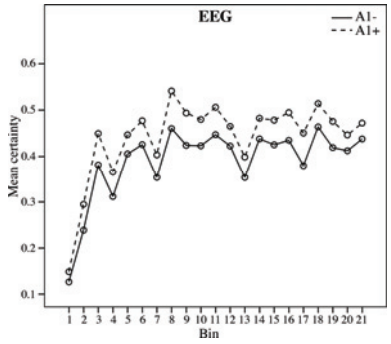


Figure 4-17 Certainty of the given response, fast timing, binned

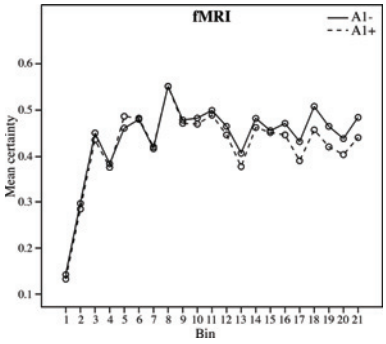


Figure 4-18 Certainty of the given response, slow timing, binned

In the fast condition mean response certainty differed significantly between the genotypes ($t = -4.3$, $p = .000$) with A1+ subjects showing a higher mean response certainty. In the slow timing the two genetic groups reached a significantly different response certainty in the last third of the experiment ($F = 2.7$, $p = .04$) with A1-subjects reaching higher values.

A further parameter indicative of individual learning success is the learning rate, i.e. the impact an individual feedback has on updating of the computational model. Here we found no influence of genotype or version in terms of main effects. But again, a significant interaction between these factors ($F = 4.9$, $p = .03$) was revealed (see fig. 4-19). In the slow condition A1- subjects showed a higher learning rate than the A1+ subjects (ns), but in the fast condition the pattern reversed and subjects from the A1+ group showed a higher learning rate ($t = -2.7$, $p = .01$). For A1- subjects the mean difference in learning rate between the timing conditions was significant ($t = 2.1$, $p = .05$), whereas this difference for the A1+ subjects failed to reach significance.

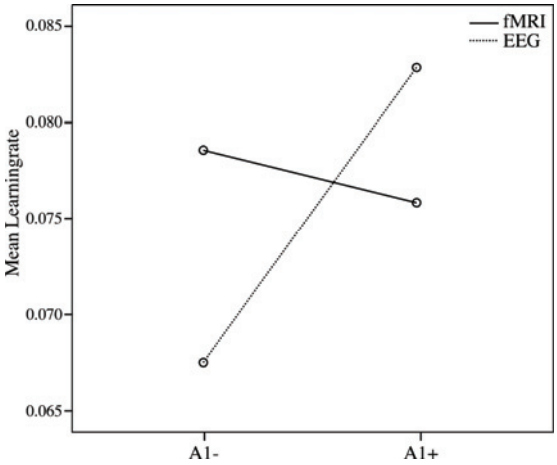


Figure 4-19 Learning rate: Interaction between genotype and trial timing

In a final analysis step we considered performance in the post-test as an indicator of learning transfer. We observed a significant interaction between version and genotype: In the slow condition A1- subjects showed a higher learning success (average of choosing the good symbol "A" and avoiding the bad symbol "B"), whereas in the fast condition the opposite was true. In this condition subjects from the A1+ group showed a higher learning success ($F = 5.2$, $p = .03$).

Dividing the learning performance into preference and avoidance learning (choose "A" and avoid "B"), there was a significant three way interaction ($F = 4.6$, $p = .04$) between version, genotype and choosing behavior in the post-test (see also figures 4-20 and 4-21). In the slow condition the A1+ subjects learned more from positive feedback but less from negative feedback ($t = 2.5$, $p = .03$). The difference between A1- and A1+ subjects with respect to avoid "B" performance was significant ($t = 2.5$, $p = .02$; see also Klein et al., 2007b). In the fast condition there was no interaction between choosing and genotype, but a main effect of genotype. Subjects from the A1+ group learned better than subjects from the A1- group to choose symbol "A" and to avoid symbol "B" (mean choose "A": $t = -1.8$, $p = .09$; mean avoid "B": $t = -1.7$, $p = .1$).

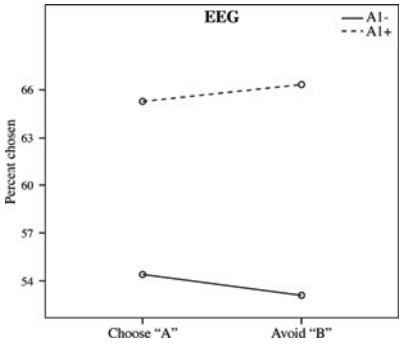


Figure 4-20 Post-test; fast version

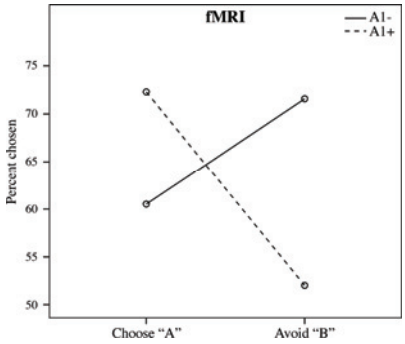


Figure 4-21 Post-test; slow version

For choosing the good symbol "A" a significant main effect of genotype ($F = 5.3$, $p = .03$) was found. Subjects from the A1- group showed a poorer choose "A" performance compared to subjects from the A1+ group in both timing conditions. Avoiding symbol "B" there was a significant interaction between genotype and version ($F = 8.7$, $p = .005$). A1- subjects showed better avoid "B" performance in the slow than in the fast condition ($t = 2.6$; $p = .02$). The opposite is true for A1+ subjects: In the fast condition they showed a better avoid "B" performance than in the slow condition ($t = -1.7$, $p = .1$). In the slow condition the difference in avoiding "B" between A1- and A1+ was significant ($t = 2.5$, $p = .02$), whereas the same difference in the fast condition was not.

Taken together these findings suggest that the influence of different trial timing is modulated by genotype. If the task is presented with a higher stimulation frequency (fast condition) subjects with a reduced receptor density show better choosing performance in the training-phase. With a lower stimulation frequency (slow version) subjects with a normal receptor density show better choosing performance.

For response certainty the same pattern can be seen: Confronted with the faster trial timing subjects from the A1+ group show a higher response certainty, but in the slow condition the A1- subjects reach higher response certainty. This is similar for the learning rate: Higher frequency of stimulation results in a higher learning rate for A1+ subjects.

In the post-test there is no interaction between genotype and choosing "A" or avoiding "B". If stimulated with a higher frequency, A1+ subjects learn more in general while showing no learning bias.

From these results the question arises, why it should be advantageous to have less D2 receptors if stimulated with higher frequency, or put the other way, why should subjects with a normal receptor density show better results in the slow condition?

4.5 Different Trial Timing: Behavioral Follow-up

To further investigate the differences between fMRI and EEG results in terms of training performance and learning success we tested additional participants (N = 15 subjects per condition; mean age ± SEM for slow group: 24.7 ± .54; mean age ± SEM for fast group = 24.5 ± .77; no genetic information). We confronted them with either the slow or the fast version of the task. These follow-up measurements were purely behavioral. We compared results from the follow-up study with the results which were acquired during "real" EEG or fMRI measurements. For all measures discussed here (choosing of good symbol in the training; certainty of the given response; learning rate of the computational model; choosing behavior in the post-test) there was a tendency for higher values in the follow-up study, but significant only for certainty of the given response. Importantly the factor measurement "on/off" did not interact with the factor timing in the above mentioned measurements.

In the slow condition subjects showed better performance in choosing good symbols ("A", "C" or "E" collapsed, see figure 4-22; version: $F = 3.2$, $p = .09$). Mean difference between the versions was significant on a trend level ($t = 1.8$, $p = .09$). Significance improved when looking only at the last third of the training ($t = 2.0$, $p = .06$).

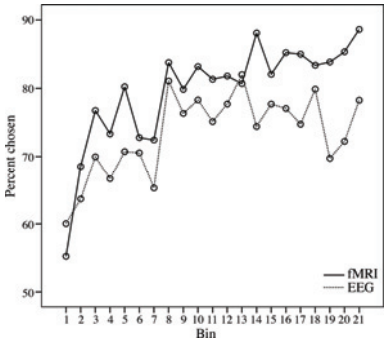


Figure 4-22 Choosing the good symbol, behavioral study, binned

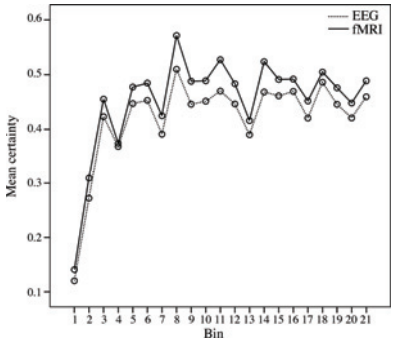


Figure 4-23 Certainty of the given response, behavioral study, binned

We found similar results for response certainty. Subjects in the slow condition reached higher response certainty (version: $F = 2.8$, $p = .1$; see figure 4-23). The difference in the mean certainty was not significant.

In the post-test a similar main effect of version could be observed ($F = 4.9$, $p = .04$; see figure 4-24). In the slow condition subjects learned better to choose the good symbol “A” ($t = 2.1$, $p = .05$) and to avoid the bad symbol “B” (ns). Within condition differences between choosing “A” and avoiding “B” were not significant (p-values > .3).

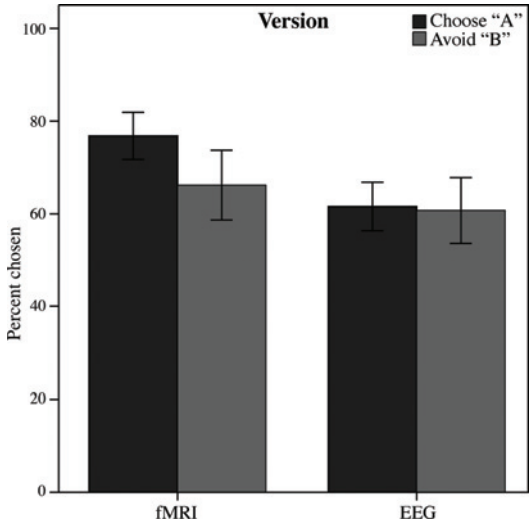


Figure 4-24 Post-test, behavioral study

Thus we replicated the findings of the EEG and fMRI studies showing an influence of trial timing on central measures of learning performance and learning success. Subjects presented with the task in a faster version, less often chose a rewarded symbol, they reached lower response certainty and they showed a poorer post-test performance. Because up until now no genetic information is available for these behavioral subjects, we are unable to test for replication of the trial timing x genotype interaction. The question remains however, why it is advantageous to have less D2 receptors when stimulated at higher frequencies. The following section is trying to shed some light on this question.

4.6 Discussion

We demonstrated timing influences on the performance in a probabilistic learning task (Frank et al., 2004). If trial duration is 5 s (slow version) subjects learn much better as compared to a trial timing of 2.8 s (fast version).

Subjects might employ different strategies working on the different task versions. Working in the fast condition may force subjects to make use of different learning mechanisms than working in the slow condition. It may be speculated that the contribution of learning systems (action-outcome learning vs. stimulus-

response-reward learning) to action guidance is differently accentuated by the timing conditions.

In the fast condition subjects may have to rely more on a working memory based strategy to handle the task. This could explain that subjects show better learning in the slow condition: both learning systems can contribute to action guidance in parallel. In the fast condition only learning systems able to deal with high stimulation frequencies (working memory) can operate.

The slow development of choosing behavior and response certainty might be caused by a mixture of action-outcome and habit learning (two learning systems working parallel). The differences observed between genetic groups in response certainty may therefore be due to differences in contribution of the habit learning system operated in the BG to action guidance (BG being the brain area where the polymorphism used exerts its highest influence).

Why should subjects with a reduced D2 receptor density show a better performance in the fast condition where they have to rely more heavily on working memory? Working memory is often discussed in the context of the PFC, whereby PFC is assumed as a central component of a network of brain regions responsible for working memory (D'Esposito, 2007). Thus the concept of two different states of DA acting in the PFC may be helpful (see section 2.8.2): state 1 vs. state 2 (Seamans et al., 2001).

Applying this logic to our genotypes could mean that subjects with a genetically determined reduction of D2 receptor density may exhibit a more state 2-like (D1 modulated) information processing in PFC. Subjects with a normal receptor density show a higher contribution of state 1 (D2 modulated) to prefrontal information processing. In the slow condition subjects assumed to have higher state 1 contribution to information processing show better learning performance. Given enough time it is beneficial in this task to be able to have multiple representations in working memory simultaneously, thus enabling the system to build up reward hierarchies between symbols in terms of a reward history. If trial timing gets faster, thereby inducing rising stimulation frequencies, a confusion of inputs might occur. Too much input needs to be processed with too little time available in order to establish stable representations. Thus, being in state 1, allowing multiple representations in working memory, may be detrimental.

The amount of D2 receptors in PFC may be reduced in subjects carrying the A1 allele. Thus, A1+ subjects might have a genetically determined bias towards a state 2-like (D1 dominated) way of information processing. In the slow timing

condition this state 2 bias might cause problems: Subjects may not benefit from having multiple inputs in working memory, because, due to slow timing, inputs may be too weak to get established as a stable task representation in state 2. In the fast condition, however, inputs may be able to become stable representations in working memory because items presented with high stimulation frequency are potentially strong enough to pass the high threshold of working memory buffer. Thus A1+ subjects may be able to build very stable representations on which they could work during the task. Furthermore, a reduction in D2 receptors might cause difficulties in switching the system back to state 1 dynamics. Switching back to state 1 is especially likely given high DA concentrations (see section 2.8.2). It may be speculated that the prefrontal DA level is high in the fast trial timing. Such a saturation of DA in prefrontal brain areas in the fast version of our task seems possible, given the slow rates of prefrontal DA turnover (Lapish et al., 2007; Lavin et al. 2005). State 1 dynamics could cause exploration of new task rules by allowing new inputs to be processed in working memory. Thus, the stable task representations kept in state 2 are not challenged by new representations in A1+ subjects, because the system is impaired in switching to state 1.

In A1+ subjects, transmission via D1 receptors is more dominant. Thus initiation and stabilization of a few goal-related representations (Seamans & Yang, 2004) should occur. A1+ subjects should therefore show a more perseverative response behavior, i.e. sticking with previous choices. This should be especially obvious if trial timing stresses contributions of working memory to task performance. After having received positive feedback for a symbol, A1+ subjects are in the fast condition less likely to switch responses than A1- subjects. If there is a tendency towards stereotyped responding, this should occur also after having received negative feedback. Indeed, subjects from the A1+ group switch significantly less also after negative feedback than A1- subjects when working on the fast version of the task.

Faster trial timing might induce a bias towards a more working memory based strategy of working on the probabilistic learning task. Memory traces of the symbols may be more prominent due to shorter trial timing. A long term integration of outcome history (promoting habit learning) would require involvement of the BG. Looking at subjects' performance in the training phase of the task, it seems that subjects are actually learning. It may be speculated that this learning performance is a predominant result of working memory function. In the post-test, integration of good or bad performance outcomes over a longer period of time is needed to choose the right symbol out of the novel test pairs. Here the relevant

information from the BG is missing (no "habit" towards one or the other symbol was built up). Hence there is no differentiation between choosing a good symbol and avoiding a bad one. In fact, subjects in the fast condition show a very poor performance in the post-test. The slow learning system may not have had the opportunity to build up a stable representation of reward history. Contributions of this learning system, which are potentially necessary to solve the post-test, are therefore missing.

Besides the BG also the ACC seems to play a role in building up a reward representation. Kennerley and colleagues (2006) were able to show that functioning of the ACC is required in order to built up a reward history thereby enabling adaptive (i.e. reward maximizing) behavior. As the ACC has connections to the lateral prefrontal cortex (van Hoesen et al., 1993; monkey data) the ability to build reward histories might rely on prefrontal "working memory"-like inputs. These inputs might in the ACC be coupled with reward-prediction error signals from the midbrain DA neurons, finally resulting in a "review" over recently rewarded/not rewarded actions.

Dopamine in the PFC and the Basal Ganglia

The model of Seamans & Yang (2004) and the model of Frank (2005) differ with respect to the brain areas involved. Seamans and colleagues focus their model on the PFC whereas Frank's model is focused on the BG. DA is a neuromodulator that might act differently on different processes located in different brain structures. It seems reasonable to assume that DA acts differently on information in the BG and the PFC. Furthermore, the type of information processed in the BG is different from information content in the PFC. Finally, the temporal resolution by which the dopaminergic influence is exerted is higher in the BG than in the PFC. The two models describe complementary systems and processes that work in parallel with various interfaces between them. In the future these two systems need to be integrated in a comprehensive model of DA action in performance monitoring and feedback-guided learning.

5 General Discussion

We tested dopaminergic influences on human performance monitoring. These influences were modulated by a genetic polymorphism affecting the DA D2 receptor density (DRD2 TAQ IA polymorphism). We confronted subjects grouped according to the presence/absence of the A1 allele (A1+ subjects vs. A1- subjects) with a probabilistic learning task. This task was constructed to disentangle contributions of learning from positive and negative action outcomes to the overall learning performance (Frank et al., 2004). An fMRI study and an EEG study using the same task were conducted to identify brain areas (or networks of brain areas) involved in the task and to gain insights into the temporal resolution of the brain responses. Table 5-1 briefly summarizes the main findings. First genetic influences on correlates of performance monitoring are shown, followed by genetic and/or dopaminergic influences on learning success. This distinction seems necessary as DA is acting differentially within performance monitoring and feedback-guided learning. Interactions between these two systems are discussed in section 2.8. The following five theses should guide and structure the discussion:

1. DA is a key player in human performance monitoring.
2. Feedback-guided learning is influenced by DA.
3. The relative contribution of different learning systems to behavior is determined by external factors (trial timing) influencing dopaminergic transmission.
4. Different learning mechanisms enable subjects to learn a new task in a feedback guided way.
5. A simple mechanistic account of DA acting in all these processes is potentially misleading.

Table 5-1 Summary of central findings from the slow and the fast version of the task, separated for measures of learning success and correlates of performance monitoring, and differentiated between members of the two genetic groups

	slow version (fMRI)	**fast version (EEG)**
Measures of learning success		
Choosing good symbol	A1- : better performance	A1+ : better performance
Response certainty (computational model)	A1- : higher response certainty in the last third of the training phase	A1+ : higher response certainty (early on)
Learning rate of the computational model	No difference between genotypes	A1+: higher learning rate
Response-switching behavior	No differences in switching behavior	A1-: switch more after negative/positive feedback
Preference/Avoidance learning (post-test)	A1-: better avoid "B" performance, A1+: learn more to choose "A"	No interaction between genotype and post-test performance
Correlates of performance monitoring		
Reactivity to negative performance feedback	A1-: show higher activation of pMFC	A1-: feedback related negativity with larger amplitude
Correlation performance monitoring with measures of learning success	A1- : pos. correlation between negative feedback-related signal in the pMFC and choose "A"/ avoid "B"	A1- : neg. correlation between amplitude of the FRN, choices in the learning phase and response certainty

5.1 Genetic Influences on Performance Monitoring: Thesis 1

We showed in the fMRI as well as in the EEG study reduced reactions of A1+ subjects to negative feedback as compared to A1- subjects. Subjects in the fMRI showed reduced reactivity to negative performance feedback in RCZ, an area implicated in performance monitoring (Ridderinkhof et al., 2004). In the EEG, A1+ subjects showed reduced FRN to negative performance feedback. In both cases this might be due to a tonically higher DA level provoked by reduced D2 autoreceptors normally controlling the amount of DA available. This tonically higher DA diminishes the impact a phasic dip in dopaminergic activity following negative performance feedback can have. This dip, occurring whenever the outcome of an action is worse than expected (Schultz et al., 1997), is assumed to improve behavior following principles of reinforcement learning (Holroyd & Coles, 2002).

Following Holroyd & Coles' (2002) subjects showing higher (negative) feedback related activity are less secure about the response to be selected. They have to rely more on external information to guide their actions. In the context of the present studies this would fit the A1- subjects as they show more signal increase in pMFC and more pronounced FRN. Given the behavioral results of A1- subjects in fast trial timing this seems plausible: They show a lower response certainty, fewer choosing of a more often rewarded symbol, and a higher FRN amplitude. In the slow condition the results for the A1- subjects are more complicated to interpret: They show a higher response certainty (at the end of the training), more choosing of a more often rewarded symbol (again only at the end) and more negative feedback related signal increase in pMFC.

These contradictory observations to Holroyd & Coles (2002) may be resolved as follows. Higher response certainty as well as the better choosing performance may be carried by the habit learning system primarily influencing later stages of the experiment. The stronger signal increase after negative feedback may be primarily found in the early stages of the experiment where subjects are heavily relying on external information to establish new task rules.

5.2 Correlates of Learning and Learning Success: Thesis 2

5.2.1 Genetic Influences on Measures of Learning Success

In the slow condition of the task we observed an interaction between genotype and central measures of learning success. A1- subjects showed higher response certainty and clear avoidance learning. We showed a strong positive correlation for these subjects between activity in the hippocampus bilaterally and the certainty of the given response. This is indicative of learning related differences between the genetic groups. We revealed a functional coupling between RCZ and the hippocampal formation. This coupling was much stronger in the first third of the experiment as compared to the last third but only for subjects with a normal receptor density.

In the fast condition A1+ subjects showed higher learning success in terms of choosing behavior in the training, the response certainty and the learning rate of the computational model. Interestingly, no post-test interaction between genotype and choosing behavior was found. A main effect of genotype could be observed: A1+ subjects generally learn better but with no bias towards preference or avoidance learning. A1- subjects show a rather poor choosing performance although choosing performance in the training was significantly above chance.

Due to different trial timing, genetic influences on performance seem to be reversed. In the slow condition A1- subjects show a superior task performance, in the fast version A1+ subjects are much better in working on the task. Thus it seems as if genetically caused alterations in dopaminergic transmission have different influences on feedback processing and learning.

5.2.2 Role of the MFG

In the fMRI we observed negative feedback related activity in the middle frontal gyrus (MFG) which we attribute to a monitoring-within-memory strategy (Petrides et al, 1993) necessary to accomplish the task. This activation is particularly strong for A1- subjects. This may be due to higher computational load within this system for A1- subjects, finally leading to a superior task performance. Thus A1- subjects should show a better task performance in the training. This is only the case at the end of the training phase. Alternatively, the higher activation for A1- subjects is a correlate of a less efficient way of system usage. It might be that A1-

subjects need to put more computational effort in this area to achieve the same output. An alternative or even complementary explanation would be that differences in MFG activity might relate to differences in state 1 vs. state 2 dominance in lateral prefrontal information processing. The concrete mechanism, however, by which state 1 and state 2 contribute to working memory function and MFG activity still needs to be elucidated.

5.3 Habit Learning vs. Working Memory: Thesis 3

The process of integrating reward over time seems to rely on dopaminergic signaling. As DA is a relatively slow acting neuromodulator this process might be especially vulnerable to violations of temporal prerequisites. If trial timing is too fast, the system might run into trouble when assigning the outcome of an action to the respective action. If performance in this form of task-related memory is reduced, the cognitive system has to rely more on another component of memory: working memory. This system is limited to keep only the last events in task history. Thus it is not very reliable when confronted with the transfer test (the behavioral post-test) of our task. Choosing between symbols implies that a clear representation of the values of the different stimuli is needed. Comparing the post-tests of the two versions of the task, we showed that in the fast version the overall learning performance expressed in the post-test is rather poor compared to the slow version.

Choosing behavior and response certainty differ between the two timing versions. Behavior in the training phase might thus also depend on the proper functioning of the two learning systems. If working memory performance is dominating, overall learning performance is weaker compared to the case in which both memory systems are working in parallel. Response certainty is most likely based on the complete history of all trials. Thus, this measure should be especially vulnerable to a reduction in function of the slow memory component especially as this component might encode reward history.

In summary, differences between genetic groups in the slow timing condition may be driven by a weaker performance of the habit learning system in the BG for A1+ subjects, whereas the differences observed in the fast condition may be attributable to differences in working memory function.

5.4 Dopamine and Working Memory in the PFC: Thesis 4

As discussed above differences observed between timing conditions may mainly be driven by different memory strategies. In the fast version contribution of goal directed learning (working memory) to action guidance is more pronounced compared to that of habit learning. Influences of DA on PFC (being "host" of working memory) can be different, depending on the relative configuration of DA receptors. A1+ subjects may have a reduced D2 receptor density in the PFC. Noble and colleagues (1997) showed that carriers of the A1 allele show reduced regional glucose metabolism in the middle frontal gyrus (BA 46). This is not necessarily indicative for reduced D2 receptor density but it may be taken as first evidence that A1+ subjects might also have alterations in dopaminergic transmission within PFC.

Two ways in which DA can act on/in the prefrontal cortex (Seamans & Yang, 2004) are commonly discussed (see also section 2.8.2):

- State 1, dominated by D2 receptor transmission
- State 2, dominated by D1 receptor transmission

A1+ subjects are more biased towards state 2 (D1 dominated). This implies that only very strong inputs will find representation in their working memory buffer. Stimulation at high frequencies as in the fast version of our task could provide such strong inputs. Thus A1+ subjects should show superior task performance during training, because their working memory is stimulated in an optimal way. A1- subjects have a bias towards state 1 (D2 dominated) of prefrontal dopaminergic transmission. This is beneficial if multiple inputs have to be managed and stored within working memory. On the other hand, if stimulation frequency is too high this low threshold working memory may "overflow". No stable representation can be built, leading to reduced task performance. These instable representations are expressed in high rates of response switching after either negative or positive feedback.

5.5 Dopamine and the PFC: An Alternative Explanation

Optimal working memory performance might need a balance between D1 and D2 receptor transmission in PFC. Working memory is highly relying on D1 receptor signaling (Sawaguchi & Goldman-Rakic, 1991). In the monkey it was shown that long-term D2 receptor blockade coincides with a down-regulation of D1 receptors in the PFC (Lidow & Goldman-Rakic, 1994; Lidow et al., 1998). A study using chronic blockade of D2 receptors by haloperidol and a subsequent pharmacological challenge with selective D1 agonist ABT 431 showed that blockade of D2 receptors leads to severe impairments in working memory which can be reversed by administration of a D1 receptor agonist.

Down-regulation of D1 receptors following chronic D2 receptor blockade might lead to suboptimal dopaminergic signaling in the PFC. Subjects from the A1+ group might "suffer" also from a reduced D1 receptor density in the PFC caused by the genetically caused down-regulation in D2 receptors. Thus their working memory capacity is limited in "normal" (in this case fMRI trial timing) task conditions. If by high stimulation frequency DA in the PFC saturates, this group of subjects could reach an optimal level of DA (inverted-U: participants would then in the middle of the distribution). The A1- group on the other hand would be "over-stimulated" by too much DA (shifted to the right of the inverted U). Thus their performance would be worse in the fast condition. A saturation of DA in the PFC seems reasonable given the fact that prefrontal DA needs up to 5 s to come back to baseline due to lower concentration of DA-transporter in this brain region (Lapish et al., 2007; Lavin et al. 2005).

5.6 A Modified Performance Monitoring Model: Thesis 5

Holroyd and Coles (2002) proposed a model (see fig. 5-1) to explain how performance monitoring interacts with dopaminergic signaling in the midbrain. In this model learning is restricted to the BG that learn to predict action outcome while working on the task. There is considerable overlap between feedback based learning and reinforcement learning in general. Figure 5-2 displays the key structures and functions in human reinforcement learning.

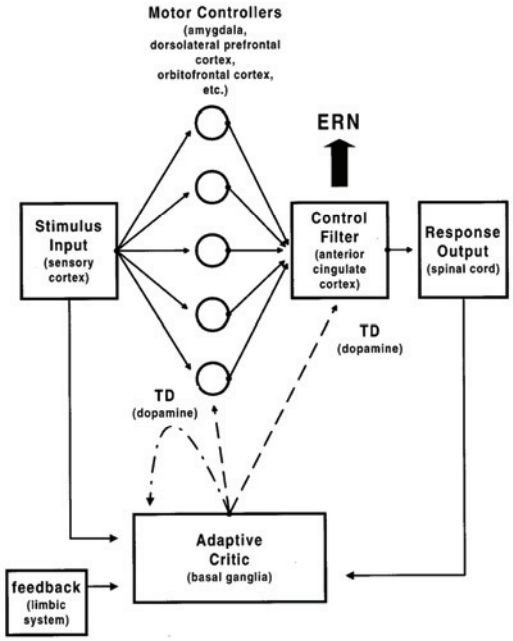


Figure 5-1 Model of performance monitoring (taken from Holroyd & Coles, 2002)

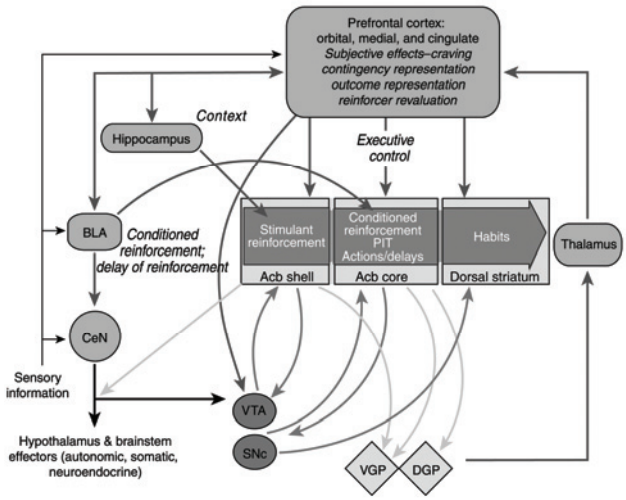


Figure 5-2 Neural systems of reinforcement learning (picture taken from Everitt & Robbins, 2005)

In order to explain our findings in a common theoretical framework, it seems necessary to extend the model of Holroyd & Coles (2002) by more general principles of learning. Adding interactions with other forms of learning might enable us to explain the interplay of performance monitoring structures, working memory related structures and long term memory related structures in the brain (see fig. 5-3).

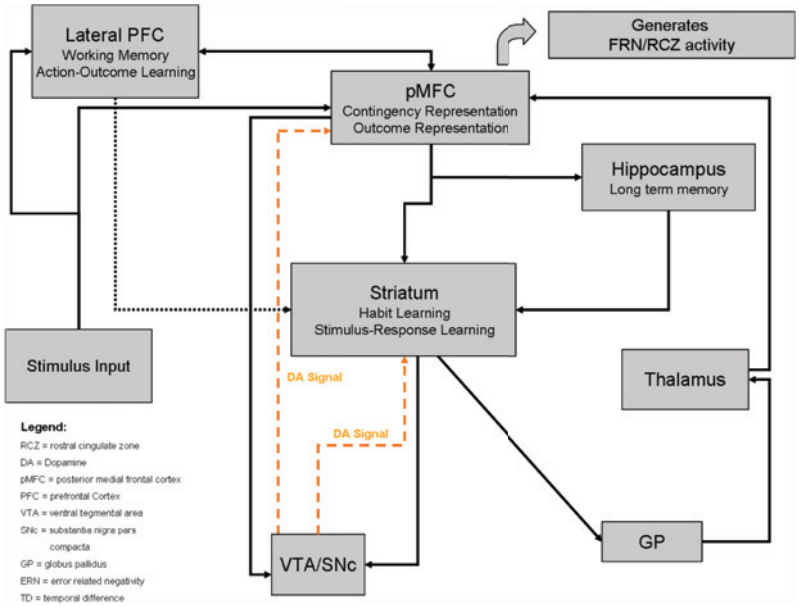


Figure 5-3 Action selection and action outcome monitoring: Interplay between performance monitoring and learning related brain structures.

Two learning related systems seem to work in parallel:

1. working memory (mainly operated by PFC)
2. habit learning (mainly operated by BG)

Both systems enable an agent to keep previous decisions in mind. In order to maximize future outcomes these former decisions need a marker signaling their valence. One connection between marker and action is made in the pMFC. Outcome related information (the marker) is provided by dopaminergic neurons in the midbrain. Dependent on the valence of this signal, activity in the pMFC is triggered to adjust performance in the future. Interactions between PFC, pMFC

and the hippocampal formation guarantee learning of rewarded actions in order to achieve maximal efficiency of behavioral output.

In principle performance monitoring and learning are interacting processes with separable contributions to human performance. They interact but are not necessarily dependent on each other. Their interaction might depend on the form of learning taking place in a given task. One shared influence is DA, acting within both systems. The role of DA is not always the same. By means of external influences mediating dopaminergic transmission it is possible to shift balance between learning systems.

5.7 Thesis 1 to 5: Summary

The following final conclusions about the theses raised at the beginning of the general discussion can be drawn:

1. *DA is a key player within human performance monitoring*: By including genetic polymorphisms acting on a central component of the dopaminergic system (D2 receptors) we were able to demonstrate that DA is indeed a neurotransmitter of central relevance for human performance monitoring.
2. *Feedback-guided learning is influenced by DA*: Here we could show that depending on the configuration of dopaminergic transmission the ability to learn from negative or positive feedback is differentially pronounced. Our results point to the direction that although performance monitoring and learning from feedback are closely related, dopaminergic influences might differentially act on both systems.
3. *The relative contribution of different learning systems to behavior is determined by external factors (trial timing) influencing dopaminergic transmission*: We showed that due to different trial timing (fast vs. slow) learning performance of our subjects varied considerably. We also showed that this timing influence is further mediated by genetic influences affecting dopaminergic transmission. Dopaminergic transmission is altered not only by genetic factors but also by external influences.
4. *Different learning mechanisms enable a subject to learn a new task in a feedback-guided way*: Extending findings from thesis 3 two learning mechanisms (action-outcome vs. habit learning) underlie the subjects'

ability to learn in the probabilistic learning task. These two systems differentially suffer/benefit from differences in trial timing. We assume that trial timing is affecting dopaminergic transmission thereby shifting the relative contribution to behavioral control from the one to the other learning system.

5. *A simple mechanistic account of DA acting in all these processes is misleading*: Genetic influences on dopaminergic transmission are altered by external influences. This effect is not the same for all areas of the human brain. Depending on brain structure and the informational context, dopaminergic and/or timing influences can lead to different effects. Thus the role of DA in human performance monitoring is not that of a constant factor – rather it is a variable neuromodulator, setting the stage for different cognitive processes.

Potential Limitations

Constraints for interpretation of our results should also be mentioned. First of all our results need replication with a bigger sample, potentially allowing for the analysis of gene/gene interactions. These interactions are particularly interesting given the fact that for dopaminergic signaling other receptors/components are relevant as well. Also, replication with another paradigm which allows disentangling preference from avoidance learning is needed.

As the dopaminergic system is more than just the D2 receptor density, our findings should not be generalized too much, especially with respect to clinical relevance. It may well be that D2 receptor density contributes in a way to addiction or obesity, but the SNP we investigated is by no means the only cause of these disorders. Disorders like addiction are not caused by a single gene – they are polygenic in nature. On average, each gene contributes to only 0.4 to 2% of variance of a trait (Comings & Blum, 2000). Polygenetic disorders are furthermore genetically heterogeneous. Variants at 100 different genes can contribute to a disorder but each individual may require only 10 such variants to acquire a given disorder. Why then do we find differences between genetic groups? This may be due to the high sensitivity of our task to subtle differences. No ceiling effects that might occur with more salient punishments and rewards, having real consequences, are masking our findings. The revealed insensitivity to negative feedback associated with the DA D2 receptor gene polymorphism may be one factor contributing to multifactor problems such as addiction. Maybe it contrib-

utes to a predisposition for a disorder. Other components of the dopaminergic system (or other transmitter systems) may contribute to pathologies as well.

6 Conclusion and Outlook

Dopamine is essential for human performance monitoring. Alterations in dopaminergic transmission lead to corresponding alterations in negative feedback processing and learning from negative feedback. A genetically determined difference in DA D2 receptor density leads to a reduced sensitivity to negative action outcomes. We found a genetically mediated bias to learn either more from negative or positive action outcomes. Response certainty and choosing rewarded stimuli were also influenced by the genetic makeup of our subjects.

Looking at the same task, the same genetic polymorphism but another trial timing gives a different picture. Different contributions of prefrontal working memory vs. striatal habit learning may underlie these results. Slow timing facilitates balance between working memory and long term integration of reward (habit learning). The fast condition may provoke a bias towards the faster acting memory system – habit learning is swamped by fast inputs causing disturbances in action-outcome assignment.

The relative contribution of D1 and D2 receptor mediated information processing in PFC is shifted accordingly to the genetically biased receptor distribution. Subjects with reduced D2 receptor densities are biased towards D1 mediated influences of DA, whereas the opposite is true for subjects with normal receptor density. They show a bias via D2 receptor mediated dopaminergic transmission. If subjects are confronted with fast trial timing their relative receptor configuration may either promote (if D1 transmission dominates) or disturb (if D2 transmission is dominating) task performance. Differences in preference/avoidance learning can thus not be expected because the contribution of reward-history learning is missing.

Our results demonstrate that DA is an effective neuromodulator in human performance monitoring. A single-nucleotide polymorphism determining the DA D2 receptor density can influence the way in which subjects react to negative feedback and, at least when given enough time, the way in which subjects learn either

by preference or by avoidance learning. Significant interactions between genotype and learning success in different timing conditions point to differential influences DA can exert on human information processing mediated by D1 or D2 receptor dominance, respectively.

Outlook

This work provides various perspectives for future research. As the dopaminergic system is not controlled by a single gene it seems promising to look for influences of other genetic polymorphisms. In the same vein it could be interesting to look for haplotypes thereby widening the focus from single-gene to multiple-gene influences. In order to get an impression of the functional relevance of carrying the A1 allele, positron emission tomography (PET) studies need to be performed. These studies could provide insights into the distribution of D2 receptors, not just limited to the striatum as many studies already showed, but also in prefrontal brain areas. This would imply using ligands that are suitable for imaging cortical D2 receptor density, because as there are not much of these receptors in this brain area it is particularly difficult to detect them. ^{18}F-Fallypride or FLB 457 would be suitable ligands for this question (e.g. Mukherjee et al., 2002).

Combining genetic influences with pharmacological challenges (agonists vs. antagonists) of either the D1 or the D2 receptors is highly interesting. It would be possible to get an impression of how these receptors interact with performance and how pharmacological effects may be different for different genotypes.

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Selbständigkeitserklärung

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Tilmann Alexander Klein

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Learning from Errors: Genetic Evidence for a central Role of Dopamine in Human Performance Monitoring

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Abstract

Human performance monitoring is highly dependent on dopaminergic signaling. Learning to maximize future outcomes requires close interaction between performance monitoring and learning related structures in the human brain. Genetically determined alterations in dopaminergic transmission (single nucleotide polymorphism affecting dopamine D2 receptor density) lead to corresponding alterations in negative feedback processing and learning from negative feedback. Depending on external factors, the contribution of different learning systems to behavioral output is biased either towards working memory in the prefrontal cortex or habit learning in the basal ganglia. One important factor in determining this relative contribution is fulfillment of temporal requirements needed for dopaminergic signaling. Thus learning performance and learning success are influenced by external factors impinging on dopaminergic transmission. Feedback-guided learning requires both learning components which in close cooperation with performance monitoring enable a subject to successfully perform within a probabilistic learning task. In conclusion, dopamine is an effective neuromodulator setting the stage for different cognitive processes dependent on brain area and type of information being processed. Dopaminergic signaling is important for error signaling and subsequently for error driven learning in the human brain.

Zusammenfassung

Menschliche Handlungsüberwachung ist abhängig von dopaminerger Signalübertragung. Die Fähigkeit zukünftige Handlungsergebnisse zu maximieren bedarf einer engen Zusammenarbeit zwischen Gehirnstrukturen die der Handlungsüberwachung dienen und lernrelatierten Hirnarealen. Genetisch bedingte Variationen in der dopaminergen Signalübertragung (Einzel-Nukleotid-Polymorphismus der die Dopamin D2 Rezeptordichte beeinflusst) führen zu korrespondierenden Veränderungen in der Verarbeitung negativer Rückmeldungen und zu Variationen im Lernen aus negativen Rückmeldungen. Abhängig von externen Faktoren ist der Beitrag verschiedener Lernsysteme in der Erzeugung des

Verhaltens entweder in Richtung eines stärkeren Beitrages des Arbeitsgedächtnisses im präfrontalen Cortex oder des Gewohnheitslernens in den Basalganglien verschoben. Ein wesentlicher Faktor in der Bestimmung dieses relativen Beitrages ist die Einhaltung zeitlicher Erfordernisse der dopaminergen Signalübertragung. Lernleistung und Lernerfolg werden somit wesentlich von externen Faktoren beeinflusst die das dopaminerge System betreffen. Rückmeldungsbasiertes Lernen erfordert einen Beitrag beider Lernkomponenten welche in enger Zusammenarbeit mit dem Handlungsüberwachungssystem es einem Menschen ermöglichen, eine probabilistische Lernaufgabe erfolgreich zu bearbeiten. Zusammengefasst lässt sich sagen, dass Dopamin ein effektiver Neuromodulator ist, der abhängig vom jeweiligen Hirnareal und der zu bearbeitenden Information den Hintergrund moduliert, vor welchem wiederum verschiedene kognitive Prozesse ablaufen. Dopaminerge Signalübertragung ist wichtig für Fehlerverarbeitung und daraus resultierendes fehlerbasiertes Lernen im menschlichen Gehirn.

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