The Role of Reward Expectations for Prospective Memory

An investigation with functional magnetic resonance imaging

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Contents

Abstract

Prospective memory is the ability to remember to carry out an intended action after a delay. However, it remains unclear how motivational aspects of the intended action, such as reward expectations, are integrated into the processes subserving intact prospective memory. The goal of this dissertation is to investigate the effects of motivational incentives on prospective memory on the behavioral and on the neural level, while taking into account individual differences in reward sensitivity and personality.

In one behavioral and two functional imaging studies, we combined a prospective memory paradigm with different levels of monetary reward and loss.

Study 1 demonstrated that while personality traits such as conscientiousness are linked to enhanced prospective memory performance in general, individual reward sensitivity can explain reward-related performance differences.

Study 2 established that midbrain and striatal regions within the reward system are sensitive to the level of reward associated with prospective memory cues and that activation differences in the midbrain region are related to individual reward sensitivity. We found that performance increases under high reward are accompanied by an increased functional coupling between frontopolar and midbrain activation.

Study 3 compared neural responses to reward and loss avoidance expectations. We found that high reward led to an elevated neural response compared to low reward or loss avoidance. Results further showed that midbrain activation reflected reward-related performance differences.

In sum, these results suggest that regions involved in reward anticipation are sensitive to the level of reward associated with prospective intentions and that reward information accordingly is part of the cognitive representation of prospective intentions. Moreover, the results directly link neural reward representations to reward-related performance differences in prospective memory. Additionally, our findings highlight the role of individual reward sensitivity in the context of prospective remembering.

1 Introduction

Whether it is remembering to buy milk on the way home from work, to meet a friend for dinner, or to attend a meeting at 3 pm - instances where we have to remember to carry out a specific action at a certain point in the future abound in our daily lives. In many of these situations, we cannot carry out the action immediately, but we have to maintain an intention of a specific action during a delay. This ability to maintain an intended action until it can be executed at a certain time in the future is called 'prospective memory' (PM). By carrying out certain actions immediately while leaving others in a pending state, we can plan and prioritize multiple actions and action sequences. In this way, intact PM is crucial to our everyday behavior as it ensures that our behavioral goals are met.

Although at first glance, PM seems to be a primarily cognitive ability, it is apparent that there are as many kinds of prospective intentions as there are many different kinds of actions, leading to different personal goals. In particular, prospective intentions can differ with respect to the underlying motivational context. For instance, in the above example, the prospect of attending a meeting which could be stressful and exhausting might not be very appealing, while meeting a friend could be something to look forward to. Thus, although in both cases a prospective intention has to be maintained, the degree of personal motivation associated with the achievement of this goal can vary widely.

Experimentally, behavioral markers of intact prospective remembering have been extensively studied within the realm of retrieval theories of PM by varying cognitive aspects of PM tasks in the laboratory or, less often, in the field (Einstein, et al., 2005; Smith, 2003). However, very few studies have investigated motivational aspects of prospective intentions, and when doing so, most of them have taken a developmental or clinical perspective.

In parallel, studies using functional neuroimaging techniques have found the frontopolar, or anterior prefrontal, cortex to be the prominent brain structure supporting PM functioning, highlighting its role in the maintenance of prospective intentions (Burgess, Scott, & Frith, 2003; Simons, Schölvinck, Gilbert, Frith, & Burgess, 2006).

In a different line of research, studies investigating incentive motivation have shown the functional involvement of the dopaminergic reward system in tasks reflecting goal-directed behavior, such as the monetary incentive delay (MID) task (Knutson, Adams, Fong, & Hommer, 2001a; Knutson, Fong, Adams, Varner, & Hommer, 2001b).

However, it has not been investigated so far if motivational aspects of prospective intentions play a role in PM functioning. Moreover, it is yet unknown if incentive motivation is reflected in the brain systems underlying PM and/or reward processing during the processing of reward-related PM intentions.

The present work aimed to shed light on this issue by investigating three main research questions in three experiments: in experiment 1, the effect of incentives on the behavioral markers of PM was investigated by means of varying monetary incentives in a PM context. In this behavioral experiment, individual differences in personality traits as well as in behavioral approach and avoidance behavior were taken into account and related to PM performance. In experiment 2, the effects of reward anticipation in the form of monetary incentives on PM were investigated on the neural level by examining the functional interaction of reward and PM brain systems by means of functional magnetic resonance imaging (fMRI). In experiment 3, the concept of motivational incentives was extended to include incentives of both positive and negative valence, discriminating the effects of reward anticipation and loss avoidance in PM with fMRI.

At the beginning of this thesis, a theoretical and empirical background will be given, consisting of two parts: first, an overview of PM retrieval theories will be provided, followed by a description of three selected aspects of PM that pertain to the focus of the present study. After this, empirical findings from studies investigating the neural systems supporting PM will be summarized. Second, a brief anatomical and functional description of the human reward system will be given, including findings relating its function to individual differences in motivated behavior. In the following experimental section of the present work, each of the three experiments will be separately described. Experiments 2 and 3 used fMRI. Thus, a short overview of this methodological approach will be given. In the last section, the findings from all three experiments will be summarized and discussed, including possible future directions of research.

2 Theoretical and Empirical Background

2.1 Prospective Memory

Experimental PM tasks are usually modeled according to several criteria defining the nature of real-life PM situations. One of the most obvious criteria is that there is an intended action that cannot be carried out immediately, but has to be suspended until a

later point in time (note that in real-life PM situations, this delay can range from several minutes to hours or days, while in most experimental PM tasks, this delay is usually much shorter, ranging from seconds to minutes). A second criterion is that the delay is filled with other activities, preventing consistent rehearsal of the PM intention. In the laboratory, this has led to the implementation of an *ongoing task*, in which the PM task is embedded. Thus, participants engage in an ongoing cognitive task (e.g., a lexical decision task or an n-back task), while simultaneously maintaining the intention to carry out the PM task at the appropriate time or in response to the appropriate cue. Thus, execution of the PM intention can be triggered by either a time or an event cue, and accordingly, these two forms of PM have been termed 'time-based' and 'event-based' PM. Although in real-life PM situations mixed forms exist (e.g., taking medication after breakfast can be associated with a specified time point (8 am) and with a certain cue (breakfast)), experimental research has separated the two forms and examined time-based PM (with and without external time-measurement aids) and event-based PM separately. The present study reports evidence from three event-based PM experiments and will thus focus on empirical evidence for event-based PM.

Empirical research has shown that performance on experimental PM tasks can vary with several characteristics or features of the PM and the ongoing task. For example, PM performance has been found to be enhanced with highly distinctive PM cues (Einstein, McDaniel, Manzi, Cochran, & Baker, 2000). On the other hand, performance decrements on the ongoing task caused by the maintenance of a PM intention (also termed "costs" or "prospective interference effect") have been found (Smith, Hunt, McVay, & McConnell, 2007) and have been related to characteristics of the ongoing task (focal vs. non-focal processing, Einstein, et al., 2005). Thus, variations in the PM and the ongoing task (or both) can lead to PM and ongoing performance increases or decreases.

These findings have been taken to suggest that there are different possible mechanisms supporting the retrieval of PM intentions, which have subsequently been integrated into one common theory. In the first three paragraphs of this chapter, these mechanisms will be shortly reviewed by summarizing the empirical evidence. In the following three paragraphs, three specific effects or features that have been investigated in the context of these retrieval theories will be briefly described: importance effects, motivational aspects, and individual differences pertain to the topic of the present study

and will thus be pointed out in more detail.

2.1.1 Theories of Prospective Memory Retrieval

Two categories of theories have been developed to explain how prospective intentions are retrieved. On the one hand, monitoring theories state that PM retrieval is based on controlled monitoring or preparatory processes (Smith, 2003; Smith & Bayen, 2004; Smith, et al., 2007). On the other hand, it has been shown that PM intentions can also be retrieved spontaneously, without the implementation of controlled monitoring processes (Einstein & McDaniel, 2005; Einstein, et al., 2005; Scullin, Einstein, & McDaniel, 2009). Both views have been integrated into the "multiprocess theory" by specifying features of the PM and ongoing task which can lead to the implementation of one or the other process.

2.1.1.1 Monitoring

Adding a prospective intention to an ongoing task leads to a decline in ongoing performance, in particular to a slowing of response times in the ongoing task. This has often been termed the "prospective interference effect" or "costs" (Guynn, 2003; Loft & Yeo, 2007; Marsh & Hicks, 1998; Marsh, Hicks, & Cook, 2005; Marsh, Hicks, Cook, Hansen, & Pallos, 2003; Smith, 2003; Smith & Bayen, 2004). This slowing on the ongoing task has been taken to indicate a controlled cognitive search process used to monitor for prospective targets, directing capacity away from the ongoing, towards the PM task (Smith, 2003; Smith, et al., 2007).

Smith (2003; Smith & Bayen, 2004; Smith, et al., 2007) has proposed the "preparatory attentional and memory processes theory" (PAM) as a framework for the investigation of monitoring processes in PM paradigms. According to the PAM theory, adding a prospective intention to an ongoing task always goes with a cost to the ongoing task, because preparatory processes draw off attentional resources that would otherwise be used for the ongoing task. Critically, task interference effects should thus be found on ongoing trials, as preparatory processes take up resources during those trials rather than during PM cue trials themselves. Consistent with this prediction, Smith (2003) found that the addition of a PM task produced slowing on the ongoing task, indicating that attentional resources are being directed away from the ongoing task. Moreover, Smith

(2003) predicted that participants showing better PM performance should exhibit greater ongoing task interference, because they rely on monitoring to a greater extent. Indeed, participants who performed the PM task at or above the mean responded more slowly to ongoing trials than participants whose PM performance was below the mean. These results were taken to suggest that participants who performed well on the PM task were directing capacity away from the ongoing task, in favor of better PM performance.

Although not explicitly designed to address specific aspects of the PM interference effect, neuroimaging studies examining PM have consistently found an increase in response times when a PM intention was maintained, compared to ongoing/baseline tasks (even in blocks in which no PM cues were presented) (Burgess, Quayle, & Frith, 2001; Burgess, et al., 2003; Simons, et al., 2006). In these studies, this finding is usually interpreted in a more general sense as the result of a prospective intention being maintained. In particular, it has been associated with the checking for PM cues and/or the switching of attention between the ongoing and the PM task. However, due to methodological constraints, these studies have often employed PM designs with a high frequency of PM cues (~20%) (Burgess, et al., 2001; Burgess, et al., 2003), thus changing the nature of the PM task (presumably boosting monitoring processes) while leaving PM performance unaffected (Ellis, Kvavilashvili, & Milne, 1999).

2.1.1.2 Spontaneous Retrieval

Although it has been widely acknowledged that the retrieval of a prospective intention can be associated with costs to the ongoing task, there have been reports of non-significant or low costs (A. L. Cohen, Jaudas, & Gollwitzer, 2008; Einstein, et al., 2005; McNerney & West, 2007; Scullin, et al., 2009; Scullin, McDaniel, & Einstein, 2010a). However, spontaneous retrieval processes are defined by the absence of costs to the ongoing task (i.e., no significant slowing of response times when a PM intention is added), and thus cannot be measured in traditional PM paradigms. Shifting participants' PM retrieval strategies experimentally towards non-monitoring would invariably lead to a decline in PM performance, thus making it impossible to compare the two retrieval processes. Einstein et al. (2005) found a solution to this dilemma by demonstrating the reverse, namely that spontaneous retrieval processes can occur in the absence of a PM instruction. Participants were told to suspend the PM intention during an ongoing

lexical decision task, although prospective cues were presented. Response times to PM target items were significantly slower than those to neutral (but previously presented) items and to retrospective memory target items, indicating the existence of spontaneous retrieval processes under conditions in which the PM demands were suspended. The possibility that subjects had monitored was excluded by showing that the response times to neutral items in the prospective blocks were not different to those in an analogous retrospective memory block (i.e., no costs).

Scullin et al. (2009) replicated these findings and could additionally show that spontaneous retrieval processes can also be deactivated. In a lexical decision task, response times to PM target items were slower compared to control items, but only in a condition in which participants had to suspend the PM intention (i.e., when they were told that they had to perform the PM task again later). When participants were told that the PM task was finished, response times to PM target and control items did not differ.

2.1.1.3 The Multiprocess Theory

Due to the fact that both monitoring and spontaneous retrieval processes can evidently support prospective remembering, there has been the need to define the prerequisites for the implementation of one or the other process. To this end, Einstein and McDaniel (2005; Einstein, et al., 2005; McDaniel & Einstein, 2000) have proposed the “multiprocess theory”, which allows for the existence of both strategic monitoring and spontaneous retrieval processes and establishes the conditions under which one or the other process is applied.

The multiprocess theory states that the use of a process in a given situation can depend on a variety of factors, such as the characteristics of the PM and the ongoing task, as well as individual differences. However, it also states that there is a general bias towards spontaneous retrieval processes, because accumulating costs caused by multiple PM intentions (as it is often the case in real-life PM situations) would be detrimental to the ongoing activities.

For instance, Cohen et al. (2008) reported that no significant costs to an ongoing lexical decision task were found when participants had to detect one or two PM target items. However, significant costs emerged with three or more target items, signaling a shift in the strategy according to the requirements of the PM task.

According to the multiprocess theory, an important factor concerning the ongoing

task that could potentially bias retrieval mechanisms towards spontaneous processing is the degree to which the ongoing task fosters focal processing of the PM target event. Focal processing entails that processes involved in performance of the ongoing task at the same time encourage processing of any given item as a potential PM target item. For example, Einstein et al.(2005) used an ongoing category judgment task in which participants had to decide if one word was a member of the category that the other word designated. In the non-focal PM task, the PM target item was a previously specified syllable, whereas in the focal PM task, the PM target item was a single word. With a focal target, the proportion of correct PM responses was significantly higher and did not lead to costs on the ongoing task, suggesting that performance relied on spontaneous retrieval in the focal, but on monitoring in the non-focal condition.

Another important factor that can have an impact on performance on a PM task relates to the characteristics of the PM cues. Salient or distinctive PM target events have been shown to elicit high levels of PM performance compared to nondistinctive cues (Einstein, et al., 2000). However, Smith et al. (2007) reported that salient PM target events do not necessarily lead to automatic retrieval of the PM intention and found costs in the ongoing task despite the use of salient PM target events.

Another parameter of the PM cue and thus a critical factor determining PM retrieval processes is the quality of the association between the PM cue and the intention. PM targets that are associated with the PM intention to a higher degree more likely lead to spontaneous noticing. McDaniel, Guynn, Einstein, and Brenneiser (2004) showed that PM performance was better for highly associated than for not-associated PM target-action pairs. Loft and Yeo (2007) extended these findings by examining reaction times (i.e., response costs) to items immediately preceding PM cue trials that were PM hits or misses. Under low-association conditions, the difference in reaction times on precue hit, compared to precue miss trials was larger, reflecting the difference in the amount of preparatory attentional processes on precue hit, compared to precue miss trials under low- and high-association conditions. Moreover, when response costs on precue trials were controlled for, response times for PM hits were significantly longer under low, compared to high association, indicating a higher degree of monitoring for PM cue events.

2.1.2 Importance Effects in Prospective Memory

As the multiprocess theory states, the retrieval of the prospective intention and PM performance can vary based on the manipulation of several features of the PM task. One of the central features that has to be taken into account when investigating motivational aspects of the PM task is the perceived importance of the PM and the ongoing task.

Several studies have reported importance effects in PM (Andrzejewski, Moore, Corvette, & Herrmann, 1991; Kvavilashvili, 1987; Loft, Kearney, & Remington, 2008), but Kliegel, Martin, McDaniel, and Einstein (2001) were the first to systematically explore the relationship between importance effects, the requirements of the PM task, and PM performance. In a time-based and an event-based PM experiment, they told participants that either the PM task or the ongoing task was more important. They found an importance effect (i.e., better PM performance in the high importance PM condition) for the time-based, but not for the event-based version of the PM task. However, the authors report that participants made more errors on the ongoing task in the high importance condition in a demanding background situation, i.e., when attentional resources were scarce.

In an effort to investigate the relationship between the characteristics of the PM task and importance effects on PM, Kliegel, Martin, McDaniel, and Einstein (2004) investigated PM performance under high and low PM importance instructions in two event-based PM tasks, of which one relied on relatively automatic retrieval processes, whereas the other relied more on controlled monitoring processes. They found an importance effect on PM performance (i.e., a greater number of prospective hits when the importance on the PM task was high). In addition, high importance of the PM task also affected performance on the ongoing task, resulting in a higher number of errors made in the ongoing task. However, this was only the case when the PM task contained non-salient cues and the ongoing task did not encourage focal processing of the PM target stimulus. That is, importance effects were only found when the processing of the PM task required strategic monitoring.

The finding of importance effects in PM tasks indicates that motivational features, such as the perceived importance of the PM task, can play a role in the processing of PM cues and can thus have an effect on performance on the PM task and on the ongoing task. Thus, these results provide an important link to the effects of more straightforward measures of motivation such as (monetary) reward on PM, which are the focus of the

present work. The respective findings will be summarized in the following paragraph.

2.1.3 Incentive Effects in Prospective Memory

Very few studies have investigated incentive effects in PM. Meacham and Singer (1977) were the first to link motivation to prospective remembering. They used a naturalistic task: subjects were asked to send postcards to the experimenter on specified dates. Incentive magnitude was manipulated between subjects. Results revealed that subjects who expected to potentially receive a reward for the completion of the task performed better (i.e., mailed postcards less often and fewer days late) than those who did not expect to receive a reward.

Most often, studies investigating the effect of incentives on PM have focused on children. Somerville, Wellman, and Cultice (1983) reported an incentive effect in toddlers in a naturalistic setting: 2-, 3-, and 4-year-old children were more likely to remind their caregivers of activities that were of high, compared to low interest to themselves.

While Guajardo and Best (2000) did not find an effect of incentive on PM performance in 3- and 5-year-olds in either a naturalistic or in a computer-based PM task, Kliegel, Brandenberger, and Aberle (2010) recently reported that PM performance did not differ between 3- and 5-year-olds in a high-incentive condition, but was reduced for 3-, compared to 5-year-olds in the low-incentive condition.

Incentive effects have also been reported in patients with brain lesions: McCauley, McDaniel, Pedroza, Chapman and Levin (2009) found incentive effects on PM performance in children with traumatic brain injury. Both children with mild and severe traumatic brain injury as well as children in the control group (orthopedic injuries) showed better PM performance in an experimental, non-computerized PM task when incentives were high (dollars), compared to when incentives were low (pennies).

Important information as to the effects of motivation also comes from a recent study investigating the ‘age-prospective memory paradox’, which describes an age-related decline of PM performance in laboratory, compared to an age benefit in naturalistic settings (Aberle, Rendell, Rose, McDaniel, & Kliegel, in press). In this study, Aberle et al. (in press) provided half of the participants in one young (mean age 24.58 years) and one old age (mean age 62.46 years) group with monetary incentives (in this case, the prospect of winning a lottery) in a naturalistic task (i.e., sending a text message to the

experimenter twice a day for five consecutive days). They found that young adults in the high motivation group overcame their age-related deficit and performed as well as the older adults. Moreover, highly motivated young adults performed better than their normally-motivated counterparts, while no incentive effect was found in the old age group (as a side note, in an unpublished data set, Aberle et al. report that high motivation also eliminates the older adults' PM deficit in a laboratory setting).

Although monetary incentives have been given in several neuroimaging studies of PM (using laboratory, computer-based PM tasks) (Burgess, et al., 2001; Burgess, et al., 2003), the effect of different levels of incentives has not been explored experimentally so far.

2.1.4 Individual Differences and Prospective Memory

Searleman (1996) found that Type A personalities (i.e., people who show high time urgency and a high need to complete tasks) showed better PM performance in interpersonal PM tasks (e.g., remembering the experimenter to make a phone call) and PM tasks that were of personal importance to themselves (e.g., returning a card to receive credit for the experiment). However, performance on a task that was neither interpersonal nor of personal importance was not related to differences in personality. Cuttler and Graf (2007a) found that the personality dimensions of conscientiousness and neuroticism predicted performance on two or one naturalistic PM tasks, respectively. Moreover, it has been reported that PM failures and self-report of PM failures are associated with high checking compulsions (an indicator of obsessive-compulsive disorder (OCD)), in sub-clinical compulsive checkers in laboratory PM tasks (Cuttler & Graf, 2007b, 2008, 2009a, 2009b).

While the above-mentioned studies used naturalistic and/or interpersonal PM tasks, Salthouse, Berish and Siedlecki (2004) administered four different PM tasks, of which three were computer-based. A composite score reflecting performance across the four tasks was then computed to define general PM performance. In addition, age, cognitive variables such as executive functioning and episodic memory, as well as personality dimensions were measured to explore the relationship with PM performance. Specifically, the NEO Five Factor Personality Inventory was used to assess differences in the five personality dimensions and to relate them to PM performance. The only trait that was significantly related to PM performance was agreeableness, but other cognitive

constructs (general intelligence, episodic memory, perceptual speed) did show similar relations to the personality factors. The authors thus state that PM performance is not uniquely related to non-cognitive (i.e., personality) factors, but rather shares these aspects with other cognitive constructs. However, by integrating performance on four PM tasks into one composite score, the authors did not account for the fact that the four tasks might have required different degrees of monitoring or spontaneous retrieval, which could have resulted in different relations to the personality dimensions.

In light of the multiprocess framework, McDaniel and Einstein (2000) proposed that individuals scoring high on conscientiousness and compulsivity should exhibit generally higher PM performance, but even more so when monitoring demands are high. However, they concur that individuals low on those dimensions might more likely adjust their strategy and thus employ monitoring only when necessary. In this case, not PM performance per se, but costs to the ongoing task would reflect personality differences.

On a related note, in a non-experimental design, Heffernan and Ling (2001) investigated the relationship between the personality dimension of extraversion and prospective remembering. Extraversion was assessed using the Eysenck Personality Questionnaire Revised (EPQR) and general PM performance was assessed using a self-rating prospective memory questionnaire (Prospective Memory Scale (PMQ)). Introverts were found to report more PM errors than extraverts which the authors interpret in terms of extraverts making more use of their prospective memory system by engaging in planning behavior to a greater extent. However, self-reports of PM performance cannot be easily related to experimental PM data, and it thus cannot be assumed that extraversion is related to PM performance in experimental settings.

Taken together, very few studies have investigated the relationship between PM and individual differences in computer-based, laboratory tasks. Studies employing naturalistic task settings have related better PM performance with personality variables such as conscientiousness and compulsivity. However, these studies differed in the degree to which strategic monitoring or spontaneous retrieval was required. Moreover, the relation of PM with other personality dimensions such as approach or avoidance motivation has not been explored systematically so far.

2.1.5 Neural Correlates of Prospective Memory

Considering the large number of studies investigating PM on the behavioral level, relatively few studies have investigated the neural mechanisms supporting PM. In this section, these studies will be reviewed. Additionally, functional specialization within the frontopolar cortex (BA10) in relation to PM will be briefly discussed (for a brief description of the anatomical location and subdivisions of BA 10, see Fig. 2.1).

While Burgess, Veitch, de Lacy Costello, and Shallice (2000a) had already described planning deficits in patients with neurological lesions in the rostrolateral prefrontal cortex in the context of multitasking, Okuda et al. (1998) explored the brain regions associated with the maintenance and retrieval of prospective intentions in healthy subjects. In their positron-emission tomography (PET) study, they asked participants to memorize ten target words before scanning began. Participants were then asked to orally repeat ten sets of five words that were presented to them auditorily. In the PM task, these sets included some of the previously learned target words (two or three targets within fifty stimuli), which participants indicated by tapping with their hand. The blocks of the control task were identical, but did not include any target words. Participants had to report the ten target stimuli at the end of both PM and control blocks. The authors found activation in the left superior frontal gyrus (BA 10) and more posterior frontal areas (BA8/9), as well as in the inferior frontal gyrus (BA 47) and the left parahippocampal gyrus (BA 28) for the PM, compared to the control blocks. While they related the activation of the dorsolateral PFC and of the parahippocampal gyrus to processes of working memory and novelty detection, respectively, they assumed that the activation of BA 10 and 47 are more directly related to the process of holding an intention mind. Burgess, Quayle, and Frith (2001) used PET to distinguish between regions involved in the maintenance and retrieval of prospective intentions. By implementing a cognitive conjunction design involving four different PM tasks, they intended to rule out any potential task-specific activation and reveal only activations reflecting the processes supporting PM. More importantly, the experimental design comprised an “expectation” condition, in which participants were asked to perform a PM task, but no PM cues actually occurred. In contrast, in the “execution” condition, PM cues did occur on ~20% of the trials. Burgess et al. hypothesized that in both expectation and execution conditions, the prospective intention should be maintained, but only in the execution condition could participants actually carry out the PM task.

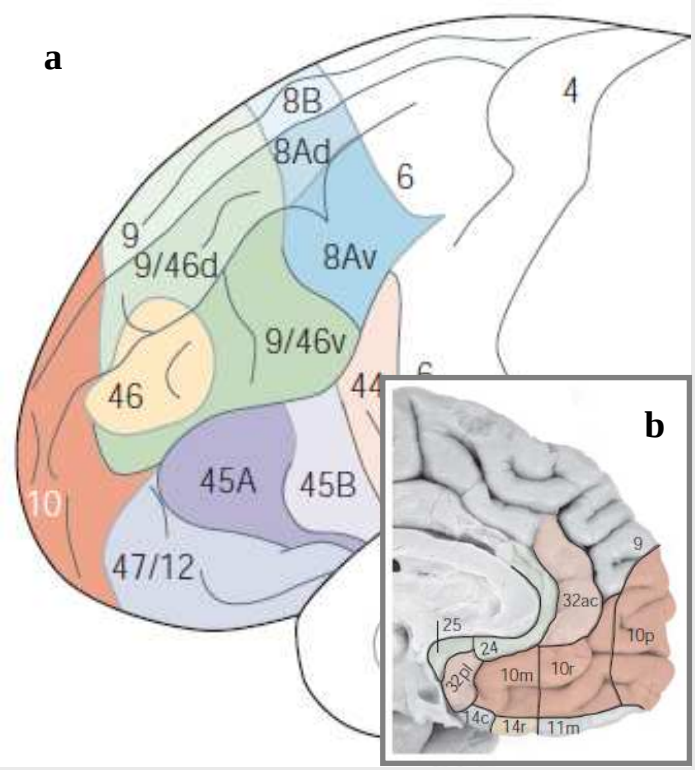

Figure 2.1: a) Schematic view of the lateral convexity of the human brain with the location of the frontopolar cortex (BA10) marked in red. b) View of the medial surface of the human brain with the location of BA 10 and its subdivisions overlaid in red (10p, 10r, 10m).

Taken and modified from Ramnani and Owen, 2004.

Brodmann area 10 (BA 10) is also known as the frontopolar cortex/frontal pole (note that the term “frontal pole” also includes parts of BA 9 in most species), the rostral frontal cortex or the anterior prefrontal cortex. In humans, BA 10 comprises a larger proportion of the cortex than in other species. It is sometimes subdivided in three parts, with area 10p occupying the frontal pole area and area 10r and 10m occupying the ventromedial PFC. In this work, the terms frontopolar cortex and BA10 are used synonymously for the region encompassing the three subdivisions.

Compared to other areas of the prefrontal cortex, the density of cell bodies is much lower, while the number of dendritic spines per cell and the spine density are much higher in BA 10, indicating that the neural processing in this area likely involves the integration of inputs from other cortical regions. Indeed, BA 10 receives inputs from more posterior, supramodal regions of the prefrontal cortex to which it has reciprocal connections (Öngür, Ferry, & Price, 2003; Ramnani & Owen, 2004).

Aside from its role in prospective memory, BA 10 has been functionally associated with the processing of internal states and relational integration (Christoff & Gabrieli, 2000; Christoff, et al., 2001), cognitive branching and sub-goal processing (Koechlin, Basso, Pietrini, Panzer, & Grafman, 1999; Koechlin & Hyafil, 2007), making exploratory decisions and prediction errors (Daw, O'Doherty, Dayan, Seymour, & Dolan, 2006; Ramnani, Elliott, Athwal, & Passingham, 2004), and evaluating self-generated decisions (Tsujimoto, Genovesio, & Wise, 2010).

Behaviorally, participants showed significant slowing of RTs in the two PM conditions compared to baseline, but RTs in the expectation and execution did not differ, suggesting that the maintenance of a PM intention caused this interference effect in both conditions. PET data revealed an increase in activation when participants expected to see a PM cue (i.e., in the expectation and in the execution condition) relative to baseline in the frontal pole bilaterally (BA10), as well as in the right lateral prefrontal and inferior parietal cortex, and in the precuneus, reflecting the maintenance of a prospective intention. In contrast, when intentions were executed, compared to only maintained, only the right thalamus showed an increase in activation, while the right dorsolateral prefrontal cortex showed a decrease.

In another PET study, Burgess, Scott, and Frith (2003) reported a lateral-medial dissociation for the role of rostral prefrontal cortex in PM. In this study, deactivation of the medial part of BA 10 was found when PM blocks were compared to blocks of ongoing trials. However, region of interest analyses based on the location of the activation found in the previous study (Burgess, et al., 2001) revealed that lateral regions of the rostral prefrontal cortex showed an increase in activation when a PM intention was present. The authors interpreted these findings by proposing a functional dissociation of BA 10: while medial areas support attention to external stimuli, which has to be withdrawn in the PM conditions, more lateral areas are involved in the switching of attention from internal (i.e., the prospective intention) to external (i.e., the PM cues) cognitive representations. In the same vein, Simons, Schölvinck, Gilbert, Frith, and Burgess (2006) found both lateral activation and medial deactivation when they compared PM conditions that drew to a different extent on PM cue identification and intention retrieval demands. Although both conditions showed a highly similar pattern, intention retrieval conditions showed a more pronounced lateral activation of BA 10 and slightly more medial deactivation. The authors interpreted this pattern of results in terms of the lateral-medial dissociation: when emphasis on the detection of the PM cues is high, attention should be directed towards external events, but when intention retrieval is demanding, the attention focus should be on internally generated information.

Gilbert, Frith, and Burgess (2005) showed that rostral prefrontal cortex was indeed differentially activated in response to stimulus-oriented (i.e., external) and stimulus-independent (i.e., internal) thoughts. Their experimental paradigm comprised phases of

stimulus-oriented and stimulus-independent thoughts through which participants cycled several times. Sustained activation of the medial rostral prefrontal cortex was found for stimulus-oriented thought, while lateral parts were transiently activated by switches between the two types of thoughts, irrespective of the direction of the switch.

On the basis of these and other findings linking lateral and medial parts of BA 10 to different functions (Burgess, Dumontheil, & Gilbert, 2007a; Gilbert, et al., 2006b; Simons, et al., 2006), a more general account of BA 10 function, the so-called “gateway hypothesis”, has been proposed (Burgess, et al., 2007a; Burgess, et al., 2008; Burgess, Gilbert, & Dumontheil, 2007b). The gateway hypothesis accounts for the differential activation of lateral and medial parts of the anterior prefrontal cortex by linking it to stimulus-independent and stimulus-oriented processing, respectively. In PM, attention is constantly switched between stimulus-oriented, or external processing, and stimulus-independent, or internal processing to maintain the prospective intention. Thus, the deactivation of medial BA 10 during PM blocks is consistent with the idea of the suppression of stimulus-oriented thoughts. At the same time, the activation of lateral parts of BA 10 could represent stimulus-independent processing as evoked by the maintenance of the prospective intention. Moreover, lateral parts of BA 10 also seem to be involved in the switching between the two forms of processing. In terms of PM, this would involve transient activity on PM cue trials, because the external stimulus has to be compared with the internally stored PM target stimulus.

2.2 The Reward System

Reward has a central function in an organism's behavior, ranging from the regulation of vegetative states to goal-directed behavior. It has been implicated in reinforcement-learning (Schultz, 1998), incentive motivation (Berridge & Kringelbach, 2008), goal-directed behavior and decision-making (Knutson, et al., 2001a; Knutson & Cooper, 2005; Knutson, et al., 2001b) and has been shown to play a role in higher cognitive processes such as working memory (Pochon, et al., 2002). In the following two paragraphs, the functional neuroanatomy of the reward system will be briefly described and findings from neuroimaging studies using reward paradigms in humans will be summarized.

2.2.1 Functional Neuroanatomy of the Reward System

The notion of a general reward or motivational system emerged from early studies in animals showing that intracranial self-stimulation of certain brain regions had reinforcing effects on behavior (Olds & Milner, 1954). In addition, single-cell recordings in non-human primates targeting midbrain dopamine neurons have highlighted the role of the neurotransmitter dopamine in reward (Mirenowicz & Schultz, 1994, 1996). Several brain regions have since been shown to be involved in reward processing. In particular, dopaminergic projections from the substantia nigra and the ventral tegmental area in the midbrain to the striatum, the so-called limbic system and prefrontal regions have been identified (Wise, 2004). Nominally, two reward systems have been described: the nigrostriatal system, projecting primarily from the substantia nigra (SN) to the striatum (nucleus caudatus and putamen) and the mesocorticolimbic system, with dopaminergic cells projecting from the ventral tegmental are (VTA) to the limbic system and to the prefrontal cortex. The latter system has often been subclassified into the mesolimbic system, including projections to the nucleus accumbens (NAcc), amygdala, septum, and hippocampus, and the mesocortical system, including projections to the prefrontal and cingular cortices. However, it has been argued that these systems cannot be separated anatomically or functionally (Wise, 2009). For example, the substantia nigra, the origin of the nigrostriatal system, has been found to project to the amygdala, a region traditionally assigned to the limbic system. Moreover, both SN and VTA have been shown to be responsive to prediction error signals, with increased firing rates to unpredicted rewards and decreased firing to the absence of an expected reward (Mirenowicz & Schultz, 1994; Schultz, 1998, 2010). Recent evidence from animal studies has also implicated the lateral habenula in the inhibition of dopaminergic neurons in the SN for non-reward, suggesting that regions outside the traditionally defined reward system also play a role in reward processing (Matsumoto & Hikosaka, 2007).

2.2.2 Activation of the Reward System in Humans

In humans, the expectation of primary rewards such as food or liquids has been shown to activate the midbrain and ventral striatum (Beaver, et al., 2006; D'Ardenne, McClure, Nystrom, & Cohen, 2008; O'Doherty, Buchanan, Seymour, & Dolan, 2006;

O'Doherty, Deichmann, Critchley, & Dolan, 2002; see Fig. 2.2 for the anatomical location of the human midbrain and striatum). However, for the most part, studies examining reward processing in humans have used monetary rewards and losses that can be manipulated in size and probability in tasks such as the monetary incentive delay (MID) task, revearsal learning, and instrumental choice or guessing tasks (Kim, Shimojo, & O'Doherty, 2006; Knutson, et al., 2001a; Knutson, et al., 2001b; Robinson, Frank, Sahakian, & Cools, 2010). For example, Zaghloul et al. (2009) recorded activity from substantia nigra neurons with microelectrodes in two patients with Parkinson's disease who performed a probabilistic learning task. They found that unexpected gains elicited higher firing rates in SN neurons compared to unexpected losses, while no differences were observed when both rewards and losses were expected.

Consistently, D'Ardenne et al. (2008) found that BOLD (blood oxygenation level-dependent) responses in the human VTA reflected positive reward prediction errors associated with monetary reward. Moreover, both midbrain areas and the ventral striatum, including the nucleus accumbens (NAcc), have been found to show increased activation for the anticipation of monetary rewards in fMRI studies using variants of the MID task (Adcock, Thangavel, Whitfield-Gabrieli, Knutson, & Gabrieli, 2006; Camara, Rodriguez-Fornells, & Münte, 2009a; Knutson, et al., 2001a; McKell Carter, Macinnes, Huettel, & Adcock, 2009; Simon, et al., 2010; Tom, Fox, Trepel, & Poldrack, 2007).

However, it is still unclear whether activation in reward-related regions primarily reflects the affective valence of the reward, the salience or magnitude of the reward, or a combination of both.

While some studies have reported activation in the ventral striatum to increase in response to monetary gains and decrease in response to monetary losses (Delgado, Nystrom, Fissell, Noll, & Fiez, 2000; Tom, et al., 2007) or to code only the reward-related prediction error (Yacubian, et al., 2006), others have found increasing activation for both monetary gains and losses, suggesting that anticipatory activation in these regions largely reflects the motivational relevance of an outcome (Cooper & Knutson, 2008; McKell Carter, et al., 2009; Robinson, et al., 2010; Seymour, Daw, Dayan, Singer, & Dolan, 2007). In order to tease apart valence- and salience-specific accounts of nucleus accumbens function, Cooper and Knutson (2008) cued participants to anticipate certain or uncertain monetary gains and losses. They found that, when the outcome was certain (i.e., independent of the response given by the participants), NAcc activation

increased for anticipated gains and decreased for anticipated losses, thus encoding the valence of the anticipated outcome.

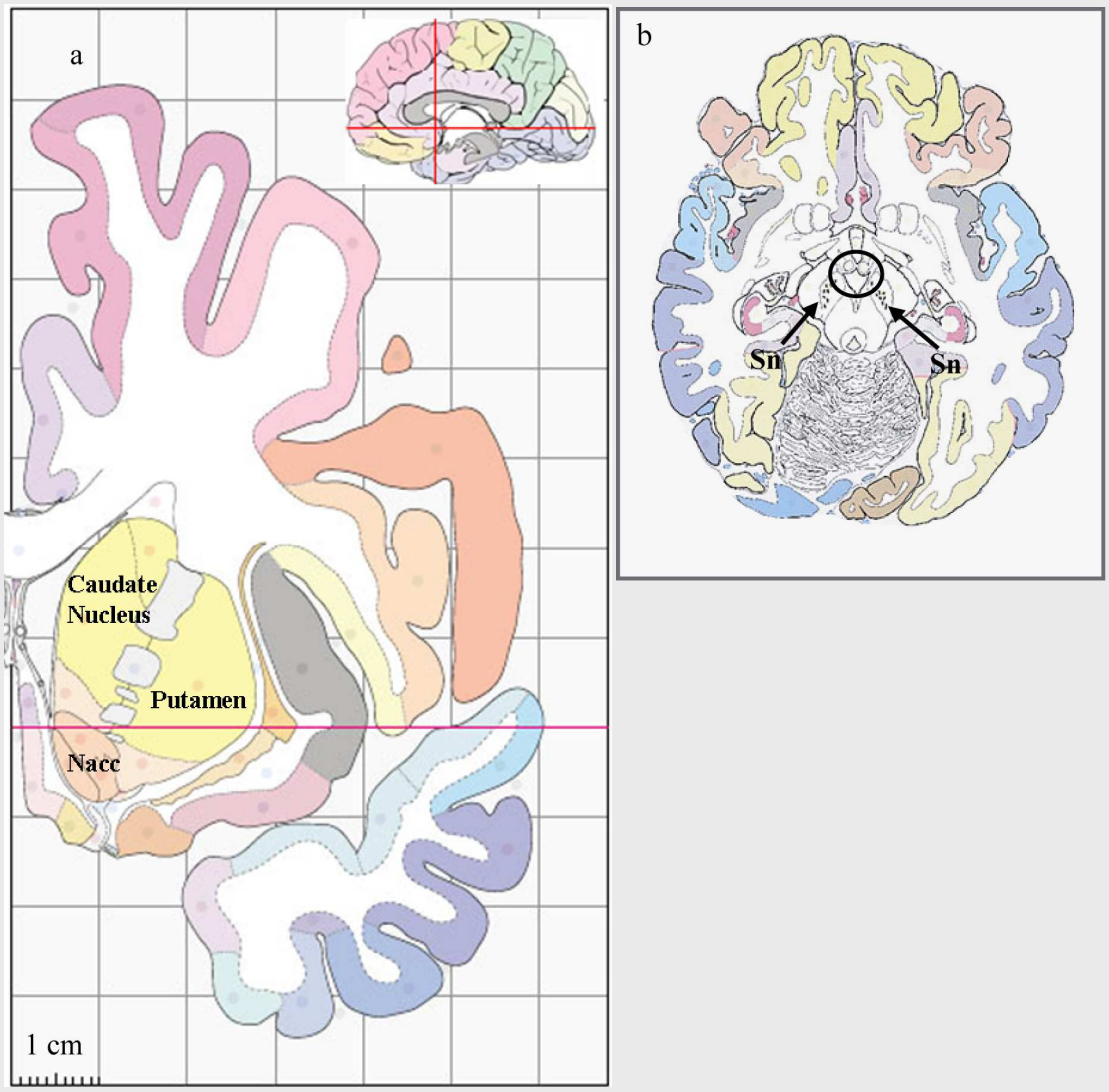

Figure 2.2: (a) Schematic drawing of a coronal plane of the human brain. The striatum (caudate nucleus and putamen) is shown in yellow. The nucleus accumbens (pink) is in the ventral part of the striatum. (b) Schematic drawing of an axial plane of the human brain with the anatomical location of the midbrain, including the substantia nigra (arrows) and the approximate location of the ventral tegmental area circled in black.

Taken and modified from Mai, Paxinos, and Voss (2007), as in www.thehumanbrain.info.

However, when the outcome was uncertain (i.e., depended on participants' response times), NAcc showed increased activation for both anticipated gains and losses, thus encoding the salience of the outcome. Thus, the salience account references the

contingency of the response, rather than the affective value of the reward cue. In this context, it is important to take into account that the anticipation of a reward and the opportunity to avoid losses are both directed at obtaining a positive outcome and thus might rely on partly overlapping neural motivational systems, especially in tasks in which the outcome is action-contingent, as opposed to risky gambles that can only be accepted or rejected. Indeed, it has been reported that relief from pain is associated with neural activity in the midbrain and in the amygdala, reflecting reward-learning signals (Seymour, et al., 2005). Moreover, Kim et al. (2006) could show that avoiding an aversive monetary outcome recruited the medial OFC, a region previously implicated in the evaluation of monetary reward, suggesting that the successful avoidance of a negative outcome is associated with positive affective valence and thus potentially represents an intrinsic reward signal.

2.2.3 Individual Differences in Reward Sensitivity

One influential model that accounts for individual differences in responses to incentive stimuli is the Reinforcement Sensitivity Theory (Corr, 2004; Gray, 1970, 1981, 1990; Gray & McNaughton, 2000). Originally, this neuropsychological theory of personality was proposed by Gray as an alternative to Eysenck's psychophysiological theory of introversion-extraversion (Eysenck, 1967; Gray, 1970). Gray suggested that Eysenck's personality factors of extraversion and neuroticism be replaced by the factors of reward sensitivity, reflecting impulsivity, and punishment sensitivity, reflecting anxiety (Corr, 2004). Thus, two behavioral systems constitute the core of this biological theory of personality: the behavioral activation system (BAS), a motivational system responding to reward and non-punishment, and the behavioral inhibition system (BIS) (but see Gray and McNaughton's (2000) revised theory for a description of a third system responsible to reactions to all aversive stimuli, the fight-flight-freeze system (FFFS)). Neurobiologically, the BAS has been associated with mesolimbic and mesocortical projections from the VTA to the ventral striatum and the prefrontal cortex (cf. section 2.2.1), while the BIS consists of the septo-hippocampal system and the amygdala (Smillie, 2008).

Carver and White (1994) have developed scales for self-report measures of the BIS and BAS, including one measure for the BIS, and three measures for the BAS: reward responsiveness, fun seeking, and drive (cf. section 3.1.3 for a precise description of the

BIS/BAS scales).

Several neuroimaging studies have since linked individual differences as measured by these scales to reward-related brain activation. For example, activation of the midbrain and the ventral striatum as measured with fMRI has been shown to be related to individual differences in approach motivation (Krebs, Schott, & Düzel, 2009a; McKell Carter, et al., 2009; Simon, et al., 2010).

While Beaver et al. (2006) reported that BAS Drive scores predicted participants' activation in the midbrain and ventral striatum for primary (food) rewards, studies using monetary rewards have consistently reported correlations between activation in midbrain or ventral striatal regions and individual differences in BAS scores or its subscales. In particular, Simon et al. (2010) found activity in the ventral striatum to correlate positively with BAS scores, and negatively with BIS scores. Krebs, Schott, and Düzel (2009a) found that, in a long-term memory paradigm, activation in the SN/VTA region correlated significantly with reward dependence as assessed with Cloninger's Temperament and Character Inventory for reward-predicting cues. McKell Carter et al. (2009) found that the difference in activation in the VTA and in the NAcc for monetary gains vs. losses was predicted by an individual reward sensitivity covariate (a combined score from the BAS and the Temporal Experience of Pleasure Scale (TEPS)). In a recognition memory study, Han, Huettel, Raposo, Adcock and Dobbins (2010) found that ventral striatal activation for rewarded hits vs. correct rejections correlated with BAS reward responsiveness.

Thus, although there is evidence that individual measures of reward sensitivity can predict activation in midbrain and striatal regions in the MID and retrospective memory tasks, no such relationship has yet been reported for PM and reward responsiveness.

2.3 Aims of the Study

The overall aim of the present work was to define the role of motivational processes in prospective memory. The study intended to tie together cognitive aspects of prospective memory that have been investigated in behavioral and neuroimaging experiments, on the one hand, and well-known findings in terms of reward representations as demonstrated in reward anticipation paradigms, on the other hand.

Based on previous findings, the focus of the present study centered on three main questions: first, is PM performance modulated by the level of reward expectation

associated with PM cues? As mentioned above (sections 2.1.1 and 2.1.3), incentive effects on PM performance in naturalistic tasks have been reported. The present study sought to investigate these effects in computer-based experimental tasks using differently sized monetary incentives (experiment 1, 2, and 3).

Second, do the neural processes supporting PM reflect the level of reward expectation associated with the prospective intentions? Previous studies have used monetary incentives in PM paradigms (section 2.1.5), but the present study is the first to examine the effects of monetary incentives on the neural mechanisms of PM (using monetary reward in experiment 2 and monetary reward and loss in experiment 3).

Third, do individual differences in personality variables play a role in the putative reward modulations of PM? Previous findings have suggested an effect of individual differences on PM and reward processing (sections 2.1.4 and 2.2.3.). Thus, the present study sought to assess possible interactions between individual differences in reward processing, personality and the behavioral and neural correlates of PM (experiment 1, 2, and 3).

3 Experiment 1

In this experiment, we set out to investigate if reward has a general effect on behavioral performance on PM tasks, as suggested by corresponding findings in the retrospective memory literature (Wittmann, et al., 2005) and in earlier studies using naturalistic PM tasks. Moreover, we explored if individual differences could account for individual reward modulation of PM performance.

To this end, we combined a traditional PM paradigm with different levels of reward expectations. Reward expectation was induced by associating PM performance with the receipt of a high or low reward, thus establishing PM-reward contingencies.

The aim of the experiment was two-fold: on the one hand, the study was designed to investigate differences in PM performance or ongoing costs when different levels of reward were anticipated. On the other hand, the present study also sought to explore individual differences in personality, which have been linked to PM performance (Cuttler & Graf, 2007a). In particular, we were interested in potential relations between differences in PM performance due to reward and individual approach/avoidance motivation.

3.1 Methods

3.1.1 Participants

Fifty healthy right-handed volunteers recruited from the general student population of the University of Heidelberg participated in the study. Data from two participants were excluded because they did not follow the instructions. Data from forty-eight participants (24 female, mean age 24 years, range 20 - 32 years) are reported here. Participants were paid according to their performance in the experiment (max. 12 Euros). The experiment lasted approximately one hour.

3.1.2 Experimental Paradigm

As an ongoing task, participants performed a 2-back version of the n-back task (Fig. 3.1). The n-back task has been used as an ongoing task in a number of previous studies (Hashimoto, Umeda, & Kojima, 2010; Jäger & Kliegel, 2008; Kliegel & Jäger, 2006; Kliegel, et al., 2005; Reynolds, West, & Braver, 2009; West, Bowry, & Krompinger, 2006; West, Krompinger, & Bowry, 2005). By using the 2-back version of this task, which is of intermediate difficulty, we intended to ensure participants' cognitive involvement in the ongoing task, but only to the extent that a PM load could be added.

Each letter stimulus was presented for 500 ms and was followed by a blank screen of 1500 ms, amounting to 2000 ms of total trial time. Stimuli were presented in white uppercase letters at the center of the screen against a black background, along with a colored frame signaling the reward magnitude associated with a correct response to the PM cues. Stimuli were presented in blocks of 100 trials.

In parallel to the work of Burgess et al. (2001, 2003), we included a PM expectation condition, in which participants were told that they *might* encounter PM cues, but no PM cues were presented in this condition.

Overall, there were four blocks of each of the following conditions: PM execution-high (containing high rewarded PM cues), PM execution-low (containing low rewarded PM cues), PM expectation (expectation of PM cues; half of the blocks were cued with a high, the other half with a low reward instruction) and ongoing/baseline (no expectation of PM cues), in random sequence.

PM cues varied between blocks and were specified at the beginning of each block along with the reward information in this block (i.e., 2 points (5 cents) for low and 10

points (25 cents) for high reward) in the center of the colored frame for 3 s (in the ongoing condition, a zero indicated that there were no PM cue trials to be expected and participants thus could not score any points in these blocks). The instruction screen was followed by the presentation of a fixation cross for 2s, before the first trial began. A response criterion of at least 60% correct responses in the ongoing task was introduced to prevent participants from ignoring the ongoing task.

In order to familiarize participants with the task, each participant completed three practice blocks consisting of 20 trials. Two of those blocks were ongoing/baseline blocks, one included 3 high reward PM trials.

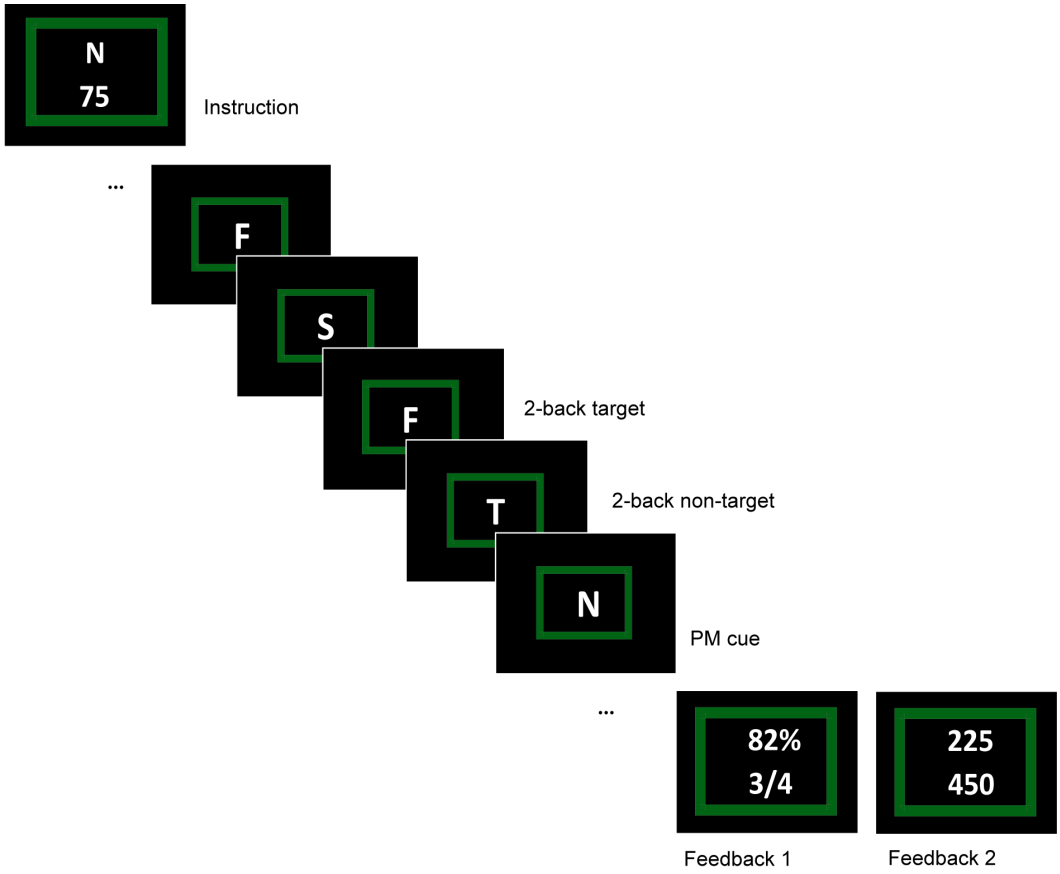

Figure 3.1: Prospective memory paradigm. Trials were one of three types: 2-back target trials, 2-back non-target trials, or prospective memory (PM) cues. Participants received either a high or low reward (and could avoid losses, exp. 3) for correctly responding to the PM cues, given that a response criterion for the ongoing task was met. No PM cues occurred in the expectation conditions (exp. 1 and 2). For a detailed description of the experimental procedures in experiment 1, 2, and 3, please refer to the method sections (3.1.2, 4.1.2, and 5.1.2, respectively).

At the end of each block, participants received a two-part feedback: first, the percentage of correct responses on the ongoing trials was presented. Next, the number of detected PM cues was presented along with the total number of PM cues presented in this block, together with the block score and the total cumulative score at this point in time.

Altogether, there were 40 PM cue trials in both the execution-high and the execution-low condition. The number of PM cues in each block varied between 6 and 14. In addition, each execution condition included 360 ongoing trials (120 2-back targets and 240 2-back non-targets), resulting in a PM/ongoing trial ratio of approximately 11%. The expectation and the ongoing/baseline conditions comprised 120 2-back target and 280 2-back non-target trials.

3.1.3 Questionnaires

We used the BIS/BAS scales to assess individual differences in the sensitivity of the behavioral approach (BAS) and behavioral inhibition (BIS) system (Carver & White, 1994; German version by Strobel, Beauducel, Debener, & Brocke, 2001). The BAS scale consists of 3 subscales: BAS Drive, BAS Fun Seeking, and BAS Reward Responsiveness. BAS Drive focuses primarily on the execution of an action in order to attain a rewarding goal. BAS Fun Seeking contains elements of impulsivity and excitement-seeking. BAS Reward Responsiveness measures the extent to which an individual is affected and motivated by the prospect of a positive outcome.

Carver and White (1994) report reasonable alpha reliabilities for the BIS/BAS scales (BIS .74, BAS reward responsiveness .73, BAS Drive .76, BAS Fun Seeking .66).

Individual differences in personality traits were assessed using the German version of the NEO Personality Inventory (NEO-PI-R; Costa & McCrae, 1992; German version by Ostendorf & Angleitner, 2004). The NEO-PI-R consists of 240 items measuring the Five Factor Model: Neuroticism, Extraversion, Conscientiousness, Agreeableness and Openness to experience. Six subscales (facets) for each of the five factors allow for specific aspects of each of the factors to be measured. The internal consistency of the NEO is high (Cronbachs α between .86 and .92).

For accuracy and reaction times, difference scores for high – low reward were computed for all conditions and trial types (e.g., the difference between accuracy for high and low rewarded non-targets in the execution condition). Correlations with NEO and BIS/BAS scores were computed using a standard statistical software package

(PASW 18.0).

3.1.4 Analysis of Behavioral Data

Response times were measured from the onset of the stimulus to the onset of the participant's response. Trials with incorrect or missing responses were excluded. Reaction times and percentages of correct responses were aggregated by participant and condition. For both response times and percentage correct responses on ongoing trials, we conducted repeated-measures analyses of variance with the factors condition (5 levels) and trial-type (2 levels), treating each experimental condition as a level of the factor 'condition'. We then performed post-hoc comparisons (using the Bonferroni correction as implemented in the PASW software package) between the different conditions. For PM cue trials, we conducted paired t-tests to compare accuracy and reaction times to high and low reward PM cues.

3.2 Results

3.2.1 Group Results

Participants performed the ongoing task at a high level of accuracy (Table 3.1). An interaction between the factors condition and trial type indicated that accuracy levels differed between non-targets and targets [$F(4, 188) = 3.15$, $p = 0.016$]. For non-targets, accuracy did not differ between the levels of the condition factor [all ps = 1; Bonferroni corrected for multiple comparisons]. For targets, accuracy was lower for execution-high, compared to ongoing target trials [$t(47) = -3.28$; $p = 0.002$].

For response times, we found an interaction between condition and trial type [$F(4, 188) = 2.6$; $p < 0.04$]. Analyses separating the two trial types revealed that participants responded faster to both non-target and target trials in the ongoing/baseline condition compared to all other levels of the factor condition [$F(4, 188) = 25.75$ and 31.1 for non-targets and targets, respectively; $p < 0.001$ for both trial types], i.e., between ongoing/baseline and ongoing trials from the conditions in which a PM expectation was maintained [all ps < 0.001]. However, target trials in the execution-low condition were more slowly responded to than target trials in the expectation-low condition [$t(47) = 2.99$; $p = 0.004$].

Table 3.1: Mean reaction times (ms) and accuracy (% correct) for ongoing trials (non-targets and targets) in all conditions and for PM cues in the execution conditions. Standard error of the mean is given in parentheses.

		Non-targets	Targets	PM cues
Execution				
high	RT *(SE)*	635.56 *(21.46)*	627.0 *(19.68)*	648.63 *(13.97)*
	Acc (*SE)*	96.58 *(0.3)*	77.77 *(1.48)*	81.41 *(1.71)*
low		632.92 *(19.93)*	625.21 *(19.33)*	659.83 *(13.54)*
		96.84 *(0.28)*	78.19 *(1.6)*	79.23 *(2.06)*
Expectation		623.73 *(21.46)*	604.98 *(18.58)*	
		96.61 *(0.28)*	78.78 *(1.51)*	
high		625.37 *(22.85)*	609.58 *(19.31)*	-
		96.3 *(0.35)*	78.62 *(1.7)*	
low		622.06 *(21.89)*	599.42 *(19.05)*	-
		96.91 *(0.33)*	78.92 *(1.55)*	
Ongoing/baseline		547.69 *(20.22)*	547.0 *(17.99)*	-
		96.46 *(0.33)*	81.31 *(1.46)*	

Accuracy on PM cue trials was slightly higher when participants expected a high, compared to a low reward, but this difference was not significant [p = 0.153]. Even though the accuracy difference between high and low reward PM cues was not significant, reward effects on accuracy ranged from -17,5% to 32,5% across subjects, and variability was substantial: SD = 10,4%, suggesting that individual differences in reward processing, rather than the absolute size of the reward, might have influenced

PM performance.

Analysis of the response times to PM cues revealed that participants were also slightly faster to respond to high reward, compared to low reward PM cues, but again, this difference was not significant [p = 0.146].

3.2.2 PM performance and individual differences

In a first step, we aimed at replicating previous findings of positive correlations between general PM performance and the personality dimensions of the Big Five (as measured by the NEO-PI-R). We found a correlation between a composite score of PM performance (collapsed across high and low reward) and the personality factor of conscientiousness [r = .30, p = 0.039], as has been reported in previous studies (Cuttler & Graf, 2007a). However, there were no correlations between PM performance and other personality variables (whereas positive correlations between PM performance and agreeableness as well as neuroticism have been reported previously (Cuttler & Graf, 2007a; Salthouse, et al., 2004)). Moreover, neither response times for PM cues nor response costs (i.e., slowing on ongoing trials) were correlated with personality factors.

As mentioned above, reward magnitude did not lead to a performance modulation per se, but reward-related performance differences varied substantially between individuals. Moreover, regions including the so-called reward system have been identified as the biological basis for approach and avoidance processes. Individual differences in the functioning of these systems have been found to manifest as personality (Gray, 1970). Therefore, in a second step, we aimed at investigating if individual differences in PM performance elicited by the magnitude of reward were related to differences in personality variables. We focused our analyses on reward-related differences in PM accuracy and response times (i.e., high – low reward).

3.2.2.1 Accuracy and personality

We found a negative correlation for the personality factor of neuroticism and the difference in accuracy for high and low rewarded target trials in the expectation condition [r = -.42; p = 0.003]. Thus, the lower participants scored on the neuroticism scale, the smaller was the difference between the accuracy in the high and low reward

condition (Table 3.2). That is, for emotionally stable individuals, high expected reward tended to enhance ongoing performance, even when no PM cues were present. This was not the case for less stable (i.e., more neurotic) individuals, whose ongoing performance dropped when they expected high, compared to low reward PM cues.

A reward-related difference in accuracy on PM trials revealed a positive correlation with the factor openness to experience [r = .29, p = 0.046], which means that the more open participants were, the better they scored on high, compared to low rewarded PM cue trials.

Table 3.2: Correlations between reward-related PM accuracy differences and the personality dimensions measured by the NEO and differences in approach/avoidance motivation as measured by BIS/BAS (difference scores for PM cues are from the execution conditions only).

% correct (high-low)	**NEO**	**BIS/BAS**
Execution		
non-targets	-	-
targets	-	-
PM cues	Openness (r = .289, p = 0.046)	-
Expectation		
non-targets	Conscientiousness (r = -.327, p = 0.023)	BAS Drive (r = -.311, p = 0.031)
targets	Neuroticism (r = -.42; p = 0.003)	-

The difference in accuracy on non-target trials in the expectation condition was negatively correlated with the factor conscientiousness [r = -.33; p = 0.023], indicating

that less conscientious individuals made fewer errors on non-target trials in the low, compared to the high reward condition. The latter difference score also correlated negatively with the BAS Drive subscale [r = -.31; p = 0.031]. This means that individuals with a lower appetitive drive motivation performed equally or better in the low, compared to the high reward expectation condition.

3.2.2.2 Reaction times and personality

All reaction time difference scores correlated positively with the BAS reward responsiveness scale (Table 3.3).

Table 3.3: Correlations between reward-related PM response time differences and the personality dimensions measured by the NEO and differences in approach/avoidance motivation as measured by BIS/BAS scales (rr = reward responsiveness; d = drive, fs = fun seeking).

RT (high-low)	NEO	BIS/BAS
Execution		
non-targets	-	BAS rr (r = .40, p = 0.005)
targets	-	BAS rr (r = .295, p = 0.042)
PM cues	-	BAS rr (r = .322, p = 0.026)
Expectation		
non-targets	-	BAS total (r = .395, p = 0.006) BAS rr (r = .34, p = 0.018)
targets	-	BAS total (r = .468, p = 0.001) BAS rr (r = .366, p = 0.01) BAS d (r = .33, p = 0.022) BAS fs (r = .31, p = 0.032)

In addition, the difference score for reaction times to non-targets and targets in the expectation condition correlated positively with the total BAS score. That is, participants with a high responsiveness to reward responded more slowly to high reward PM cues. Moreover, high reward responsive individuals also demonstrated an increase in response time costs on ongoing (non-target and target) trials under high reward expectation. Thus, for those individuals, high reward induced greater costs to the ongoing task, presumably as a result of increased monitoring processes triggered by the prospect of high reward PM cues.

3.3. Discussion

The goal of the present experiment was two-fold: on the one hand, we wanted to investigate reward-related performance differences in PM. On the other hand, we examined the influence of personality, including measures based on biological models of reward and punishment, on potential reward-related PM performance differences.

While reward-related modulations of behavioral performance (in most cases, as in faster response times for rewarded trials), have been reported in the context of studies investigating goal-directed behavior (Knutson, et al., 2001b; Simon, et al., 2010) and retrospective memory (Adcock, et al., 2006), there has been no report of reward-induced changes in behavior in the PM literature. Thus, our primary goal was to shed light on the question if reward effects can be found in PM performance.

Overall, our data revealed significant response costs on the ongoing trials when a PM intention was present, which were evident in the slowing of response times in all PM conditions, compared to the ongoing/baseline condition. The amount of anticipated reward did not have an influence on the magnitude of these costs. Greater costs were observed, however, on low reward execution ongoing trials, compared to the low reward expectation ongoing trials (2-back targets), probably as a result of the disruption in the 2-back rhythm whenever PM cues appeared in the execution condition.

Although accuracy and response times on the PM cues themselves did not show reward-related effects, a somewhat indirect effect of the reward magnitude associated with the PM cues was apparent in the performance decline on ongoing (2-back target) trials, in the high reward, compared to the ongoing/baseline condition. A cautious interpretation would be that participants invested a high amount of effort into the

detection of the PM cues when a high reward was at stake, leading accuracy on the ongoing task to decline. This decline in ongoing accuracy was not accompanied by a significant increase in PM cue detection accuracy, i.e., the number of detected PM cues did not increase with high reward. However, participants were restrained by the ongoing task accuracy criterion which was employed to avoid that the ongoing task was completely ignored. Had this criterion been lower or non-existent, participants might have shifted their attention even more towards the PM cues associated with high reward. However, the same would have been true for low reward PM cues such that potential differences would have been ruled out. For future studies, it would be interesting to manipulate the incentives/constraints for the PM and the ongoing task separately (much like in studies investigating importance effects), e.g., high reward PM, ongoing criterion: 60% vs. high reward PM, ongoing criterion: 40%, to investigate potential accuracy effects on both tasks.

The second part of the goal of the present experiment was to elucidate potential effects of individual differences in personality on reward modulations of PM performance. This investigation was motivated by earlier findings reporting that measures of personality could predict PM performance (Cuttler & Graf, 2007a). Moreover, biologically based models of personality link the behavioral responses to reward and punishment stimuli to the expression of personality traits (Corr, 2004; Gray, 1970). Evidence from neuroimaging studies lend support to these theories by reporting correlations between functional activation of the reward system and individual differences in personality traits (Beaver, et al., 2006; M. X. Cohen, Young, Baek, Kessler, & Ranganath, 2005; Simon, et al., 2010).

Here, we found a positive correlation between general PM performance (i.e., the percentage of correctly detected PM cues independent of reward information) and conscientiousness, replicating earlier findings with naturalistic PM tasks in our computer-based PM paradigm, supporting the idea that more conscientious individuals are inclined to perform well on tasks involving planning (Cuttler & Graf, 2007a).

Reward difference scores in terms of accuracy and response times do not provide such a straightforward interpretation, as reward effects should pan out in opposing directions in the ongoing and in the PM task (e.g., high reward should lead to an increase in accuracy for the PM cues, but to greater costs on the ongoing task). We found that reward difference scores describing accuracy in the ongoing task (in

particular, for non-targets and targets in the expectation condition) showed negative correlations with the personality factors of consciousness and neuroticism. That is, highly conscientious individuals performed equally well on high and low reward ongoing trials (or even better in the low reward conditions), seemingly able to ignore the distraction caused by the reward information of the PM cues or investing the same amount of effort, irrespective of incentive motivation.

Interestingly, we also found a negative correlation between neuroticism and reward-related difference scores, complementing previous findings of correlations between PM performance and conscientiousness as well as neuroticism (Cuttler & Graf, 2007a). In the same vein as conscientiousness, the personality trait of neuroticism seems to be associated with the ability to ignore distracting information about the reward value of the PM cues and ensure that performance levels on the ongoing task are not affected by motivational incentives.

Interestingly, we also observed a positive correlation between PM difference scores (i.e., accuracy on high – accuracy on low reward PM cues) and openness, meaning that more open individuals tended to score better on PM cue trials when a high reward was involved, whereas the reverse was true for less open individuals.

A more consistent pattern was observed for response time differences: participants with a high approach motivation, in particular with high reward responsiveness, tended to take longer to respond to both PM and ongoing trials in the high reward context. Thus, under high reward, they seemed to take more time (within the time window given by the trial definition) to decide about the trial status of an item, probably to avoid missing the high reward PM cues.

In summary, our findings fit well with previous studies reporting a link between PM performance and personality traits such as conscientiousness or neuroticism which are related to high planning and structuring abilities (Cuttler & Graf, 2007a). Our findings are in line with McDaniel and Einstein's (2000) prediction in light of the multiprocess framework that these differences would emerge when the PM task required strategic monitoring processes, which was the case in this experiment.

In addition, we show that, on the group level, there was a tendency to sacrifice accuracy on the ongoing task in a high reward context, but no reward-related differences were found in response costs (i.e., response times for ongoing trials). However, response time differences for high and low rewarded trials were found to covary with individual

reward responsiveness, indicating that, in high reward responsive individuals, information about the reward magnitude of an upcoming PM event is incorporated in the response pattern of an otherwise purely cognitive task.

Taken together, these findings are in line with previous reports of correlations between personality measures based on the Five Factor Inventory (NEO), and PM performance. At the same time, we extend previous findings by relating them to biologically based aspects of personality as in measures brought forth by the reinforcement sensitivity theory, explaining the expression of personality by individual responses to reward and punishment. As these self-reported biologically based traits have also been associated with an increase in functional activation in neuroimaging experiments, it seems likely that they might also play a role in the neural processing of possible reward modulations of PM.

4 Experiment 2

Experiment 2 was designed to investigate the effects of reward on the neural mechanisms supporting PM. On the one hand, this was motivated by the fact that behavioral and correlational findings from experiment 1 suggested a potential reward modulation of PM, as did findings from earlier behavioral studies (Aberle, et al., in press; Meacham & Singer, 1977; Somerville, et al., 1983).

On the other hand, the involvement of reward-related brain regions such as the midbrain and the ventral striatum has been reported in the context of goal-directed behavior and retrospective memory (Adcock, et al., 2006; Knutson, et al., 2001a; Knutson, et al., 2001b). Although previous neuroimaging studies of PM have used monetary incentives to emphasize the importance of the PM task, the involvement of these regions has not been explored systematically so far.

We used fMRI to investigate if the level of reward anticipation associated with a prospective intention would differentially affect PM related neural activity, suggesting an interaction between the cognitive processes mediating PM and motivational processes associated with the anticipation of reward. In addition, we used an independent localizer experiment to identify brain regions associated with reward anticipation per se. We then used these regions as regions-of-interest for the PM experiment which involved rewarded PM cues.

Specifically, the following three questions were examined: First, we were interested in whether or not the maintenance of the prospective intention as reflected in the activation of BA 10 would be affected by the level of anticipated reward associated with the PM cue.

Second, we examined if neural reward effects on PM were modulated by individual differences in reward-related personality traits measured by the BIS/BAS scores (Gray, 1970, 1990) reflecting individual sensitivity to rewarding stimuli.

Third, we also explored if the functional coupling between reward related dopaminergic systems and the frontopolar cortex, during PM, was modulated by reward magnitude.

General Methods: Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI) is a non-invasive technique that allows the mapping of variations in blood flow in different brain areas to cognitive tasks and functions. The basic principle of fMRI is the measurement of the hemodynamic changes that accompany task-related neural activity. In the following section, the underlying physiological changes and the measurement methods of fMRI will be shortly summarized.

Increased metabolism in the populations of neurons that are active during a specific cognitive task leads to a decrease in oxygen, which is compensated by a dilation of blood vessels and increased blood flow in these specific areas. Usually, the amount of oxygen provided by this compensation mechanism exceeds the need for oxygen in the respective brain region. Blood has different magnetic properties depending on the amount of oxygen: while oxygenated hemoglobin is diamagnetic, deoxygenated hemoglobin is paramagnetic. This change in the ratio of oxygenated and deoxygenated hemoglobin leads to inhomogenities in the magnetic field that can be measured with fMRI by using T2*-weighted images that are susceptible to field inhomogenities. This effect is called the blood-oxygen-level-dependent (BOLD) effect and was first described in rodents (Ogawa, Lee, Kay, & Tank, 1990; Öngür, et al., 2003). It was subsequently applied to functional studies in humans (Bandettini, Wong, Hinks, Tikofsky, & Hyde, 1992; Kwong, et al., 1992; Ogawa, et al., 1992).

The BOLD response consists of a short onset (note that an initial decrease, the “initial dip” has also been reported (Vanzetta & Grinvald, 1999)), a rise to peak, followed by a return to baseline, with a total duration of 4-12 seconds. Due to the sluggishness of the hemodynamic response, early functional MRI studies used experimental block designs in which events of a certain type or condition were repeatedly presented over an extended period of time and compared to a control condition, allowing for a strong signal to develop over the course of the block. In contrast, in event-related designs, the hemodynamic response function (HRF) is determined for individual trials, allowing for the comparison of trials within blocks as well as the possibility to exclude error trials (Friston, et al., 1998). In both kinds of design, two conditions can then be contrasted using the subtraction logic, leaving only the part of the signal which reflects neural activity going back to the effect of the one component in which the two conditions differ.

For a detailed introduction and overview of the fMRI method, see Huettel, Song and McCarthy (2004).

4.1 Methods

4.1.1 Participants

Sixteen healthy right-handed volunteers participated in the study (8 female, mean age 23.8 years, range 21 - 29 years). All had normal or corrected-to-normal vision and no history of psychiatric or neurological diseases. Informed consent was obtained according to a protocol approved by the local ethics committee.

4.1.2 Experimental Paradigm

Prospective Memory Experiment

As in Experiment 1, participants performed a 2-back version of the n-back task as ongoing task (cf. Fig. 3.1).

Stimuli were presented in blocks of forty trials and consisted of 20 consonants of the alphabet, presented in white uppercase letters at the center of the screen against a black background. A colored (i.e., gray, light green, or dark green) rectangle framing the letter stimuli informed the participants of the magnitude of the potential reward associated with correct responses to the PM cues (i.e., no, low, or high reward). For half of the participants, high reward was associated with the dark green, for the other half, with the light green color. This frame remained on the screen throughout each entire block. Each letter stimulus was presented for 500 ms and followed by a blank screen for 500 ms, amounting to 1000 ms of trial time. Participants were instructed to indicate during this time whether the letter they were seeing matched the stimulus presented two letters before (2-back target) or not (2-back non-target) or if it was identical to the prospective memory cue (PM) by pressing one of three keys on a response box. Each trial was followed by a variable inter-trial interval of 1, 3, or 5 s (occurring with a frequency of ~60, ~30, and ~10%, respectively, for each trial type). During this time, a small white square serving as fixation point was displayed at the center of the colored frame. PM cues varied between blocks and were specified at the beginning of each block, by displaying the letter that served as the PM cue for the following block and the associated reward (i.e., 15 points for low, 75 points for high reward; 1 point = 1 cent, max. 36 Euro) in the center of the colored frame for 4 s. This instruction screen was followed by the presentation of the white square for another 4s, before the first trial began.

Overall, there were five blocks of each of the following five conditions: PM execution-high (containing high rewarded PM cues), PM execution-low (containing low rewarded PM cues), PM expectation-high (expectation of high rewarded PM cues, but they do not occur), PM expectation-low (expectation of low rewarded PM cues, but they do not occur), and ongoing/baseline (no PM expectation, no reward), presented in random sequence. In the ongoing/baseline condition, participants were instructed by the word “2-back” along with a zero indicating that they could not score any points during the following block. Both execution and expectation conditions were cued with a prospective stimulus and the respective reward information, but only in the two execution conditions did the PM stimuli actually occur. To prevent participants from ignoring the ongoing task in those conditions, participants were informed that they had to achieve at least 60% correct responses in the ongoing task in order to obtain the money they earned for correctly responding to the PM stimuli. In order to familiarize participants with the task, each participant completed 4 practice blocks outside, and 3 practice blocks inside of the scanner, during the acquisition of the anatomical scans.

As in experiment 1, participants received a two-step feedback at the end of each block, indicating their performance in the PM and ongoing task as well as the total cumulative score (cf. Fig. 3.1). We collected five runs for each participant, including five blocks of each of the five conditions with a different block sequence for each participant. Each run lasted approximately 10 minutes.

Altogether, there were 40 PM cue trials in the execution-high and 40 PM cue trials in the execution-low condition. The number of PM cues in each block varied between 4 and 12. In addition, each execution condition included 160 ongoing trials (40 2-back targets and 120 2-back non-targets), resulting in a PM/ongoing trial ratio of 25%. The expectation and the ongoing/baseline conditions comprised 150 2-back non-target and 50 2-back target trials to assure that the target/non-target ratio was the same in all conditions (~33%). The number of 2-back target trials per block varied between 6 and 10 in the execution and between 8 and 12 in the expectation and ongoing-baseline conditions.

Monetary Incentive Delay (MID) Localizer Task

In a separate scanning session, participants took part in a slightly modified version of the monetary incentive delay (MID) task (Knutson, et al., 2001a; Knutson, et al., 2001b)

that served as a localizer task to independently identify regions associated with the anticipation of reward, such as the ventral striatum (nucleus accumbens) and brainstem dopaminergic nuclei (ventral tegmental area (VTA), substantia nigra). During each of 60 trials, participants were shown one of two cue shapes (250 ms) signaling a potentially high rewarding outcome (20 cents; 30 trials) or no monetary outcome (30 trials), followed by a delay interval in which they fixated on a crosshair. The duration of this delay interval varied between 2000 and 2500 ms (Knutson, et al., 2001a; Knutson, et al., 2001b). Participants then responded to a solid white target square with either the middle or right forefinger (the correct response was indicated by the cue). Feedback (1500 ms) informed participants whether or not they responded fast enough to receive the expected reward. Information about the magnitude of the anticipated reward was additionally present one second prior to the onset of the cue shapes and throughout the trial, signaled by a dark (high reward) or light gray (no reward) frame surrounding the stimuli.

An individual response time criterion was set on the basis of each participant's response times to ensure that participants would succeed on ~80% of the trials. Each participant completed 14 of these individually adjusted trials as practice (based on 14 criterion trials) outside of the scanner. Inside the scanner, a new criterion based on 40 trials completed during the acquisition of the anatomical scans was set before the experiment began.

In the localizer experiment, participants made fewer errors when they anticipated a high reward (7,7% ± 5,3%, mean ± SD) compared to no reward (19% ± 14,6%), [$F(1,15) = 8.61$; $p = .01$] and responded more quickly when they expected a high (228 ± 19 ms), compared to no monetary reward (232 ± 19ms), [$F(1,15) = 5.8$; $p = .029$]. Brain activations (see below for methods) showed that high reward anticipation activated foci in the reward system, notably in one midbrain cluster and in the basal ganglia, including the right caudate nucleus (head and body) along with the putamen bilaterally (Table 4.1). These clusters were used for ROI analyses (see below). Additionally, in line with earlier reports (Knutson, Taylor, Kaufman, Peterson, & Glover, 2005), activation in the anterior cingulate cortex and in premotor areas (BA 6) was observed.

Table 4.1: MNI coordinates and anatomical location of the peak activations for the regions of interest in the midbrain and basal ganglia as determined from the reward anticipation localizer task.

Brain region	Hemi.	Peak voxel (in mm)			t-value	cluster size
		x	y	z		
Midbrain						
Midbrain	R	10	-20	-6	5.85	815
Basal Ganglia						
Caudate nucleus (head)	R	16	16	-10	6.03	587
Putamen	L	-26	0	14	5.09	454
Putamen	R	18	14	-8	6.30	747

4.1.3 Questionnaires

Individual differences in the sensitivity of the behavioral approach (BAS) and behavioral inhibition (BIS) systems (Gray, 1970, 1990) were assessed using the BIS/BAS scales (Carver & White, 1994; German version by Strobel, et al., 2001). For correlation analyses, parameter estimates were extracted from the activated brain regions and correlated with the BIS/BAS scores with a standard statistical package (PASW 18.0).

4.1.4 Analysis of Behavioral Data

Reaction times were measured from the onset of the stimulus to the onset of the participant's reaction. Trials with incorrect or missing responses were excluded from the analysis of reaction times (and from fMRI analysis). Reaction times and percentages of correct responses were aggregated by participant and condition. For both reaction times and percentage correct responses, we conducted repeated-measures analyses of variance with the factors condition (5 levels) and trial-type (2 levels), treating each experimental condition as a level of the factor 'condition'. We then performed post-hoc comparisons

(using the Bonferroni correction as implemented in the PASW software package) between the different conditions. In the MID localizer task, reaction times were measured from the onset of the target stimulus until the onset of the participant's response. Trials with incorrect or missing responses were excluded from the analysis of reaction times (and fMRI analysis). We conducted a repeated-measures ANOVA with the factor reward (2 levels: high, no) for the percentage of correct responses and reaction times.

4.1.5 fMRI Data Acquisition and Analysis

Hemodynamic responses were measured using a Siemens Trio 3T Scanner with a standard circularly polarized head coil. Foam cushions were used to minimize head movement. 32 oblique axial slices (3 mm thickness, 1mm gap) were acquired using a T2*-weighted BOLD-sensitive gradient echo, echo planar imaging (EPI) sequence (TR = 2000 ms, TE = 30 ms, FOV = 192 mm, flip angle = 80°, in-plane resolution = 3 x 3 mm). The first 4 images of each run were discarded to allow for stable magnetization. For coregistration, a T1 anatomical scan with the same slice prescription as the functional images was acquired. A high-resolution, structural T1-weighted MP-Rage scan was acquired after the functional scans.

All analyses were carried out with the Statistical Parametric Mapping software package (SPM5, Wellcome Department of Cognitive Neurology, London). First, each participant's functional data set was slice-time and then motion-corrected. Data were spatially normalized into standard MNI atlas space (MNI 152), which involved also a resampling to voxel size 2 x 2 x 2 mm. Data were spatially smoothed with an 8 mm full-width-half-maximum (FWHW) Gaussian kernel. In the case of the event-related model, a high-pass filter of 1/128 Hz was used to remove low-frequency noise, and an AR(1) + white noise model corrected for temporal autocorrelation. For the block analysis, we used a high-pass filter of 1/192 Hz and did not correct for temporal autocorrelations.

Random effects statistical analysis was undertaken twice, once using a block design to estimate sustained effects due to reward anticipation and the maintenance of the PM intention, and once using an event-related design to separately investigate the effects associated with the detection of the PM cues and with the processing of ongoing non-target and target trials. In the case of the blocked analysis, blocks lasted from the onset of the first trial until the end of the last trial of the block. Blocks of all conditions were

modeled by convolving a boxcar function that had a specific onset and duration with a canonical hemodynamic response function. Instruction and feedback trials were modeled as regressors of no interest for each run. For the event-related analysis, separate regressors were introduced for the three different trial types (ongoing: 2-back non-targets; ongoing: 2-back targets; PM cue trials) in each condition. Additionally, separate regressors coded for missed PM cue trials and for incorrect ongoing trials. Again, instruction and feedback trials were modeled as two additional regressors.

For the analysis of the MID localizer task, we modeled the anticipation phase as the delay interval from the onset of the reward frame for the duration of the fixation cross in that particular trial, implementing one regressor for correct responses yielding a high monetary reward, and one regressor for correct responses with no monetary outcome. We included one regressor each for errors and missing responses, as well as two regressors coding for feedback: one for correct responses and one for incorrect responses.

For both the MID and PM task, subject-specific estimates for the contrasts of interest were obtained using linear contrasts across sessions. These estimates were entered into the second stage of analysis treating subjects as random effects, using a one-sample t-test across subjects. Statistical parametric maps of the contrasts of interest were constructed.

For ROI analyses explicitly testing the involvement of reward related brain regions, we used the midbrain and basal ganglia clusters identified in the MID localizer task. As the above described statistical thresholding procedure resulted in large subcortical clusters in the localizer task that extended beyond the midbrain, we derived our functional ROIs by combining an anatomical mask of the midbrain as defined by the Talairach Daemon Labels Masks (WFU pickatlas; Lancaster, Summerln, Rainey, Freitas, & Fox, 1997; Lancaster, et al., 2000; Maldjian, Laurienti, Kraft, & Burdette, 2003) with the clusters from the MID localizer task, using a logical ‘AND’ operation. In the same vein, separate anatomical masks of the caudate nucleus as well as the putamen as defined by the Automated Anatomical Labeling (AAL) masks (Tzourio-Mazoyer, et al., 2002) were combined with the respective clusters from the MID localizer task.

Additionally, we used the activation clusters found in the frontopolar cortex (cf. Fig. 2, Table 4.4) in the PM vs. ongoing contrast as functionally defined regions of interest to assess reward modulation of this region by comparing high and low rewarded PM

cues. Functional activation was restricted by a structural mask of BA 10 (taken from the same set as the midbrain mask) which was dilated in 3-dimensional space by a factor of 1 voxel in order to ensure complete masking of frontopolar gyri.

To protect against false positive activations, we used a double-threshold approach that involves combining a voxel-based threshold with a minimum cluster size (Forman, et al., 1995). This nonarbitrary cluster size was determined on the basis of Monte Carlo simulation (1000 iterations) determined with AFNI's AlphaSim tool (Ward, 2000; http://afni.nimh.nih.gov/afni). For all four ROIs, we determined the minimal cluster size for an individual voxel height threshold of $T > 2.95$ ($p < 0.005$, uncorrected) to ensure an overall image-wise false positive rate of 5%. This resulted in the following cluster size thresholds: midbrain: 15, caudate: 16, putamen: 19, frontpolar cortex: 18.

An additional Monte Carlo simulation (1000 iterations) was conducted to determine cluster size thresholds for whole brain analyses. This yielded a cluster size of 145 voxels. Activations exceeding this threshold are considered to be activated at an experiment-wise threshold of $p < .05$, corrected for multiple comparisons.

Subsequent psychophysiological interaction analyses (PPI; Friston, et al., 1997) were conducted to determine if functional connectivities between brain regions were modulated by reward magnitude. We used the result of the ROI analysis in the midbrain for the block high vs. low reward contrast as a seed region (cf. Results). For the PPI analysis, a novel GLM was set up that encompassed three regressors, i.e., the time series (averaged across all active voxels) from the seed region as a physiological predictor, the block high vs. low reward contrast as psychological predictor, as well as the interaction of these two variables which served as the psychophysiological interaction term. The second-level random effects analysis of the psychophysiological interaction term was thresholded at $p < 0.005$, $k = 145$.

4.2 Results

4.2.1 Behavioral Results

Participants' ongoing accuracy exceeded 60% at all times. Thus, all five blocks in each condition were included in the behavioral (and fMRI) analyses reported here.

Participants performed the ongoing 2-back task at a high level of accuracy, i.e., 94% (Table 4.2). A main effect of condition indicated that ongoing task performance differed

between the experimental conditions (i.e., high execution, low execution, high expectation, low expectation, and ongoing-baseline) [$F(4, 60) = 7.05$, $p < 0.001$]. Accuracy was lower on trials containing 2-back targets than on non-target trials [$F(1,15) = 35.9$; $p < 0.001$]. In addition, we found an interaction between condition and ongoing trial type [$F(4,60) = 6.6$; $p < 0.001$], indicating that the presence of a PM intention affected performance for the two types of ongoing trials, i.e., 2-back targets and 2-back non-targets, in a different manner. Accuracy for 2-back non-targets did not differ between conditions [all ps > 0.28], which was most probably due to a ceiling effect caused by non-targets being the most frequent trial type and thus maybe the default response. Accuracy on target trials was lower in the two PM execution conditions as compared to the ongoing condition [ps < 0.02]. Accuracy on target trials in the two PM expectation conditions did not differ significantly from either the two PM execution conditions or the ongoing condition [all ps > 0.09]. Reward magnitude (i.e., high vs. low) did not affect performance on the ongoing target trials.

Accuracy on PM trials was above chance for both levels of reward anticipation (note that this was the case for all but one subject who detected PM cues only in about 32.5% of trials in which they occurred), but slightly better for high (mean [m] = 82.9%) compared to low (m = 79.8%) reward. However, a paired t-test comparing accuracy for high and low rewarded PM trials did not yield a significant result [$t(15) = 1.17$; $p = 0.261$].

Reaction times for the ongoing trials differed with respect to the factors condition [$F(4,60) = 19.72$; $p < 0.001$] and ongoing trial type [$F(1,15) = 7.45$; $p = 0.015$)], but no interaction of the two factors [$F(4,60) = 0.95$; $p = 0.423$] was observed. Thus, we used pairwise comparisons for the levels of the condition factor collapsed across targets and non-targets. We found a prospective interference effect for all PM conditions: reaction times to the ongoing trials were longer for all conditions in which PM cues could potentially occur (i.e., both execution and expectation conditions), compared to the ongoing/baseline condition [all ps < 0.003]. However, neither for non-targets nor for targets was this interference effect modulated by the magnitude of PM-cue associated reward [all ps > 0.15].

There was no significant difference in reaction times between PM execution and PM expectation conditions [all ps > 0.9]. A paired t-test comparing reaction times for high and low rewarded PM cues was marginally significant: participants responded faster to

PM cues that were associated with a high (m = 585 ms) compared to a low expected reward (m = 600 ms), [t(15) = -2.11; p = 0.053; cf. Table 4.2].

In sum, both accuracy and response times of the ongoing task reflected increased processing demands in the PM conditions, but there was no modulation of ongoing processing by the magnitude of the expected reward. A reward magnitude effect was, however, observable on the response times to the PM cues.

Table 4.2: Mean reaction times (ms) and accuracy (% correct) for ongoing trials (non-targets and targets) in all conditions and for PM cues in the execution conditions. Standard error of the mean is given in parentheses.

		Non-targets	Targets	PM cues
Execution				
high	RT *(SE)*	571.88 *(18.86)*	607.5 *(22.89)*	584.94 *(18.91)*
	Acc (*SE)*	94.98 *(.79)*	70.94 *(4.38)*	82.97 *(4.09)*
low		573.5 *(17.69)*	611.56 *(23.73)*	599.63 *(15.12)*
		95.2 *(.76)*	71.41 *(3.63)*	79.84 *(3.84)*
Expectation				
high		577.69 *(20.2)*	602.63 *(26.9)*	-
		94.26 *(.64)*	77.36 *(4.17)*	
low		569.88 *(20.01)*	596.38 *(26.21)*	-
		95.09 *(.51)*	76.74 *(3.73)*	
Ongoing/baseline		524.5 *(13.49)*	552.87 *(20.63)*	-
		96.41 *(.47)*	82.18 *(2.59)*	

4.2.2 fMRI Results

In a first step aiming at replicating previous findings, we examined whether or not the PM network reported in earlier studies would be responsive to the occurrence of PM cues, irrespective of the level of reward anticipation. To this end, we conducted an event-related analysis, contrasting activation for PM trials (collapsed across both execution conditions, i.e., high and low reward) with non-target and target trials from the same conditions. We found left lateral BA 10 activation extending from the frontopolar cortex dorsally into the superior frontal gyrus, and slightly less extended activation in the right superior frontal gyrus, for PM trials relative to ongoing trials. Additionally, we found activation in the medial portion of the right superior frontal gyrus, extending into the anterior cingulate cortex (BA 32) (Fig. 4.1, Table 4.3).

Table 4.3: MNI coordinates and anatomical location of the peak activations for the contrast between PM cue trials (high + low reward) and ongoing trials (high + low reward).

Brain region	Hemi.	Peak voxel (in mm)			t-value	cluster size
		x	y	z		
Frontal						
Superior Frontal Gyrus, Frontal Pole (BA 10/11)	L	-44	48	-12	8.37	637
Parietal						
Precuneus (BA 7)	L	-2	-72	44	6.99	14512
Postcentral Gyrus (BA1)	L	-52	-20	22	5.07	171
Inferior Parietal Lobe (BA 40)	R	46	-66	48	6.87	822
Temporal						
Middle Temporal Gyrus (BA 21)	R	68	-48	-2	7.46	835
Middle Temporal Gyrus (BA 21)	L	-62	-46	-12	6.31	383
Fusiform Gyrus (BA37)	L	-52	-60	-18	4.77	260
Other						
Cerebellum	L	-48	-72	-30	4.35	436
Cerebellum	R	24	-42	-44	5.66	204

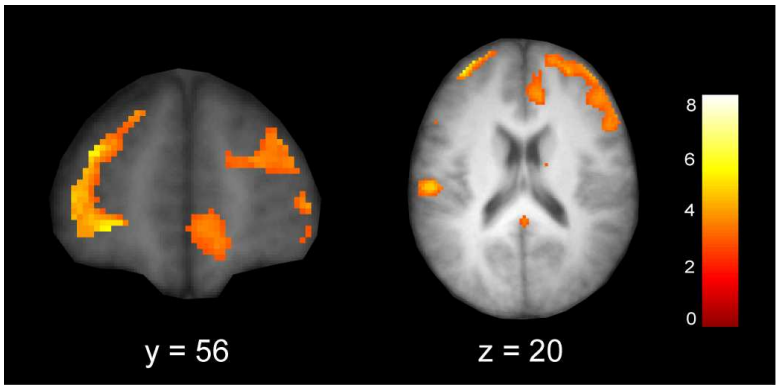

Figure 4.1: Group functional activation maps, overlaid on the average of the normalized structural images of the study participants. Activation in lateral BA 10 in the contrast of prospective memory versus ongoing (2-back non-target and target) trials, irrespective of reward magnitude (i.e., collapsed across high and low reward). Images are thresholded at $p < .005$, $k > 145$.

We did not find activation of BA 10 on the whole brain level when we compared non-target and target trials from the expectation conditions with those from the ongoing/baseline condition. We thus constrained our following analyses on the two execution conditions, in which PM cues actually occurred.

As our primary interest lies in the effects of the magnitude of anticipated reward on PM, we next conducted a block analysis, contrasting the execution-high and the execution-low conditions, which differed only in the amount of reward that participants received when they correctly responded to the PM cues. While this analysis produced no clear effects at the whole-brain level, we observed reward modulation of brain activations during PM execution when testing midbrain and basal ganglia regions of interest (ROI) derived from the localizer task (see Methods). This analysis revealed that voxels in the left midbrain (x = -6; y = -16; z = -12; $T = 4.93$; $k = 29$), most probably incorporating dopaminergic brainstem nuclei, as well as in the right putamen (x = 30; y = 6; z = -4; $T = 2.81$; $k = 22$) were more active for high reward as compared to low reward PM execution (Fig. 4.2 a), b), c)). Interestingly, we also observed that fMRI activation in this midbrain region for high reward PM cues was correlated positively across participants with the self-reported positive affect towards reward, as reflected in the BAS reward responsiveness subscale [$r = .50$, $p = 0.049$], (Fig. 4.2 d)). No such correlation was observed between activation in this region for low reward PM cues and

BAS reward responsiveness scores [p > 0.91]. No reward modulation was found in the frontopolar cortex.

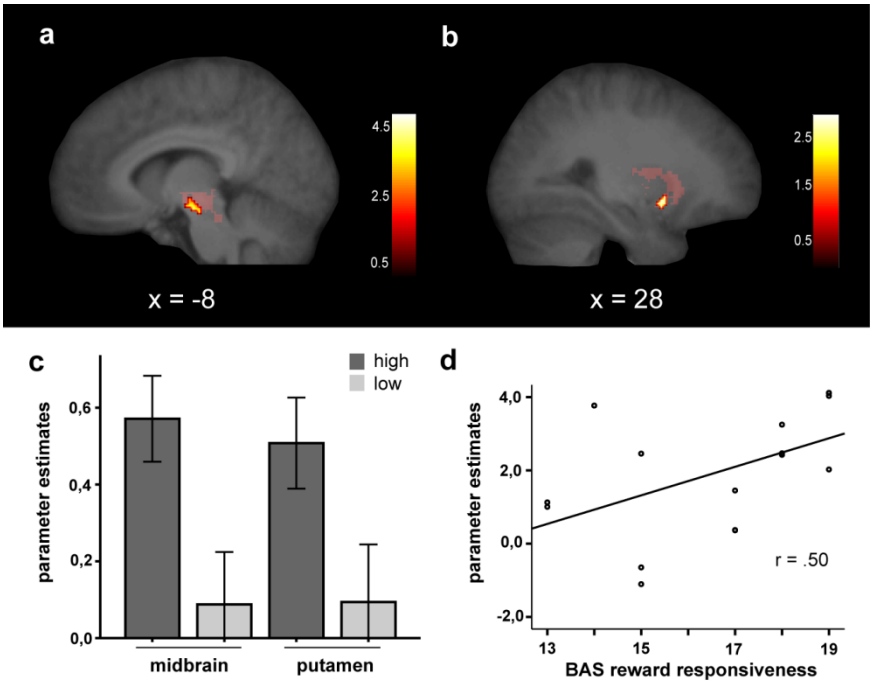

Figure 4.2: Activation in the midbrain (a) and in the right putamen (b) for the effect of reward magnitude across blocks in the ROIs determined from the reward anticipation localizer task. Group functional activation maps are overlaid on the shapes of the ROIs depicted in red. Parameter estimates for activation at the peak voxels in the midbrain (left) and putamen (right) are shown in (c). Error bars denote the standard errors. Midbrain activation for high reward PM cue trials correlated with scores on the BAS reward responsiveness scale (d).

While this initial analysis indeed suggests a modulation of PM by reward, it does not allow us to more specifically isolate possible effects of reward expectation on the retrieval of the prospective intention (during PM cue trials). We therefore next investigated, in the PM execution conditions, whether or not the level of prospective reward differentially modulated the processing of PM cues.

We directly contrasted activity in the midbrain, striatum and frontopolar ROIs for PM cue trials. We did not observe an effect of reward in the midbrain ROI for PM cue trials. There was no significant effect of reward magnitude on BOLD signals in the striatum and frontopolar ROIs. Rather, we observed activation for both high and low

rewarded PM cues compared to the respective ongoing trials (Table 4.4).

Table 4.4: MNI coordinates and anatomical location of the peak activations for the contrast between high and low PM cue trials and the respective ongoing trials in the regions of interest in the frontopolar, midbrain and basal ganglia ROIs.

		Peak voxel (in mm)				
Brain region	**Hemi.**	**x**	**y**	**z**	**t-value**	**cluster size**
		High reward				
Frontal						
Frontopolar Cortex (BA 10)	L	-38	50	20	6.04	83
Frontopolar Cortex (BA 10)	L	-30	52	-2	4.7	57
Superior Frontal Gyrus (BA 10 / 46)	R	48	42	22	3.98	54
Medial Frontal Gyrus (BA 10)	R	8	58	0	3.49	46
Midbrain						
Midbrain	R	2	-14	-10	4.46	53
		Low reward				
Frontal						
Medial Frontal Gyrus	R	6	40	-12	3.84	46
Middle Frontal Gyrus (BA 10)	R	44	50	16	5.01	166
Basal ganglia						
Putamen	R	20	16	-8	4.06	45

We had hypothesized that frontopolar cortex might be involved in integrating reward-related information with the cognitive processes underlying PM. However, given that the results reported thus far provided no evidence that the frontopolar cortex codes directly for the magnitude of reward associated with the PM cues, we used

functional connectivity analyses to explore whether or not the information about the reward magnitude encoded by the midbrain would be reflected in the coupling between reward-related midbrain regions and frontopolar cortex. To explore the functional connectivity pattern of the midbrain, we applied a psychophysiological interaction analysis (PPI; Friston, et al., 1997) to the block high vs. low reward contrast. The physiological predictor was the time series from the seed region, i.e., the midbrain activation cluster that responded stronger to high than to low reward on the block level. It was modulated by the contrast between high and low reward blocks (i.e., psychological predictor). The individual difference between accuracy on high and low reward trials was entered as a covariate on the second level of the ppi analysis.

Analysis of the psychophysiological interaction term, which reflects the reward related change in functional coupling with the midbrain seed region, revealed a positive effect in the left frontopolar cortex, extending into the left inferior frontal gyrus (x = 52, y = 36, z = 6; T = 5.38; k = 316) (Fig. 4.3).

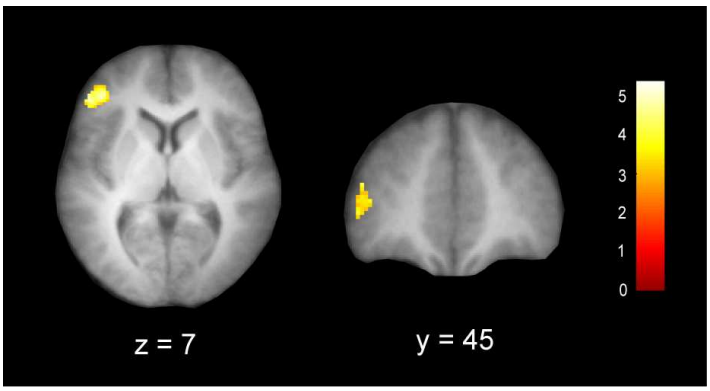

Figure 4.3: Psychophysiological interactions of the midbrain for the high vs. low reward block contrast. Midbrain regions showed an increased coupling with anterior prefrontal cortex for high reward. Images are thresholded at $p < 0.005$, $k > 145$.

4.3 Discussion

In this study, we investigated the effects of reward anticipation on the maintenance of prospective intentions. As mentioned before, some studies have used monetary reward to emphasize the importance of the prospective intention (Burgess, et al., 2001; Burgess, et al., 2003). However, the effect of reward anticipation has not yet been investigated

systematically in the context of PM. Here, we varied the magnitude of the reward that participants received for correct responses to prospective cues implemented in an ongoing 2-back task. Thus, prospective intentions were either associated with a high or low reward anticipation.

We replicated previous studies by showing prospective interference at the behavioral level, and by showing that PM is associated with the activation of frontopolar BA 10 bilaterally. Moreover, we observed a modulation of reward-related brain regions by the magnitude of reward expectancies during PM, with high reward expectancies giving rise to activation in midbrain and striatum. The strength of the midbrain activity during PM was dependent on trait-level reward sensitivity. Finally, a psychophysiological interaction analysis demonstrated that functional connectivity between midbrain and frontopolar cortex was modulated by reward magnitude and reward-related effects on behavior.

4.3.1 The Role of the Frontopolar Cortex in Prospective Memory

Replicating earlier studies (Burgess, et al., 2001; Okuda, et al., 2003; Okuda, et al., 1998; Simons, et al., 2006), we found an increase in the BOLD signal in the frontopolar region of the prefrontal cortex for prospective memory. More specifically, we observed this activation to be specific for PM cues, in contrast to ongoing trials. Thus, the present results suggest that sustained frontopolar activation reported in earlier studies might to a large part be due to activity in response to the occurrence of prospective memory cues. While the present results do not argue against a role of frontopolar cortex for the maintenance of the PM intention as such, our results suggest that the detection of PM cues gives rise to additional processing that exceeds sustained activation elicited by the maintenance of the prospective intention.

Studies using event-related potentials (ERPs) have associated the detection of PM cues with the N300, a phasic negativity at 300 ms after stimulus onset that is greatest in amplitude over the parietal-occipital region of the scalp (West, et al., 2006; West, Wymbs, Jakubek, & Herndon, 2003). Moreover, PM cue trials have been associated with a frontal positive slow wave differentiating PM hit trials from PM miss trials. In these studies, ‘realized intention formation trials’ – i.e., specific trials preceding the PM cues that indicate the intention to be performed and that were later followed by a correct response to the respective PM cue trial - have been associated with a greater negative

frontal slow wave than unrealized intention formation trials (West & Ross-Munroe, 2002). The positive frontal slow wave has been suggested to reflect the activity of a neural system supporting disengagement from ongoing activity, whereas the negative frontal slow wave has been taken to reflect processes supporting intention encoding that facilitates the detection of the PM cue when it is later encountered (West & Ross-Munroe, 2002). Although these electrophysiological results cannot be directly compared to our data, they suggest that mechanisms supporting the processing of PM cues can be reflected in transient activation over frontopolar brain regions, which provides a possible link to the PM trial specific frontopolar activation observed in the present study.

The activation in anterior prefrontal cortex found in our study can be placed in a broader framework based on more general functions of anterior prefrontal cortex. This area has been found to be active in a variety of complex cognitive tasks involving long-term memory retrieval (McDermott, Jones, Petersen, Lageman, & Roediger, 2000; Rugg, Henson, & Robb, 2003; Velanova, et al., 2003), subgoal processing and cognitive branching (Braver & Bongiolatti, 2002; Koechlin, et al., 1999), relational integration (Christoff, et al., 2001; Raposo, Vicens, Clithero, Dobbins, & Huettel, 2010), mentalizing (Kelley, et al., 2002), and the evaluation of internally generated information (Christoff & Gabrieli, 2000; Christoff, Ream, Geddes, & Gabrieli, 2003). A common theoretical framework has been proposed that describes anterior prefrontal cortex to be involved when the results of two or more cognitive operations have to be integrated to achieve a more general behavioral goal (Ramnani & Owen, 2004). Furthermore, the “gateway theory” accounts for differential activation of lateral and medial parts of the anterior prefrontal cortex by linking it to stimulus-independent and stimulus-oriented processing, respectively (Burgess, et al., 2007a; Burgess, et al., 2008; Burgess, et al., 2007b; Simons, et al., 2006). Gilbert, Frith, and Burgess (2005) compared phases of stimulus-oriented thought with phases relying on stimulus-independent thought and reported transient activation of lateral rostral prefrontal cortex associated with the switching between the two forms of trials. The finding of lateral BA 10 activation for PM cues in the present study can be interpreted in the same vein: on PM cue trials, participants had to switch from the processing of the ongoing task to retrieving the prospective intention from memory. Thus, it is possible that activation on PM cue trials reflects the neural mechanisms associated with coordinating the switch between the

mostly externally-determined ongoing task and the internally guided retrieval of the prospective intention.

Consistent with this interpretation, we did not find evidence for the activation of BA 10 during PM expectation blocks, in which no PM cues actually occurred. Although PM cue trials were randomly distributed throughout the execution blocks, we cannot fully rule out the possibility that the lack of lateral rostral PFC activation was caused by participants becoming aware that a certain block of trials would not contain PM cue trials. However, this account is unlikely given that prospective interference effects were obtained behaviorally in the two expectation conditions, which indicates according to the generally accepted line of reasoning that a PM intention was maintained in these experimental blocks. Yet, it is possible that, as participants prepared to, but did not actually have to switch between the PM and the ongoing task, monitoring processes declined over time, especially given the length of the blocks (~2 min).

4.3.2 Reward Modulation of Prospective Memory

Concerning the hypothesized modulation of PM by reward expectations, we observed an increase in midbrain activation and activation in the putamen for PM associated with high, as compared to low reward. We did not observe a modulation of BA 10 activation by reward magnitude. However, we found a reward-related coupling between midbrain and anterior prefrontal cortex, as reflected in the observation of increased functional connectivity for high as compared to low reward. These results indicate that PM is not a purely cognitive phenomenon, but that motivational components of behavior can also be part of the PM system.

The behavioral data showed an effect of reward magnitude on the processing of PM cue trials, rather than on the ongoing task: participants responded faster to high reward compared to low reward PM cues. We did not observe a modulation of the prospective interference effect or the accuracy on ongoing trials by anticipated reward magnitude. However, concerning ongoing accuracy data, it needs to be stated that the prospective interference effect is usually observed in reaction times while leaving performance accuracy of the ongoing task relatively unaffected (Einstein, et al., 2005; Loft, et al., 2008; Marsh, et al., 2003). Moreover, accuracy on PM cue trials did not differ in terms of reward magnitude, suggesting that participants were motivated to a similar extent by high and low rewards, presumably eliciting comparable interference effects in the

ongoing task. Thus, it cannot be fully resolved if the accuracy pattern found in the present data represents an insensitivity to reward magnitude in particular, or if accuracy on the ongoing task is generally unaffected by PM cue characteristics.

Supporting the conclusion that motivational processes play a role in PM, we found that individual levels of reward sensitivity (as measured using the BAS reward responsiveness self report scales) correlated with activation in midbrain areas for high rewarded PM cue trials.

Activation in dopaminergic midbrain areas, including the ventral tegmental area and the nucleus accumbens in the ventral striatum, have been previously associated with reward anticipation in tasks involving monetary rewards (Adcock, et al., 2006; D'Ardenne, et al., 2008; Schultz, 2006; Simon, et al., 2010; Wittmann, et al., 2005). Furthermore, reward-related activity in the midbrain and ventral striatum has been shown to be related to individual differences in reward responsiveness and approach motivation, most precisely BAS (Simon, et al., 2010), BAS reward responsiveness (Han, et al., 2010), and reward dependence as assessed with Cloninger's Temperament and Character Inventory (Krebs, et al., 2009a). Like the ventral striatum, the dorsal striatum has been shown to be activated during the anticipation of primary or secondary rewards (Knutson, et al., 2001a; O'Doherty, et al., 2002).

Some studies have reported activation in BA 10 to be sensitive to monetary rewards and have accordingly proposed a role for this region in the monitoring of reward values (Pochon, et al., 2002; Ramnani & Miall, 2003). However, recent findings have suggested that the frontopolar cortex seems to be generally insensitive to absolute reward magnitude or to individual differences in reward responsiveness (Han, et al., 2010), but rather responds to the coordination of two concurrent goals and their respective reward representations (Charron & Koechlin, 2010).

In line with these findings, we did not find a direct modulation of frontopolar activity by reward magnitude. Our functional connectivity analysis, however, revealed that increasing reward led to an increased coupling of the lateral frontopolar cortex with midbrain dopaminergic regions during PM, which was stronger for individuals showing a larger reward-related modulation of behavior. On the basis of these findings, we propose that, in the case of rewarded PM intentions, the frontopolar cortex has a general monitoring function, assuring that goals are met by maintaining delayed intentions. In addition, information about the value of these goals are relayed from dopaminergic

midbrain areas, which show an increase in connectivity to the frontopolar cortex when a high reward brings about a change in behavior.

In summary, our results confirm the role of the frontopolar cortex (BA 10) in the maintenance of prospective intentions and show that reward-related brain regions are sensitive to the magnitude of the expected reward conveyed by the prospective cues. In addition, we show that reward-related midbrain activity for PM cues varies with individual responsiveness to reward. Moreover, we report an increased functional coupling of the midbrain and frontopolar cortex under high reward PM context, which depends on reward modulations in PM performance.

Thus, our findings support the conclusion that processes assessing the motivational value of a prospective intention are involved in its maintenance and realization.

5 Experiment 3

Experiment 3 was designed to investigate potential differences in PM due to different kinds of incentive motivation. In experiment 2, we had varied the magnitude of monetary reward to elicit reward-related brain activation in the context of PM. However, in real-life PM situations, prospective intentions are not only used to achieve positive outcomes, but we also often try to avoid negative outcomes (e.g., although it might be highly unpleasant to remember to attend a dentist’s appointment, we have to do so in order to avoid even more unpleasant consequences). Thus, the anticipation of a reward and the opportunity to avoid losses are both directed at obtaining a positive outcome and might rely on partly overlapping motivational neural systems. Indeed, it has been reported that relief from pain is associated with neural activity in the midbrain and the amygdala, reflecting reward-learning signals (Seymour, et al., 2005). Moreover, Kim et al. (2006) could show that avoiding an aversive monetary outcome recruited the medial OFC, a region previously implicated in the evaluation of monetary reward, suggesting that the successful avoidance of a negative outcome is associated with positive affective valence and thus potentially represents an intrinsic reward signal.

Thus, experiment 3 was designed to extend findings from experiment 2 and to compare the effects of reward and loss avoidance in a PM context. Specifically, we set out to investigate if the kind of incentive motivation (reward or loss avoidance) associated with the PM intention would differentially affect PM related neural activity,

suggesting an interaction between the cognitive processes mediating PM and the motivational processes associated with the anticipation of a potential reward or with the avoidance of a loss.

As in experiment 1 and 2, we combined a PM paradigm with varying monetary incentives. In the reward conditions, the PM cues were associated with either a high or low monetary reward. In the loss conditions, PM cues were associated with the possibility to avoid or reduce a monetary loss.

We set out to investigate three issues: First, we were interested if activation and deactivation of the frontopolar cortex would be sensitive to the motivational context associated with the PM cue. Moreover, we investigated if brain regions usually responding to anticipated rewards and losses such as dopaminergic midbrain regions, the ventral striatum, and the amygdala, would encode information about reward and loss in the PM context. In particular, we were interested in the question if the anticipation of a higher positive net outcome would be associated with increasing activation in reward-related regions, compared to a lower net outcome and differences between anticipation of a reward and the avoidance of a loss of the same size. We further set out to examine differences due to the magnitude of the anticipated reward and loss.

Secondly, we were interested in the question if brain regions such as the ventral striatum would be responsive to both stimulus contingencies (i.e., the PM/ongoing distinction) and incentive motivation (i.e., reward/loss). As loss avoidance has been suggested to rely, at least in part, on the same systems that respond to the anticipation and evaluation of reward, we intended to examine if the neural pattern associated with the avoidance of loss PM cues would involve these reward systems. Moreover, we were interested in the question if the interaction between the PM status and the kind of incentive motivation would be reflected in the activation pattern in this system.

Third, we examined if neural reward and loss avoidance effects on PM were modulated by individual differences in reward-related personality traits as measured by the BIS/BAS.

5.1 Methods

5.1.1 Participants

Twenty healthy right-handed volunteers participated in the study. All had normal or

corrected-to-normal vision and no history of psychiatric or neurological diseases. Informed consent was obtained according to a protocol approved by the local ethics committee. Participants were paid 15 Euro for their time. In addition, they received the amount individually earned in the experiment (cf. 5.1.2 for details about the payout rules). One participant was excluded from the analysis due to excessive movement artifacts. Thus, all behavioral and fMRI analyses reported here include data from nineteen participants (9 female; mean age 22.5 years, range 20 - 28 years).

5.1.2 Experimental Paradigm

As in experiment 2, participants performed a 2-back version of the n-back task as the ongoing task (cf. Fig. 3.1). The basic experimental setup and trial timing were the same as in experiment 2 (see the description of the PM paradigm in section 4.1.2 for details).

The five following conditions were included here: PM high reward, PM low reward, PM loss reduction, PM loss avoidance and ongoing/baseline. Thus, the two expectation conditions in experiment 2 were replaced by the two PM loss conditions.

The payout rules were the following: in the PM conditions, participants could earn money or avoid losing money by correctly responding to the PM cues: in the high and low PM reward condition, participants earned 50 or 10 points, respectively, when they correctly responded to the PM cues. In these two conditions, they did not win (or lose) any points for missing PM cues. In the PM loss reduction condition, participants lost 10 points for every PM cue that appeared, but only if they responded correctly. If their response was incorrect, they lost 50 points. Thus, participants could reduce the potential loss by correctly responding to the PM cues (i.e., -10 instead of -50 points). In the PM loss avoidance condition, participants could avoid losing points altogether by correctly detecting the PM cues. However, as in the loss reduction condition, 50 points were subtracted from their score for each missed PM cue (i.e., 0 instead of -50 points). We chose to match the absolute amounts that participants expected to win or lose in order to be able to directly compare reward to loss avoidance trials (i.e., the expectation of an outcome of +50 points compared to the avoidance of a 50 point loss), rather than to adjust the relative outcome differences for correct and incorrect answers within each kind of incentive motivation. This was done because experiment 1 and 2 had shown that accuracy on the PM task was very high and PM miss responses could not be analyzed due to low trial numbers.

In order to prevent participants from ignoring the ongoing task in the presence of the more important PM cues, participants were informed that they always had to reach a criterion of at least 65% correct responses in the ongoing task for each block to be valid. Invalid blocks (i.e., accuracy on the ongoing task < 65%) resulted in the following payout changes: for each invalid block in the ongoing/baseline condition, 100 points were subtracted from the participant's total score. In the reward conditions, points earned in invalid blocks were not paid out (i.e., correct PM responses did not add to the total score). In the loss conditions, all PMs presented in invalid blocks were counted as errors (i.e., -50 points for every PM cue). For all participants, the start score was set to 3000 points to allow for subtraction of points in the loss conditions. Points were converted at a ratio of 1 point = 0.5 Cents, with a maximum gain of 25 Euros (i.e., 50 points = 25 Cents, 10 points = 5 Cents).

Information about the motivational incentive (i.e., the outcome for correct PM responses) was presented in the instruction at the beginning of each block (i.e., 50, 10, 0 or -10) along with the PM stimulus (in the case of the ongoing/baseline condition, the word “2-back” along with a zero indicated that no points could be scored). In addition, a colored (i.e., gray, light green, dark green, light purple, dark purple) rectangle framing the instruction informed the participants about the motivational context of the block. This frame remained on the screen throughout each entire block. Color mappings were counterbalanced across participants.

Overall, there were five blocks of each condition. Each of five scanner runs comprised five blocks (one of each condition) in random sequence. Participants completed 6 practice blocks consisting of 20 trials outside of the scanner (2 ongoing; one of each PM condition, comprising 3 PM cue trials each) and 4 practice blocks consisting of 40 trials inside the scanner (2 ongoing; 1 low reward, 1 loss avoidance, 6 PM cue trials each), during the acquisition of the anatomical scans.

There were 40 PM cue trials in each of the PM conditions. The number of PM cues in each block varied between 4 and 12. The PM conditions included 160 ongoing trials (40 2-back targets and 120 2-back non-targets), resulting in a PM/ongoing trial ratio of 25%. The ongoing/baseline condition comprised 150 2-back non-target and 50 2-back target trials to assure that the target/non-target ratio was the same in all conditions (~33%). The number of 2-back target trials per block varied between 6 and 10 in the PM and between 8 and 12 in the ongoing-baseline condition.

Again, participants received feedback at the end of each block in two steps: the number of detected PM cues was presented in relation to the total number of PM cues present in this block, together with their percentage of correct responses on the ongoing trials. Next, the number of points that participants had scored in the current block was displayed together with the total cumulative score at this point in time.

5.1.3 Questionnaires

Individual differences in the sensitivity of the behavioral approach and inhibition systems were assessed using the BIS/BAS scales (Carver & White, 1994; cf. section 3.1.3). For correlation analyses, parameter estimates were extracted from the activated brain regions and correlated with the BIS/BAS scores.

5.1.4 Analysis of Behavioral Data

Reaction times were measured from the onset of the stimulus to the onset of the participant's response. Trials with incorrect or missing responses were excluded from the analysis of reaction times (and from fMRI analysis). Reaction times and percentages of correct responses were aggregated by participant and condition. For both reaction times and percentage correct responses on ongoing trials, we conducted repeated-measures analyses of variance with the factors condition (5 levels) and trial-type (2 levels), treating each experimental condition as a level of the factor 'condition'. We then performed post-hoc comparisons (using the Bonferroni correction as implemented in the PASW software package) between the different conditions. For PM cue trials, we conducted repeated-measures analyses of variance with the factors 'motivation' (reward/avoidance) and 'magnitude' (high/low). Post-hoc comparisons were used to test for differences between the levels of each factor.

5.1.5 fMRI Data Acquisition and Analysis

Hemodynamic responses were measured using a Siemens TimTrio 3T Scanner with a 12-channel head coil. Foam cushions were used to minimize head movement. 32 oblique axial slices (3 mm thickness, 1mm gap) were acquired using a T2*-weighted BOLD-sensitive gradient echo, echo planar imaging (EPI) sequence (TR = 2000 ms, TE

= 30 ms, FOV = 192 mm, flip angle = 80°, in-plane resolution = 3 x 3 mm). The first 4 images of each run were discarded to allow for stable magnetization. For coregistration, a T1 anatomical scan with the same slice prescription as the functional images was acquired. A high-resolution, structural T1-weighted MP-Rage scan was acquired after the functional scans. One participant was excluded due to excessive head-movement, leaving 19 participants for the final analysis.

All analyses were carried out with the Statistical Parametric Mapping software package (SPM5, Wellcome Department of Cognitive Neurology, London). First, each participant's functional data set was slice-time and then motion-corrected. Data were spatially normalized into standard MNI atlas space (MNI 152), which involved also a resampling to voxel size 2 x 2 x 2 mm. Data were spatially smoothed with an 8 mm full-width-half-maximum (FWHW) Gaussian kernel. A high-pass filter of 1/192 Hz was used to remove low-frequency noise, and an AR(1) + white noise model corrected for temporal autocorrelation.

Random effects statistical analysis was undertaken using a mixed design to estimate sustained effects due to reward anticipation and the maintenance of the PM intention, and transient effects associated with the detection of the PM cues and with the processing of ongoing non-target and target trials.

Blocks lasted from the onset of the first trial until the end of the last trial of the block. Blocks of all conditions were modeled by convolving a boxcar function that had a specific onset and duration with a canonical hemodynamic response function. Instruction and feedback trials were modeled as regressors of no interest for each run. Transient effects were modeled using separate regressors for the three different trial types (ongoing: 2-back non-targets; ongoing: 2-back targets; PM cue trials) in each condition. Additionally, separate regressors coded for missed PM cue trials and for incorrect ongoing trials. Instruction and feedback trials were modeled as two additional regressors.

Subject-specific estimates for the contrasts of interest were obtained using linear contrasts across sessions. These estimates were entered into the second stage of analysis treating subjects as random effects, using a one-sample t-test across subjects. Statistical parametric maps of the contrasts of interest were constructed.

Anatomical masks taken from the same set as in experiment 2 were used for ROI analyses (the only difference being that here, the original anatomical masks were used

without constraining the search space by means of functional activation). More specifically, in order to test explicitly the involvement of reward related brain regions, we used anatomical masks of the midbrain, as defined by the Talairach Daemon Labels Masks (WFU pickatlas; Lancaster, et al., 1997; Lancaster, et al., 2000; Maldjian, et al., 2003). For an explorative analysis of the amygdala, an Automated Anatomical Labeling (AAL) mask from the same set was used (Tzourio-Mazoyer, et al., 2002).

Additionally, we constructed two functionally defined regions of interest in the frontopolar cortex to assess potential modulations of incentive motivation in this region. Functional activation was restricted by a structural mask of BA 10 (taken from the same set as the midbrain mask) which was dilated in 3-dimensional space by a factor of 1 voxel in order to ensure complete masking of frontopolar gyri. For block analyses, this resulted in four activation foci from the ongoing vs. PM block contrast which comprised medial parts of the frontopolar cortex, while the ROI that was defined by the PM cues vs. ongoing trials contrast included medial and lateral parts of the frontopolar cortex.

As our data did not allow for anatomical localization of the nucleus accumbens or the ventral striatum based on each individual's structural scan, we used an anatomical voxel mask retrieved from a publication-based probabilistic MNI atlas as a binary mask at the threshold of .50 to define the region of interest in the ventral striatum (Nielsen & Hansen, 2002, please refer to http://neuro.imm.dtu.dk/services/jerne/ninf/voi/index-alphabetic.html, access date June 2010).

To protect against false positive activations, we used a double-threshold approach that involves combining a voxel-based threshold with a minimum cluster size (Forman, et al., 1995). This nonarbitrary cluster size was determined on the basis of Monte Carlo simulation (1000 iterations) determined with AFNI's AlphaSim tool (Ward, 2000; http://afni.nimh.nih.gov/afni). For all five ROIs, we determined the minimal cluster size for an individual voxel height threshold of $T > 2.88$ ($p < 0.005$, uncorrected) to ensure an overall image-wise false positive rate of 5%. This resulted in the following cluster size thresholds: midbrain: 34; amygdala: 12; ventral striatum: 20; frontopolar (block): 21; frontopolar (event): 41. An additional Monte Carlo simulation (1,000 iterations) was conducted to determine cluster size thresholds for whole brain analyses. This yielded a cluster size of 148 voxels. Activations exceeding this threshold are considered to be activated at an experiment-wise threshold of $p < 0.05$, corrected for multiple comparisons.

The specific pattern of the effect of incentive motivation as well as the modulation of PM trial status by incentive motivation was examined by extracting mean parameter estimates from the beta images that were calculated during model estimation of the original general linear model, and by subjecting these to further analyses using standard statistical software (PASW 18.0).

5.2 Results

5.2.1 Behavioral Results

Participants' ongoing accuracy exceeded 65% at all times. Thus, all five blocks in each condition were included in the behavioral (and fMRI) analyses reported here.

As in experiments 1 and 2, participants' performance at the ongoing 2-back task was very high, i.e., 94% for non-targets and 72% for targets (Table 5.1). An interaction between the factors condition and trial type [$F(4,72) = 6.04$; $p < 0.001$] indicated that accuracy on targets vs. non-targets of the 2-back task was potentially affected differentially by the presence of a PM intention and the associated reward or loss.

Thus, we conducted separate analyses for non-targets and targets: for non-target trials, there was no effect of condition ($p > 0.786$). An effect of condition on target trials [$F(4,72) = 6.157$; $p < 0.001$] indicated that accuracy on target trials was lower in the low reward and both loss conditions compared to the ongoing/baseline condition (all ps < 0.028). Accuracy in the high reward condition did not differ from accuracy in the ongoing/baseline condition ($p = 0.314$). There was no significant difference in accuracy between any of the other conditions.

Accuracy on PM trials did not differ with respect to incentive (i.e., reward or loss) or magnitude (i.e., high or low).

For reaction times, an interaction between the factors condition and trial type [$F(4,72) = 5.69$; $p = 0.001$] indicated that the effect of trial-type was modulated by incentive condition. Again, we conducted separate analyses for non-target and target trials: we found a main effect for the factor condition on non-target trials [$F(4,72) = 25.6$; $p < 0.001$]. Pairwise comparisons revealed prospective interference effects (i.e., longer reaction times for the PM, compared to the ongoing/baseline condition) for all PM conditions (all ps < 0.001), but there was no difference between either of the PM conditions (all ps > 0.28). The same pattern was found for target trials: a prospective

interference effect was present in all PM conditions [main effect condition: $F(4,72) = 17.56$; $p < 0.001$; all ps < 0.001]. Reaction times did not differ between the PM conditions (all ps > 0.18).

Table 5.1: Mean reaction times (ms) and accuracy (% correct) for ongoing trials (non-targets and targets) in all conditions and for PM cues in reward and loss avoidance conditions. Standard error of the mean is given in parentheses.

			Non-targets	Targets	PM cues
Reward					
	high	RT *(SE)*	585.26 *(19.02)*	611.37 *(20.04)*	585.11 *(16.79)*
		Acc (*SE)*	93.41 *(1.73)*	73.16 (*3.59)*	87.76 *(2.47)*
	low		578.79 *(17.95)*	608.11 *(18.66)*	608.11 *(13.95)*
			93.61 *(1.22)*	70.52 *(3.64)*	87.86 *(1.95)*
Loss					
	reduce		576.26 *(19.02)*	617.79 *(19.81)*	597.53 *(14.13)*
			93.41 *(1.17)*	71.02 *(3.48)*	86.97 *(2.31)*
	avoid		577.0 *(17.48)*	638.79 *(17.69)*	603.79 *(12.71)*
			94.32 *(0.91)*	72.12 *(2.91)*	85.92 *(2.5)*
Ongoing/baseline			534.63 *(19.04)*	565.74 *(17.38)*	-
			93.81 *(0.85)*	79.56 *(3.43)*	-

For PM cue trials, an interaction between the factors incentive and magnitude was found [$F(1,18) = 5.22$; $p = 0.035$]. Follow-up paired t-tests revealed that while participants responded significantly faster to high reward, compared to low reward PM cue trials [$t(18) = -3.56$; $p = 0.002$], the difference between PM cues associated with loss reduction and avoidance was not significant ($p = 0.266$). Response times did not

differ for reward and loss PM cues, collapsed across incentive magnitude ($p = 0.445$).

Correlation analyses with the BIS/BAS scores revealed that PM accuracy difference scores for high and low reward correlated negatively with the BIS score [$r = -.57$, $p = .011$]. Thus, individuals with low BIS scores performed better on high compared to low reward PM cue trials.

5.2.2 fMRI Results

We analysed the fMRI data with regard to four different aspects. First, we aimed at examining the involvement of BA 10 in sustained and transient processes in PM. Second, we analyzed potential effects of incentive motivation, irrespective of incentive magnitude, thus contrasting effects of reward and loss avoidance. Third, we were interested in the interaction of incentive motivation and magnitude. Fourth, we explored potential effects of the interaction between PM trial status and incentive motivation. In the case of the first three types of analyses, results of both block and event-related data are reported, while the fourth analysis required a differentiation of trial types and thus included only event-related data.

5.2.2.1 Sustained and Transient Activation of the Frontopolar Cortex

In order to replicate previous findings of BA 10 in prospective memory, our first analyses aimed at comparing sustained activation in PM and ongoing/baseline conditions, irrespective of incentive motivation. Consistent with earlier studies, we found deactivation of medial BA 10 in the PM conditions, compared to the ongoing/baseline conditions on the whole brain level (Table 5.2).

Analyses of transient activity based on the comparison between PM cues and ongoing trials of the same conditions revealed activation in a large cortical network, including medial and lateral parts of BA 10, extending laterally into the superior frontal gyrus and medially into the anterior cingulate cortex (ACC). Moreover, we found a large activation focus in the precuneus, extending ventrally into the posterior cingulate gyrus. In addition, we observed activation in the thalamus, extending into the caudate nucleus and putamen, as well as into the parahippocampal gyrus and the midbrain (Fig. 5.1, Table 5.3).

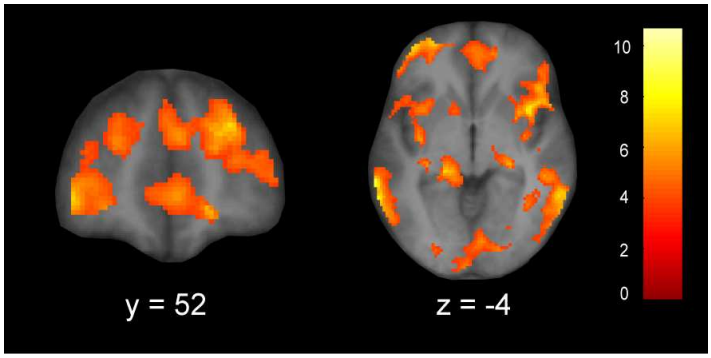

Figure 5.1: Group functional activation maps, overlaid on the average of the normalized structural images of the study participants. Activation in BA 10 in the contrast of PM vs. ongoing (non-target and target) trials, collapsed across reward and loss avoidance. For illustration purposes, images are thresholded at $p < .001$, $k > 15$.

Table 5.2: MNI coordinates and anatomical location of the peak activations in regions showing a decrease in sustained activation during PM, compared to ongoing blocks.

Brain region	Hemi.	Peak voxel (in mm)			t-value	cluster size
		x	y	z		
Frontal						
Frontopolar Cortex (BA 10)	L	-14	58	16	5.75	361
Frontopolar Cortex (BA 10)	R	14	60	4	4.92	875
Dorsolateral Prefrontal Cortex (BA 46)	R	46	46	10	5.20	302
Inferior Frontal Gyrus (BA 46/47)	L	-50	36	14	5.03	289
Anterior Cingulate Cortex (BA 32/10)	L	-14	30	-8	6.30	172
Temporal						
Occipitotemporal Cortex	R	56	-70	2	6.26	266
Occipitotemporal Cortex	L	-60	-62	4	4.73	394

Table 5.3: MNI coordinates and anatomical location of the peak activations in regions showing an increase in transient activation during PM cues (reward+loss), compared to ongoing trials from the same conditions.

Brain region	Hemi.	Peak voxel (in mm)			t-value	cluster size[1]
		x	y	z		
Frontal						
Superior Frontal Gyrus (BA 6)	R	20	4	70	6.22	239
Superior Frontal Gyrus (BA 6/32)	R	20	8	52	5.21	80
Dorsolateral Prefrontal Cortex (BA 9)	R	50	24	38	6.39	442
Dorsolateral Prefrontal Cortex (BA 9)	L	-56	6	38	4.85	32
Middle Frontal Gyrus (BA 6/8)	L	-46	8	50	5.24	35
Middle Frontal Gyrus (BA 6/8)	R	12	0	54	4.39	26
Medial Frontal Gyrus (BA 6)	R	8	-14	64	5.29	62
Inferior Frontal Gyrus (BA 44/45)	R	58	16	22	6.27	257
Parietal						
Precuneus (BA 7)	L	-42	-34	54	11.7	49541
Temporal						
Perirhinal Cortex (BA 35)	R	20	-24	-18	4.66	16
Basal Ganglia						
Ventral Striatum	L	-14	10	0	5.09	79
Other						
Cerebellum	L	-44	-66	-44	5.45	27

[1]For a more precise localization of the activation sites in this contrast, the whole brain threshold was set to $p < 0.001$, uncorrected, with a cluster size of $k > 15$.

5.2.2.2 Effects of Reward vs. Loss Avoidance

In a first step, we set out to investigate if PM maintenance and cue detection was modulated by motivational incentive (i.e., reward or loss), independent of reward magnitude.

The direct comparison of reward and loss blocks in BA 10 did not yield a significant result. ROI analyses of transient activity in BA 10 for ongoing trials (non-targets and targets) in the PM conditions confirmed the block analyses. However, ongoing trials in the reward, but not in the loss conditions revealed significantly greater activation when compared to the ongoing/baseline condition (x = 10, y = 44, z = -12; T = 5.26; k = 57).

We did not find differential activation for reward, compared to loss blocks, in the midbrain ROI. Analyses of transient activation for reward vs. loss PM cues confirmed the block results: both reward and loss PM cues led to an increase in midbrain activation when compared to the respective ongoing trials, but did not show any differences in this midbrain ROI when compared directly. ROI analyses in the ventral striatum did not lead to significant results on the block level or when PM cues were compared directly.

The whole brain analysis showed two significant activation clusters for the reward vs. loss block contrast in the middle temporal (including the amygdala as well as the parahippocampal gyrus) and inferior temporal/middle occipital gyrus (x = -32, y = 0, z = -26; T = 5.64; k = 210 and x = 50, y = -66, z = -8; T = 4.62; k = 239, respectively), while the reverse contrast revealed an activation cluster in the precentral gyrus (x = 64, y = -12, z = 24; T = 5.41, k = 343). Comparisons of reward and loss PM cues did not reveal significant results.

Accordingly, the ROI analysis in the amygdala revealed increased activation in reward, compared to loss blocks (x = -30, y = 0, z = -26; T = 4.85; k = 15). This modulation was however not reflected in differences in transient activity in response to the outcomes, i.e., reward vs. loss PM cue hits.

5.2.2.3 Interaction of Incentive Motivation and Magnitude

In the next step, we aimed at investigating potential differences due to the size of the incentive by including information about the amount of the potential gain/loss avoidance in the analyses.

Midbrain areas showed a response profile sensitive to the interaction of incentive

motivation and magnitude (x = 20, y = -20, z = -4; *T* = 5.77; *k* = 48) (Fig. 5.2). On the whole brain level, these midbrain activations were accompanied by an incentive type x magnitude interaction in the superior temporal cortex/temporal pole, bilaterally, and in the occipital cortex (Table 5.4). Activation in the regions of interest in the ventral striatum, the amygdala, and BA 10 was not sensitive to this interaction.

To resolve this interaction, we next analyzed both kinds of incentive motivation separately, comparing high to low reward blocks, and loss avoidance to loss reduction blocks in the midbrain. High reward blocks led to greater activation of midbrain regions compared to low reward blocks (x = 12, y = -16, z = -14; *T* = 4.47; *k* = 44), while no such difference was found for loss avoidance, compared to loss reduction blocks or the reverse contrast (Fig. 5.2 b)).

Interestingly, the activation difference for high, compared to low reward PM cues in this midbrain region correlated significantly with response time differences for high and low reward PM cues [r = -.49, p = 0.034], suggesting that an increase in reward-related midbrain activation was associated with faster response times for high, compared to low reward (Fig. 5.2 c)).

In order to investigate if reward and loss avoidance differ in the degree of reward anticipation associated with a positive outcome (i.e., the receipt of a reward or the avoidance of a loss), we directly compared sustained activation for high reward vs. loss avoidance (i.e., the gain of 50 points vs. the avoidance of a loss of 50 points). We did not find any differences in sustained activation in the midbrain ROI for high reward compared to loss avoidance, or the reverse contrast. The amygdala showed increased activation in response to high reward, compared to loss avoidance (x = 32, y = -2, z = -24; *T* = 3.7; *k* = 23), but no such difference was found in the BA 10 and ventral striatum ROIs. No activation differences were found for high reward PM, compared to loss avoidance PM cues in the regions of interest in the midbrain, amygdala, ventral striatum or BA 10.

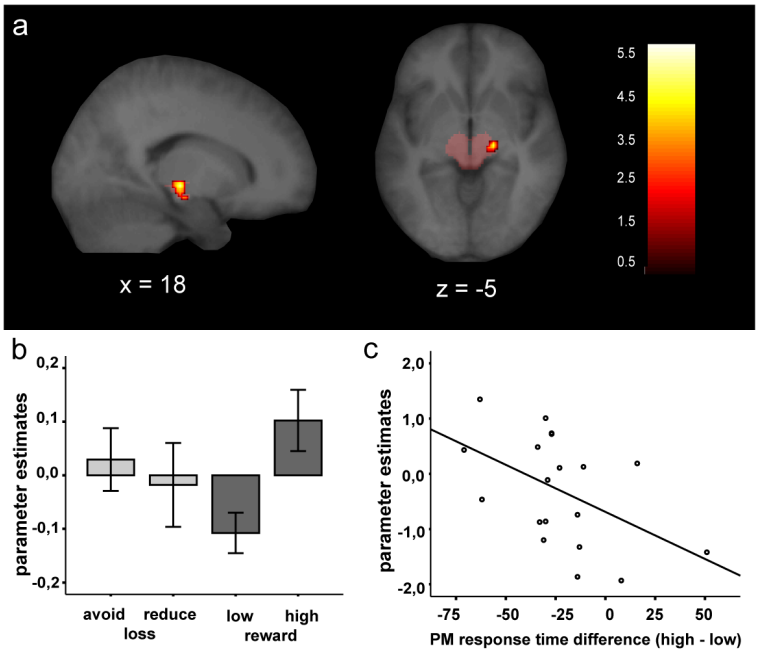

Figure 5.2: Activation in the midbrain for the effect of the net positive outcome across blocks (i.e., collapsed across high reward and loss avoidance blocks, compared to low reward and loss reduction blocks). Group functional activation maps are overlaid on the shapes of the anatomical ROIs depicted in red (a). Parameter estimates for reward and loss blocks: midbrain activation is increased for high, compared to low reward blocks (b). The increase in midbrain activation for high reward PM cues is associated with faster response times for high reward PM cues (c). Parameter estimates in (b) and (c) are extracted from the peak activation in the high vs. low reward block contrast.

Table 5.4: MNI coordinates and anatomical location of the peak activations in regions showing increased activation during anticipation of a high positive outcome (i.e., high reward and loss avoidance blocks compared to low reward and loss reduction blocks).

Brain region	Hemi.	Peak voxel (in mm)			t-value	cluster size
		x	y	z		
Parietal						
Cingulate Gyrus (BA 31/5)	R	16	-32	46	5.67	245
Temporal						
Temporal Pole (BA 38)	R	52	6	-16	8.08	193
Occipital						
Cuneus (BA 18)	R	14	-52	-10	4.65	648
Cuneus (BA 19)	R	18	-76	30	4.10	543

5.2.2.4 Interaction of PM Status and Incentive Motivation

In an explorative analysis, we were interested in the neural mechanisms supporting the interaction between the trial status of a specific item (i.e., the PM/ongoing distinction) and the incentive motivation (i.e., reward/loss). ROI results revealed that, in the right ventral striatum, there was a trend towards a significant response pattern encoding this interaction. In order to increase the sensitivity of the analyses, we focused our analyses to the ROI of the right ventral striatum, using a binary mask derived from a probabilistic mask atlas (cf. Methods section). This analysis confirmed that activation in the ventral striatum encoded the interaction between the PM status and incentive motivation (x = 16, y = 12, z = 0; T = 3.79; k = 14) (Fig 5.3 a)). The whole-brain analyses confirmed the activation focus in the right ventral striatum, but this activation did not survive the whole brain cluster threshold (x = 18, y = 16, z = 0; T = 3.81; k = 28). The regions of interest in the amygdala, midbrain, and BA 10 were not responsive to this interaction.

To follow up this interaction in the ventral striatum, parameter estimates were extracted for each subject, separately for reward and loss PM and ongoing trials, collapsed across incentive magnitude. Paired t-tests revealed that in the loss, but not

reward conditions, parameter estimates were increased for PM, compared to ongoing cues [loss: $t(18) = 5.08$; $p < 0.001$; reward: $p = 0.72$]. Moreover, ongoing reward trials exhibited increased activity compared to ongoing loss trials [$t(18) = -3.12$; $p = 0.006$] (Fig 5.3 b)).

Interestingly, individual differences in reward responsiveness correlated positively with activation differences in this region for reward, compared to loss avoidance PM cues [$r = .50$; $p = 0.03$] (Fig 5.3 c)).

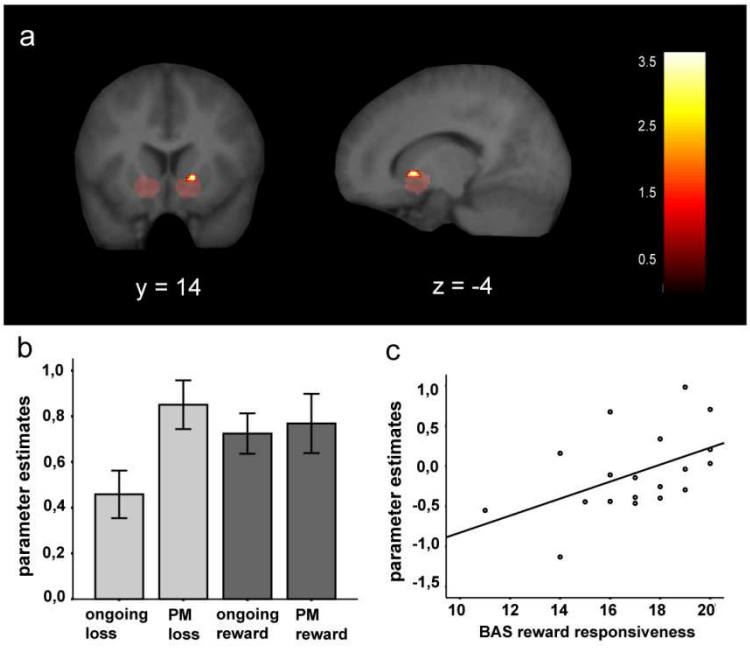

Figure 5.3: Activation in the right ventral striatum encodes the interaction between PM/ongoing and reward/loss (a). Group functional activation maps are overlaid on the shapes of the ROI depicted in red. Parameter estimates differ for loss, but not reward PM and ongoing trials (b).The difference in activation between reward and loss PM cue trials correlates with scores on the BAS reward responsiveness scale (c). Parameter estimates in (b) and (c) were extracted from the peak activation in the ventral striatum.

5.3 Discussion

The intention of experiment 3 was to investigate the neural effects of different kinds of motivational incentives on the maintenance and retrieval of prospective intentions.

Using fMRI, we combined a PM paradigm with monetary rewards and losses.

We replicated previous findings by showing that the maintenance of a PM intention is reflected in the deactivation of medial frontopolar cortex (BA 10). Importantly, we observed a modulation of reward-related midbrain regions reflecting the anticipation of a net positive outcome (obtain reward or avoid loss), while amygdala regions coded the intensity of the expected outcome, which was highest when a high reward was expected.

Moreover, ventral striatal activity encoded the interaction between PM status and incentive motivation, extending the previous implications of this region in reward-related behavior to a role in motivated prospective remembering.

5.3.1 The Role of the Frontopolar Cortex in Prospective Memory

In experiment 3, we replicated previous findings that implicate the frontopolar cortex in intact prospective memory functioning. Specifically, our results show a sustained deactivation of the medial frontopolar cortex for the PM, compared to the ongoing context. While these results are in accordance with findings from earlier studies (Burgess, et al., 2001; Burgess, et al., 2003), they differ from experiment 2, in which we did not find this pattern of results. One possible reason is the inclusion of PM expectation blocks in experiment 2, which could have resulted in a loss of statistical power, compared to experiment 3, in which only PM execution blocks were included.

We further show that medial and lateral parts of BA 10 are more active for PM, compared to ongoing trials and herewith replicate the activation pattern found in experiment 2. We thus extend previous findings in terms of a role of frontopolar cortex in switching between externally and internally oriented processes (Gilbert, et al., 2005).

We did not find the activity in the frontopolar cortex to be modulated by different kinds of reward or rewards of increasing magnitude. This pattern of results is in line with hierarchical models of anterior prefrontal cortex functioning and with recent evidence suggesting a more general role of the frontopolar cortex in the processing of reward-related information: while earlier studies have implicated this region in the integration of reward information into cognitive processes per se (Pochon, et al., 2002), recent studies have suggested that the frontopolar cortex is only involved in combining rewards from two tasks, but not in response to rewards associated with a specific task alone (Charron & Koechlin, 2010). Based on the results of the present study, we hypothesize that in PM, the frontopolar cortex primarily mediates switching processes

between the PM and the ongoing task, while other, reward-related brain regions, process information about the motivational value of each specific task.

5.3.2 Effects of Incentive Motivation

We observed differential midbrain activation related to variations in the net outcome of PM cues: blocks comprising high reward and loss avoidance PM cues showed an increase in sustained activation in midbrain regions compared to blocks with low reward or loss reduction PM cues. Thus, midbrain areas seemed to code the prospect of achieving the highest relative outcome. In particular, sustained activation in this region showed an increase for high, compared to low reward, as has been found for the anticipation of monetary gains (McKell Carter, et al., 2009), while the avoidance, compared to the reduction of a loss, did not give rise to increased midbrain activation.

Importantly, we found midbrain activation differences for high vs. low reward PM cues to correlate with response time differences for those cues, indicating that higher levels of midbrain activation as a result of high reward expectation were directly linked to reward modulations in behavior. Previous research has shown that high reward can be associated with higher accuracy or faster response times to cued targets and gives rise to an increase in activation in reward-related regions such as the ventral striatum (Knutson, et al., 2001b; Knutson, Fong, Bennett, Adams, & Hommer, 2003; Simon, et al., 2010). Here, we show that midbrain activation reflects differences in incentive motivation of PM cues. Moreover, our results indicate that these activation differences are directly related to the behavioral response to the differently rewarded PM cues, demonstrating a crucial link between the reward modulation of events in the context of PM and the differential activity of the underlying reward system.

We did not find a difference between high reward and the avoidance of a loss of the same size in the midbrain. Prospect theory implies that losses have a larger impact than gains (Kahneman & Tversky, 1979). The reverse however, does not seem to explain the data in the present study: the possibility of avoiding a loss did not elicit higher BOLD responses in areas related to reward anticipation than the possibility of obtaining a reward of the same size.

We found the amygdala to be differentially involved in the processing of the motivational information conveyed by the PM cues. We observed higher sustained activation in the amygdala for reward than for loss avoidance blocks, and activity in this

region also differentiated between high and low reward. Although the amygdala has long been associated with fear conditioning in the context of emotional learning, evidence from studies in non-human primates and in humans suggest a role in the processing positive reward signals (Baxter & Murray, 2002; Hommer, et al., 2003; Murray, 2007). In particular, it has been proposed that the amygdala contributes to both positive and negative affect, by mediating a general arousing effect of reward (Anderson & Sobel, 2003; Murray, 2007) and to contribute (in concert with the orbitofrontal cortex) to goal-directed behavior by representing the value of an upcoming reward (Gottfried, O'Doherty, & Dolan, 2003; Hampton, Adolphs, Tyszka, & O'Doherty, 2007). Amygdala activation in combination with activation of midbrain areas has also been reported to code appetitive prediction errors in humans during reward- and loss-driven reinforcement learning (Seymour, et al., 2005). In the present study, amygdala activation was enhanced when reward anticipation was high. Given that amygdala activation reflects a general arousing effect of incentive motivation, it can be assumed that the prospect of receiving a high reward was perceived as more intense than receiving a low reward or being able to avoid financial loss. The behavioral data are in agreement with this view, showing faster response times for high reward PM cues. Moreover, accuracy on ongoing target trials decreased in all conditions compared to ongoing/baseline, except under high reward. Thus, when a high reward was at stake, this detrimental effect of the PM monitoring process on ongoing accuracy seemed to be canceled out by a general effect of enhanced attention to specific outcome-related trials.

5.3.3 Encoding of Incentive Motivation and PM status

We found that only the ventral striatal region encoded the interaction between the PM status and the motivational incentive. The nucleus accumbens and ventral striatal regions in general have been associated with the anticipation and outcome of monetary reward (Knutson, et al., 2001a; Knutson, et al., 2001b; Simon, et al., 2010). However, conflicting evidence exists concerning loss-related activations. While some studies have reported decreases in ventral striatal activation or distinct spatial loci for losses (Breiter, Aharon, Kahneman, Dale, & Shizgal, 2001; Robinson, et al., 2010; Seymour, et al., 2007; Tom, et al., 2007; Yacubian, et al., 2006), other studies have reported activations in reward-related regions (Cooper & Knutson, 2008; McKell Carter, et al., 2009). Cooper and Knutson (2008) cued participants to anticipate monetary gains and losses

that were either certain or uncertain (i.e., were independent of or did depend on participants' response speed). For certain outcomes, the activation of nucleus accumbens increased for anticipated gains and decreased for anticipated losses. For uncertain outcomes, however, activity increased for both monetary gains and losses and did not differ between them, suggesting that both the valence (gain or loss) and the salience (certain or uncertain) contributed to the activation of the nucleus accumbens in response to monetary reward.

Here, we extend these findings by showing that activation in the ventral striatum, encompassing the nucleus accumbens, is differentially modulated by incentive motivation and PM status. In particular, activity in this region was higher during reward, compared to loss avoidance ongoing trials, which we take to reflect the reward anticipation associated with the motivational context and a higher motivational salience of reward, compared to loss avoidance. Importantly, this region also seemed to encode differences in the PM status (PM vs. ongoing), which were more pronounced for loss trials. PM, relative to ongoing trials, can be considered to be more salient due to outcome contingencies. Thus, these findings fit well with an account of nucleus accumbens being implicated in the processing of valence and salience features of a stimulus: during reward ongoing trials, the anticipation of a positive outcome is higher than during loss avoidance ongoing trials. On the other hand, under loss, compared to reward conditions, PM cues might be more salient due to their aversive characteristics, thus giving rise to a larger PM-ongoing activation difference.

We found that activation differences in the ventral striatal region for reward and loss avoidance significantly correlated with individual reward responsiveness. Reward-related activity in the ventral striatum has been shown to be related to individual differences in reward responsiveness and approach motivation (Han, et al., 2010; Krebs, et al., 2009a; Simon, et al., 2010). In particular, individual reward sensitivity has been reported to predict differential activation in the nucleus accumbens for the relative difference between gains and losses, suggesting that responses in these regions are primarily sensitive to aspects of motivational salience, but can be modulated by affective valence, especially in highly reward sensitive individuals (McKell Carter, et al., 2009). Here, we extend these findings by showing that PM cues fulfill the characteristics of motivational salience and that individual reward responsiveness is reflected in BOLD responses to the valence of the PM cues.

6 Summary and General Discussion

6.1 Behavioral Data

In all 3 experiments, costs on the ongoing task (i.e., longer response latencies for ongoing trials in PM, compared to ongoing/baseline conditions) were found. If these costs do indeed reflect the maintenance of a PM intention or strategic monitoring processes as the literature suggests, we can in turn assume that prospective intentions were maintained in each of our 3 experiments.

Concerning a modulation of behavior by the motivational context, the results revealed that accuracy as well as response times were affected by the kind of incentive motivation and the size of the incentive.

Consistently across the three experiments, we found that accuracy on PM trials was not affected by motivational incentive or magnitude. Instead, accuracy on the ongoing task, in particular, on 2-back target trials, was differentially affected by reward. This is perhaps not surprising for the following reasons: participants could lose money by missing PM cues. On the other hand, they would only forfeit this extra money if accuracy on the ongoing task dropped below 60% (65% in experiment 3). Thus, it is highly probable that participants sacrificed some degree of accuracy on the ongoing task in order to succeed on the PM task, which is apparent in the high levels of accuracy for PM cues. The fact that a modulation of accuracy by incentive was only found on target trials, which were the more difficult trial types, supports this view.

While in experiment 2, accuracy on target trials in both the high and low reward condition was lower than in the ongoing/baseline condition (most probably as a result of the interference with PM cue detection processes), experiment 1 and 3 showed somewhat contradictory findings: in experiment 1, accuracy on target trials in the high reward condition was lower than in the ongoing/baseline condition, but in experiment 3, accuracy did not differ in these two conditions (while accuracy in all other incentive conditions was lower than ongoing/baseline accuracy). One possible explanation for this is that different kinds of motivational incentives were used in experiment 3 (reward and loss), compared to only one (reward) in experiment 1. Thus, subjective evaluation differences between these incentives could account for the different findings in experiment 1 and 3 (e.g., a high reward could appear even more rewarding compared to the avoidance of a loss, while this is not the case if it is only compared to a low reward).

We found a clear effect of reward on response times in experiment 2 and 3: response

times to PM cues were faster when participants expected a high, compared to a low reward. Based on the fact that faster response times for high reward targets have been found in simple reaction time tasks such as the MID task (as was also the case in our localizer task), where a direct stimulus-response mapping was implemented, it can be assumed that, in our PM task, participants directly related the incentive to the PM stimulus. In addition, they seemed to be more attentive if they expected a high reward.

Taken together, it seems that incentive effects on PM are primarily found in response times to the PM cues rather than on the costs on the ongoing task. In addition, accuracy on the ongoing task can increase or decrease in the presence of PM-related rewards, presumably reflecting the amount of attention that is allocated to the ongoing task according to the evaluation of the incentive motivation.

Another important factor that was in the focus of our investigations was the potential effect of individual differences on the processing of reward in the context of PM. On the basis of Gray's reinforcement sensitivity theory which proposes a biological model of personality based on individual approach and avoidance behavior, we expected individual differences to have an impact on reward-related modulations of behavior. We found substantial inter-individual variability in reward-related accuracy and response time differences in all 3 experiments, thus accounting for the investigation of individual personality variables. Accordingly, we found both neuroticism and conscientiousness to prevent decreases in accuracy in the ongoing task caused by the reward associated with the PM cues. Furthermore, in line with previous findings of correlations between individual differences in self-reported behavioral approach and avoidance measures and neural responses to reward (Krebs, et al., 2009a; Simon, et al., 2010), we found that approach and avoidance behavior based on reward expectations is directly related to PM performance. Thus, here we show that individual differences in approach and avoidance behavior are important in understanding the link between biological and behavioral effects of reward and must be taken into account when reward-related modulations of behavior in PM are investigated.

6.2 fMRI Data

In two fMRI experiments, we investigated the effect of incentive motivation on the neural mechanisms supporting PM. While experiment 2 was designed to examine the effects of different levels of reward on PM, experiment 3 aimed at extending findings

from experiment 2 by varying the kind of incentive motivation, comparing reward anticipation and loss avoidance motivation in PM.

6.2.1 The Role of the Frontopolar Cortex in Prospective Memory

In experiment 3, we replicated previous findings of a sustained deactivation of the medial frontopolar cortex during the PM, compared to the ongoing tasks (Burgess, et al., 2003). Generally, this sustained medial frontopolar deactivation has been associated with the processing of internal, compared to external information. In the PM context, this pattern of results has been associated with the maintenance of the prospective intention, in particular, with the monitoring for PM cues (Burgess, et al., 2003; Gilbert, et al., 2005). In experiment 2, we did not find the frontopolar cortex to be differentially activated in response to PM (execution and expectation) vs. ongoing blocks. Two potential reasons can account for this: first, the PM expectation condition did not contain any PM trials, which might have led to reduced maintenance/monitoring. For this explanation to be valid, the comparison between PM execution and ongoing blocks should still have given rise to an increase in BA 10 activation, because PM cues were present in this condition. However, neither PM expectation nor execution conditions led to an increase in BA 10 activation when compared to the ongoing/baseline condition. Thus, an explanation in terms of reduced maintenance processes is unlikely.

Second, for the above reason, experiment 2 only comprised half of the number of PM cues compared to experiment 3, which might have led to a lack of statistical power. Indeed, lowering the statistical threshold to $p = 0.01$ revealed a small activation cluster in medial BA 10 for the ongoing vs. expectation and execution comparison.

In both experiment 2 and 3, we observed activation of the frontopolar cortex in response to the PM cues. In both cases, PM cues, compared to ongoing trials, gave rise to an increased BOLD response in the medial and lateral parts of BA 10. On the basis of the findings of Gilbert et al. (2005), we hypothesize that activity on PM cue trials reflects the switching from the ongoing towards the PM task. As mentioned above, the medial deactivation of the frontopolar cortex on the block level is generally interpreted as a disengagement from the ongoing activity. In turn, activation of this area could reflect the fact that some degree of attention was still directed at the ongoing task, presumably due to the function of the PM cue trials in the 2-back rhythm.

While we did not find sustained or transient activation in BA 10 to be modulated by

reward magnitude (experiment 2) or variations of incentive motivation and magnitude (experiment 3), we found that lateral parts of BA 10 showed increased connectivity with the midbrain under high, compared to low reward conditions and reward-related performance increases. The lack of a reward effect in BA 10 is in line with recent findings claiming that activation in the frontopolar cortex is not dependent on reward per se, but rather responds to the joint increase of two separately rewarded tasks (Charron & Koechlin, 2010; Tsujimoto, et al., 2010). In particular, a study using single-cell recordings in two behaving monkeys found that cells in the frontopolar cortex encoded the monkey's decision at the time of feedback, but were not responsive to reward anticipation when the reward served as a cue (Tsujimoto, et al., 2010). Although there are several caveats in terms of location and cytoarchitecture when comparing brain areas and subdivisions in humans and rhesus monkeys, this study suggests that the frontopolar cortex monitors decisions made in the context of correct task performance, but does not encode reward information per se. Moreover, in humans, frontopolar cortex has shown to be responsive to the integration of reward information from two combined cognitive tasks, but not to each reward information separately (Charron & Koechlin, 2010). In light of these findings, the present data suggest that the frontopolar cortex is not responsive to the magnitude of the reward information conveyed by the PM cues, but that it monitors the shifting process between the PM and the ongoing task. In this function, it seems to receive information about the reward value of the PM task from midbrain areas mediating information about the reward at stake. This connection seems to be increasingly stronger when a high reward is at stake, suggesting that in the case of highly motivated cognitive goals, these brain regions work "in tune" to assure that a successful outcome is achieved and is repeated in the future.

6.2.2 Effects of Incentive Motivation in Prospective Memory

In both experiments 2 and 3, we found that high reward anticipation led to an increase in sustained activation in the midbrain. Activity on PM and ongoing trials, however, did not differ with respect to reward magnitude, suggesting that it was the anticipation of high rewards associated with the outcome of both the PM and ongoing task that led to an increase in midbrain activation levels. Activity in the midbrain has been reported to increase with high reward anticipation, especially under high probabilities (Knutson, et al., 2005). In our study, the probability of earning the reward

depended on the participants' response to the unpredictable occurrence of PM cues, independent of the reward context. Moreover, although the emphasis was on the PM cues, both PM and ongoing task performance contributed to the prospect of earning the reward. However, while above-criterion ongoing task performance only ensured participants the receipt of any reward (instead of no reward at all), the magnitude of the reward was closely linked to PM performance. Thus, it can be assumed that the information about the magnitude of the potential reward was maintained during the processing of the ongoing task as well.

The role of the PM cues in the mediation of the reward value is further emphasized by the fact that the activation on high reward PM trials correlated with individual levels of BAS reward responsiveness. These results suggest that reward expectations were elicited by the appearance of the PM cues. While we can assume that reward expectations were maintained in all participants, individual reward sensitivity was directly linked to the level of reward-related activation.

Further support as to the existence of reward-related changes in the processes underlying PM comes from the fact that we found individual response times to be modulated by reward magnitude and that these effects were associated with a parallel modulation of midbrain activation.

Moreover, individual differences in reward responsiveness were found to relate to activation differences in the ventral striatum for PM cues. This region has been reported to relate to positive arousal associated with reward anticipation (Knutson, et al., 2005).

In our study, activity in the ventral striatal region was most pronounced for the interaction of PM status and incentive motivation. These results are in line with recent findings of the involvement of the nucleus accumbens in the processing of both the valence and the salience of appetitive stimuli (Cooper & Knutson, 2008). Here, we show that the ventral striatal region is sensitive to the distinction between PM and ongoing trials. Evidence from a recent study investigating the effects of alternative available options on nucleus accumbens activation suggests that this region represents the incentive value relative to the current context of available gains and losses, with the worst available loss serving as an anchor for the computation of the relative value of an event (Cooper, Hollon, Wimmer, & Knutson, 2009; Tversky & Kahneman, 1992). In the present data, such an anchor effect could have played out in the loss condition, leading to a clear distinction between the actual loss events (PM) and events not as clearly

linked to the potential loss (ongoing trials), while the PM-ongoing distinction was not as clear-cut in the reward conditions.

An additional factor, or else, an alternative explanation, is the increase in positive arousal associated with high reward. As mentioned above, activation in the nucleus accumbens has been associated with high arousal ratings in the case of high reward anticipation. In our study, high reward did not only lead to higher midbrain activation, but also in amygdala activation, which was greatest when reward was high, even compared to the avoidance of a loss of the same size. Greater intensity of high reward events, especially for ongoing (i.e., anticipation) trials, could explain the decrease in the activation difference between PM and ongoing trials under high reward.

6.3 Conclusion

The aim of the present study was to tie together findings of reward modulations in goal-directed behavior and aspects of goal achievement in prospective remembering. The present findings suggest that reward expectations pertaining to the PM intention have to be taken into account when the neural substrates underlying PM are investigated.

In particular, we have shown here that information about the incentive value of an upcoming PM cue is represented in activation differences in reward-related limbic brain structures. Moreover, our results suggest that the extent of these differences is largest under high reward conditions.

Specifically, we report that in the PM context, high reward leads to an increase in activation in the midbrain and in the amygdala, which is accompanied by a performance increase. Based on the present findings, we suggest that the role of the frontopolar cortex in PM is to monitor switching processes in response to PM cues, irrespective of the incentive value or the size of the incentive that is associated with those cues. However, we present evidence that, under high reward, the functional connectivity between reward-related midbrain regions and the frontopolar cortex is enhanced, especially in the case of reward-related performance increases.

We further report that reward-related activation differences in the midbrain and in the ventral striatum in the context of PM are linked to individual reward sensitivity.

We conclude that reward expectations can be part of PM and that the neural substrates supporting these reward expectations are integrated into the neural processes

underlying intact PM performance.

6.4 Outlook

The present study investigated the effects of reward on the neural mechanisms supporting prospective memory. It was observed that reward effects were primarily mediated by regions traditionally associated with the processing of reward features such as the midbrain and the striatum, whereas frontopolar regions were not responsive to reward levels per se, but showed enhanced connectivity to the midbrain region for highly motivating events. Although these findings are in line with recent reports of frontopolar function in the monitoring, but not anticipation, of rewards, there are several open questions that further studies could investigate.

First, it should be established if the frontopolar cortex is indeed not sensitive to differences between rewarded and non-rewarded PM cues. For the reasons outlined above, high reward PM cues were compared to low reward PM cues, but no non-reward condition was included in the present study. Although the present results demonstrate that this difference led to distinct neural processing in midbrain and striatal regions, the possibility that the frontopolar cortex would be responsive to the difference between reward and non-reward should be ruled out by including this additional condition in further studies.

Beyond this, it would be particularly interesting to manipulate reward contingencies separately for the ongoing and the PM task. Charron and Koechlin (2010) have demonstrated that frontopolar cortex activity increases in response to the combination of rewards in two tasks. Thus, for example, a PM paradigm could be developed in which some PM cues, but also some ongoing trials lead to a high reward, whereas other PM and ongoing trials are associated with low reward. Accordingly, PM and ongoing failures would result in high or low punishment. This would allow for an investigation of a putative boosting of the already more salient PM, compared to the ongoing trials. A clinical aspect of this issue would involve the question if patients with obsessive-compulsive disorder (in which basal ganglia dysfunction has been proposed to play a role), or even healthy individual with high levels of conscientiousness, could actually refrain from checking or excessively monitoring for PM cues when the ongoing task is associated with high reward, supposedly counteracting the satisfaction coming from the execution of the compulsive action.

A more applied, developmental perspective on motivation and PM would involve the investigation of the neural processes underlying the age prospective memory paradox by examining reward effects on the neural mechanisms supporting PM performance by means of fMRI in groups of young and old adults.

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