Neural circuitry and neurochemistry of motivated cognitive control

A cross-species approach

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Chapter 1

Striatal dopamine and motivated cognitive control

Based on:

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Imagine for a minute that you are a squirrel and that you and your friend are in the forest, looking for nuts and berries. While collecting food, you follow a path, taking you along nut trees and berry bushes. When you encounter a fork in the road, you decide to go left and your furry squirrel friend takes the path to the right.

Along the chosen path you initially encounter many nuts which you gather and hide with diligence. After a while, nut trees become increasingly scarce. Luckily, the amount of berry bushes increase, so you shift your focus to indulging in berries. Your squirrel friend on the other hand has chosen a more challenging road where nut trees and berry bushes quickly alternate. As he proceeds along his road, he will need to sometimes eat a berry, then collect nut or two, followed again by a berry. After a while your paths meet and you find yourself waiting for your friend for quite some time. Why was your fellow squirrel so much slower? Well, each time he had to switch his focus from nuts to berries and vice versa, he had to construct a new set of appropriate responses. Switching your focus (whether it is between collecting berries and nuts or between updating your Facebook status and writing your thesis) is more costly compared with repeating the same behaviour. Therefore alternating between tasks takes more time to complete. This process is known as *task switching*.

Finally your friend arrives, you continue foraging together. Suddenly you stumble upon another Y-junction. This time your friend insists on taking the path to the left and you go right. Unfortunately, nut trees and berry bushes randomly alternate along both paths and you both need to exert quite some control over your behaviour to switch between the two tasks (i.e. finding nuts and berries). Your friend finally catches a break: the trees and bushes on his road produce enormous nuts and berries. When you reach the end and the two roads meet up again, your friend is waiting for you with a smug grim on his squirrel face. Why was your squirrel friend faster this time around? Well, your friend anticipated a higher payout for his efforts, which may have made it easier for him to alternate between tasks. Why is this and how does this work in the brain?

We refer to the internal and external factors that can orient and invigorate behaviour in order to obtain a goal as *reward motivation* (e.g. when you can obtain large berries). We know that reward motivation can alter *cognitive control*, a set of processes and mental abilities allowing the pursuit of goals in a volatile and distracting environment. For example, knowing that you can obtain large berries (reward motivation) can alter the ability to quickly alternate between tasks (i.e. task switching). Moreover, the neurotransmitter dopamine plays an important role in reward motivation and cognitive control. Recent work has shown that dopamine also plays a role in the interaction between reward motivation and cognition (such as when the anticipated size of the berries and nuts alters the ability of the squirrel to quickly alternate between tasks). In the following section I will provide an overview of the status of the literature prior to the start of the experiments presented in this thesis. In addition, I will propose a hypothesized neural mechanism by which information about rewards may influence cognitive processes. In **chapter 2** I will present an outline and general introduction of the work in this thesis.

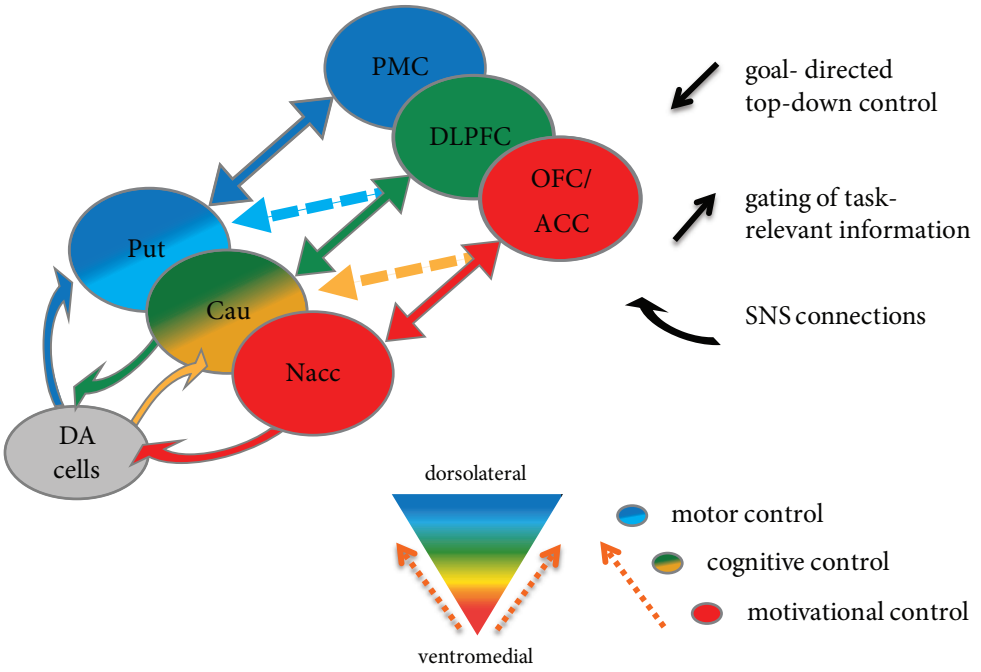


Figure 1.1 Ventromedial to dorsolateral direction of information flow through frontostriatal-nigral circuitry

Interactions between the different frontostriatal loops involved in motivational control (red/orange), cognitive control (green), and motor control (blue) can take place at the level of the SNS connections (bend arrows) or at the level of the frontostriatal connections (straight arrows). The direction of information flow is always from ventromedial to dorsolateral regions in the frontostriatal circuitry. SNS, striato-nigral-striatal; N. Acc, nucleus accumbens (ventromedial striatum); Cau, caudate nucleus (dorsomedial striatum); Put, putamen (dorsolateral striatum); OFC, orbitofrontal cortex; ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; PMC, premotor cortex.

Striatal dopamine and the interface between motivation and cognition

The ability to control our behaviour requires our actions to be goal-directed, and our goals to be organized hierarchically. Goals can be defined at different levels: motivational goals (e.g. rewards), cognitive goals (e.g. task-sets), and action goals (e.g. stimulus-response mappings). Thus, goal-directed behaviour requires, among other things, the transformation of information about reward into abstract cognitive decisions, which in turn need to be translated into specific actions. The mechanisms underlying this hierarchy of goal-directed control are not well understood.

This paper focuses on the degree to which such goal-directed behaviour is controlled by incentive motivation. We have restricted our discussion to the effects of appetitive motivation, while taking note of the wealth of evidence indicating that stimuli that activate the appetitive motivational system have an inhibitory influence on behaviour that is controlled by the aversive motivational system (Konorsky, 1967; Dickinson and Balleine, 2002). Unlike aversive

motivation, appetitive motivation refers to the state triggered by external stimuli that have rewarding properties and has been argued to have a general potentiating or enhancing effect on behaviour and cognition (Dickinson and Balleine, 2002; Robbins and Everitt, 2003; Krawczyk et al., 2007; Jimura et al., 2010; Pessoa and Engelmann, 2010). Its effects on behaviour and cognition have been associated with changes in neurochemical activity, such as increases in dopamine signalling in the striatum (Lyon and Robbins, 1975; Ikemoto and Panksepp, 1999; Robbins and Everitt, 2003; Berridge, 2007). This observation is generally in keeping with proposals that dopamine plays an important role in reward-related effort (Salamone et al., 2007) and generalized activation/energization of behaviour (Robbins and Everitt, 2007). It is also consistent with data suggesting that dopamine might direct information flow from ventromedial frontostriatal circuits, implicated in reward and motivation, to more dorsal frontostriatal circuits, associated with cognition and action (Alexander et al., 1986; Haber and Knutson, 2010) (**figure 1.1**).

Although the widely distributed and diffuse nature of its projection system to large parts of the forebrain concurs with an account of dopamine in relatively non-specific terms, such as serving activation or energization, it is also clear that dopamine does not simply amplify (or suppress) all forebrain activity in a functionally non-specific manner. Indeed extensive evidence indic l systems (Robbins, 2000; Cools et al., 2001a; Frank et al., 2004). In line with these insights, we suggest here that changes in appetitive motivation, which may result from changes in neurochemical activity, for example, due to stress, fatigue, or neuropsychiatric abnormality, also have functionally selective consequences for cognition.

More specifically, we put forward the working hypothesis that appetitive motivation might promote selectively our ability to switch between different tasks, providing us with some of the cognitive flexibility that is required in our constantly changing environment. Conversely, we speculate, based on preliminary data, that dopamine-mediated appetitive motivation might also have detrimental consequences for cognition, e.g. by impairing cognitive focusing and increasing distractibility. The implication of this speculation is that dopamine-mediated appetitive motivation might potentiate flexible behaviour, albeit not by potentiating the impact of current goals on behaviour. This speculation stems partly from the recognition that the motivational forces that drive behaviour are not always under goal-directed control and can be maladaptive (Dickinson and Balleine, 2002). Moreover dopamine is well known to play an important role in mediating the detrimental (i.e. non goal-directed) consequences of reward (Berridge, 2007; Robbins and Everitt, 2007).

Our working hypothesis is grounded in (albeit preliminary) empirical evidence indicating opposite effects of both dopaminergic and motivational/affective state manipulations on cognitive flexibility and cognitive focusing, which have been argued to reflect distinct striatal and prefrontal brain regions respectively (Crofts et al., 2001; Bilder et al., 2004; Dreisbach and Goschke, 2004; Dreisbach, 2006; Hazy et al., 2006; Cools et al., 2007a; Rowe et al., 2007; van Steenbergen et al., 2009; Cools and D'Esposito, 2011). Indeed current models highlight a role for dopamine, particularly in the striatum, in the flexible updating of current

task-representations (Hazy et al., 2006; Maia and Frank, 2011). The finding that appetitive motivation is associated with robust changes in dopamine levels particularly in the striatum, thus concurs with our hypothesis that appetitive motivation potentiates (at least some forms of) cognitive flexibility, perhaps even at the expense of cognitive focusing. Such a bias towards cognitive flexibility should be generally adaptive, given that motivational goals in the real world are not often readily available, thus requiring preparatory behaviour that is flexible rather than focused (Baldo and Kelley, 2007).

Together these observations suggest that appetitive motivation acts to enhance cognition in a manner that is functionally specific, varying as a function of task demands, and that these functionally specific effects are mediated by dopamine. Clearly, as in the case of dopamine (Cools and Robbins, 2004; Cools et al., 2009b), effects of appetitive motivation will vary not only as a function of task demands, but also as a function of the baseline state of the system. Thus both motivational and neurochemical state changes will have rather different effects in individuals with low and high baseline levels of motivation, consistent with the existence of multiple Yerkes Dodson 'inverted U shaped' functions (Yerkes and Dodson, 1908; Cools and Robbins, 2004).

Let us briefly discuss the role of striatal dopamine in the two separate domains of motivation and cognitive control before addressing its role in their interaction.

Dopamine and appetitive motivation

The ventromedial striatum (VMS, including the nucleus accumbens) is highly innervated by mesolimbic dopaminergic neurons and is well known to be implicated in reward and motivation (Robbins and Everitt, 1992; Berridge and Robinson, 1998; Ikemoto and Panksepp, 1999; Schultz, 2002; Knutson and Cooper, 2005; Baldo and Kelley, 2007). Thus dopamine manipulations in the VMS affect performance on multiple paradigms thought to measure motivated behaviour, including conditioned reinforcement, Pavlovian-instrumental transfer paradigms, effort-based decision making tasks, and progressive ratio schedules (Taylor and Robbins, 1984; Dickinson et al., 2000; Wyvell and Berridge, 2000, 2001; Parkinson et al., 2002). These experiments primarily reveal effects of dopamine on so-called preparatory conditioned responses, which are thought to reflect activation of a motivational system (Dickinson and Balleine, 2002), while leaving unaffected, or if anything, having the opposite effect on the more stereotypic patterns of consummatory responding (Robbins and Everitt, 1992; Baldo and Kelley, 2007). Thus administration of the indirect catecholamine enhancer amphetamine in the VMS of hungry rats potentiated locomotor excitement in the presence of food and increased lever pressing in response to, or in anticipation of a reward-predictive cue, while decreasing or leaving unaffected food intake as well as appetitive hedonic responses like taste reactivity (Taylor and Robbins, 1984; Bakshi and Kelley, 1991; Pecina et al., 1997; Wyvell and Berridge, 2000, 2001). Conversely, dopamine receptor blockade or dopamine lesions in the VMS reduced locomotor activity and cue-evoked incentive motivation for reward (Dickinson

et al., 2000; Parkinson et al., 2002), while again leaving unaffected or even increasing food intake (Koob et al., 1978). These animal studies emphasize the importance of VMS dopamine in appetitive motivation and suggest that the hedonic or consummatory aspects of reward are likely mediated by a different, possible antagonistic system (Floresco et al., 1996; Robbins and Everitt, 1996; Berridge and Robinson, 1998; Ikemoto and Panksepp, 1999; Robbins and Everitt, 2003; Baldo and Kelley, 2007; Berridge, 2007; Phillips et al., 2007; Salamone et al., 2007), (for similar suggestions in humans, see Aarts et al., 2010).

At first sight, this well-established observation provides apparently clear grounds for assuming that dopamine contributes to optimal reward- or goal-directed behaviour. However, psychologists have also long recognized that there are multiple distinct components to the motivation of behaviour (Konorsky, 1967; Dickinson and Balleine, 2002). Thus instrumental behaviour is motivated not only by the goals that we set ourselves, but also by generalized drives and/or so-called Pavlovian 'wanting', the latter two processes not necessarily always contributing to adaptive, optimized behaviour. To clarify this point, it may help to consider the operational definition that psychologists have invoked for distinguishing instrumental behaviour that is goal-directed from instrumental behaviour that is not goal-directed, i.e. habitual (Dickinson and Balleine, 2002). Following this tradition, behaviour is goal-directed only if it accords to two criteria; first, it has to be driven by knowledge about the contingency between the action and the outcome (as measured with contingency degradation tests); second, it has to be sensitive to changes in the value of the goal (as measured with outcome devaluation tests, involving for example selective satiety). Using these operational definitions, Balleine and Dickinson (2002) have established that Pavlovian conditioned stimuli that induce so-called 'wanting' can modify instrumental behaviour without accessing action-outcome representations, that is, in a manner that is not goal-directed. This is illustrated most clearly by the role of reward-predictive stimuli in compulsive craving for drugs of abuse or other targets of addiction, which almost always implicates dopamine dysfunction (Berridge and Robinson, 1998; Everitt and Robbins, 2005; Volkow et al., 2009a). In keeping with this observation are suggestions that motivational influences on instrumental behaviour by Pavlovian stimulus-reinforcer contingencies might reflect modulation of well-established habits rather than of goal-directed behaviour (Dickinson and Balleine, 2002). Data showing that dopamine D1/D2 receptor antagonists attenuated Pavlovian-instrumental transfer without affecting instrumental incentive learning (Dickinson et al., 2000) indeed suggested that dopamine might act through Pavlovian processes rather than through modifying action-outcome representations (Dickinson and Balleine, 2002).

In this context, it is perhaps not surprising that the effects of appetitive motivation on cognition that are mediated by dopamine are functionally specific, leading to cognitive improvement or cognitive impairment depending on the specific task demands under study. An important implication of this observation is that effects of dopamine on interactions between motivation and cognitive control that appear to be mediated by a modification of motivational influences on cognitively mediated, goal-directed behaviour may in fact reflect modification of motivational influences on habitual behaviour.

Dopamine and cognition

Accumulating evidence in the domain of cognitive control indicates that manipulations of dopamine can have contrasting effects as a function of task demands. For example, opposite effects have been observed in terms of cognitive flexibility and cognitive focusing (Crofts et al., 2001; Bilder et al., 2004; Cools et al., 2007a; Durstewitz and Seamans, 2008; Durstewitz et al., 2010; Cools and D'Esposito, 2011). Mehta and colleagues (2004) have shown that dopamine D2 receptor blockade after acute administration of the antagonist sulpiride impaired cognitive flexibility (measurWed in terms of task switching), but improved cognitive focusing (measured in terms of delayed response performance with task-irrelevant distracters). Similar contrasting effects on cognitive flexibility and focusing have been reported after dopamine lesions in non-human primates (Roberts et al., 1994; Collins et al., 2000; Crofts et al., 2001), after dopaminergic medication withdrawal in patients with Parkinson's disease (Cools et al., 2001a, 2003; Cools et al., 2010) and as a function of genetic variation in human dopamine genes (Bilder et al., 2004; Colzato et al., 2010a). Evidence from functional neuroimaging and computational modelling work has suggested that these opposite effects might reflect modulation of distinct brain regions, with the striatum mediating effects on at least some forms of cognitive flexibility, but the prefrontal cortex (PFC) mediating effects on cognitive focusing (Hazy et al., 2006; Cools et al., 2007a; Cools and D'Esposito, 2011). This hypothesis likely reflects an oversimplified view of dopamine's complex effects on cognition, with different forms of cognitive flexibility implicating distinct neural and neurochemical systems (Robbins and Arnsten, 2009; Kehagia et al., 2010; Floresco and Jentsch, 2011). In particular, the striatum seems implicated predominantly in a form of cognitive flexibility that involves shifting to well-established ('habitized') stimulus-response sets, that does not require new learning or working memory. For example 6-OHDA lesions in the striatum of marmosets impaired set shifting to an already established set, but left unaffected set shifting to a new, to-be-learned set (Collins et al., 2000). This finding paralleled the beneficial effects of dopaminergic medication in Parkinson's disease, which implicates primarily the striatum. These effects were restricted to task switching between well-established sets, and did not extend to switching to new, to-be-learned sets (Cools et al., 2001b; Lewis et al., 2005; Slabosz et al., 2006). The PFC might well be implicated in higher-order forms of switching that do involve new learning and/or working memory (Monchi et al., 2004; Floresco and Magyar, 2006; Cools et al., 2009a; Kehagia et al., 2010). Interestingly, the beneficial effects of dopaminergic medication in Parkinson's disease on this striatal form of well-established, habit-like task switching were accompanied by detrimental effects on cognitive focusing, as measured in terms of distracter-resistance during the performance of a delayed response task (Cools et al., 2010). These findings paralleled pharmacological neuroimaging work with the same delayed response paradigm demonstrating that effects of dopamine D1/D2 receptor agonist administration to healthy young volunteers on flexibility (task switching) and focusing (distracter-resistance) were accompanied by drug effects on the striatum and the PFC respectively (Cools et al., 2007a).

In sum, dopamine's effects on cognition are known to be functionally specific rather than

global, with opposite effects on cognitive flexibility and cognitive focusing. These opposite effects have been proposed to reflect modulation of distinct brain regions, with dopamine in the striatum playing a prominent role in a form of flexibility that involves shifting to well-established, i.e. 'habitized' stimulus-response sets.

Dopamine and the motivation-cognition interaction

So far we have seen that striatal dopamine's effect on motivated behaviour is most prominent in terms of its preparatory component and that such preparatory effects can be maladaptive. This observation that dopamine's effect on motivation might have maladaptive consequences for behaviour concurs with observations that effects of dopamine in the cognitive domain depend on task demands and associated neural systems, so that dopaminergic drugs can have detrimental as well as beneficial consequences for cognition. Together these insights have led to the speculation that incentive motivation might act to enhance cognitive performance by potentiating dopamine in the striatum in a manner that is functionally specific, i.e. restricted to a form of cognitive flexibility that involves shifting to well-established habits, and not extending to, or even at the expense of cognitive focusing. Below we review empirical evidence that addresses the different aspects of this working hypothesis.

Evidence from neuroanatomical studies

Motivation-cognition interactions have long been proposed to reflect dopamine-dependent interfacing between different parallel fronto-striatal circuits associated with motivation and cognition (**figure 1.1**). For example, neuroanatomical studies in rats from the 70s have suggested that activity in the dorsal striatum is modulated by activity in the ventral striatum via the dopaminergic cells in the substantia nigra (Nauta et al., 1978). Tracer experiments in nonhuman primates have revived this notion by revealing an arrangement of spiralling striato-nigro-striatal (SNS) connections between the dopaminergic cells in the midbrain and striatal regions that were defined on the basis of their frontal cortical input (Haber et al., 2000; Haber, 2003). Similar connections have been found in rodents (Ikemoto, 2007). The SNS connections are thought to direct information flow in a feed-forward manner via stepwise disinhibition of the ascending dopaminergic projections from the VMS (including the nucleus accumbens), via the dorsomedial striatum (DMS, caudate nucleus), to the dorsolateral striatum (DLS, putamen). The resulting information flow from ventromedial to dorsolateral striatal regions provides a hierarchical (or heterarchical, seeHaruno and Kawato, 2006) mechanism by which motivational goals can influence cognitive and subsequent motor control processes. Indeed, the VMS has long been hypothesized to provide the basis for the interface between motivation and action on the basis of its major inputs from limbic areas like the amygdala, hippocampus and the anterior cingulate cortex (ACC) and output to the motor areas via the globus pallidus (Mogenson et al., 1980; Groenewegen et al., 1996). However, rather than a direct limbic-motor connection, the SNS connections provide a more physiologically and

psychologically plausible mechanism by which motivational goals exert their influence on action (Haber et al., 2000).

Evidence from psychopharmacological studies in animals

Rodent research on drug addiction has provided evidence for the functional importance of dopamine-mediated interactions between ventral and dorsal parts of the striatum. For example, Belin and Everitt (2008) have adopted an intrastriatal disconnection procedure in rats to investigate the necessity of the SNS connections in the transition of reward-directed drug-seeking behaviour to habitual behaviour associated with the DLS. The authors lesioned the VMS selectively on one side of the rat brain and, concomitantly, blocked dopaminergic input from the substantia nigra in the DLS with a receptor antagonist on the contralateral side of the brain. Thus, they functionally disconnected the VMS and DLS on both sides of the brain, while leaving unilateral VMS and DLS on opposite sites intact. This functional disconnection between VMS and DLS greatly reduced the transition of VMS-associated to DLS-associated habitual behaviour, whereas the unilateral manipulations were ineffective in isolation (Belin and Everitt, 2008). These data show the functional importance of the spiralling SNS connections in VMS control over dorsal striatal functioning in addiction (Belin et al., 2009).

Functional evidence for a role of dopamine in interactions between motivation and DMS-associated functions has also been established in non-human primates. For example, neurophysiological recordings by Hikosaka and colleagues during the performance of a memory-guided saccadic eye-movement task revealed sensitivity of neuronal firing in the DMS as well as midbrain dopamine neurons to appetitive motivation. In this task, one of four directions was randomly assigned as the target location by a cue that also signalled the anticipation of reward. Subsequently, the monkey had to make a saccade to the remembered location. It was found that cues that predicted reward resulted in earlier and faster saccades relative to cues that predicted no reward. Firing patterns in caudate nucleus (DMS) neurons correlated with the change in saccade behaviour, changing their preferred direction to the rewarded direction (Kawagoe et al., 1998). In a follow-up study, the authors observed that reward-predictive cues resulted in increased firing of dopaminergic neurons in the midbrain, as well as in neurons of the caudate nucleus (DMS) (Kawagoe et al., 2004). Together, these findings demonstrate that effects of reward anticipation on DMS activity and associated motor-planning behaviour were accompanied by changes in dopamine activity.

In humans, a role for dopamine in the effects of motivation on cognition has so far been addressed only in the domain of long-term memory associated with the hippocampus (Wittmann et al., 2005; Adcock et al., 2006; Schott et al., 2006; for a review, see Shohamy and Adcock, 2010). This relatively young field suggests that dopamine may well play a role in the long term plasticity-enhancing effects of motivation. In the next section, we address studies that focus on dopamine-dependent effects of motivation on shorter term plasticity, involving the striatum.

Evidence from human studies: motivation & cognitive flexibility

Data from two recent studies support the hypothesis that dopamine is critical for interactions between motivation and cognitive control. Specifically, these studies highlight an important role for dopamine in the modification by appetitive motivation of switching between well-established habits. The task-switching paradigm involved cued task switching between well-learnt task-sets, minimizing learning and working memory processes (Rogers and Monsell, 1995). Subjects switched between responding according the direction of the arrow (task A) and responding according to the direction indicated by the word (task B) of a series of arrow-word targets (consisting of the words "left" or "right" in a left or right pointing arrow; **figure 1.2a**). Repetitions or switches of task-set were pseudo-randomly preceded by high or low reward cues. In the first study, young healthy adults performed the task in the magnetic resonance scanner and both behavioural and neural responses were assessed as a function of inter-individual variability in dopamine genes (Aarts et al., 2010). In particular, we focused on a common variable number of tandem repeats (VNTR) polymorphism in the dopamine transporter gene (*DAT1*), expressed predominantly in the striatum. Relative to the 10R homozygotes, the 9R carriers exhibited significant reward benefits in terms of overall performance and increased reward-related BOLD responses in VMS. However, most critically, they also demonstrated significant reward benefits in terms of task switching (i.e. reduced switch costs in the high versus low reward condition). This effect was accompanied by a potentiation of switch-related BOLD responses in DMS (caudate nucleus) in the high reward versus the low reward condition (**figure 1.2b and c**). Importantly, the reward-related activity in VMS correlated positively with the effects of reward on subsequent switch-related activity during the targets in DMS, with high dopamine subjects demonstrating high activity in both striatal regions (**figure 1.2d**) (Aarts et al., 2010). These dopamine-mediated motivation-cognition interaction effects were recently replicated in an independent dataset (van Holstein et al., 2011) and strengthened our working hypothesis that striatal dopamine mediates motivational modification of certain forms of cognitive control in humans.

In a second study, we investigated the effect of appetitive motivation on cognitive flexibility in patients with PD using the same paradigm (figure 1.2a). Effects within the PD group were associated with the degree of dopamine depletion in different striatal sub-regions as measured with 123I-FP-CIT single photon emission computed tomography (SPECT). First, we replicated previous studies by demonstrating a switch deficit in PD relative to healthy controls. Interestingly, this deficit was restricted to certain conditions of the task, revealing a disproportionate difficulty with switching to the best established, most dominant "arrow" task. Additionally, the SPECT measurements showed that this switch deficit in PD was associated with dopamine cell loss in the most affected striatal sub-region (posterior putamen, figure 1.2e), thus demonstrating the involvement of striatal dopamine in this particular "habit-like" type of cognitive flexibility. More critically, our results demonstrated compensatory capacity of reward-predictive signals to facilitate cognitive flexibility in mild PD. Specifically, when anticipating reward, patients were able to reduce the switch cost in the dominant arrow task

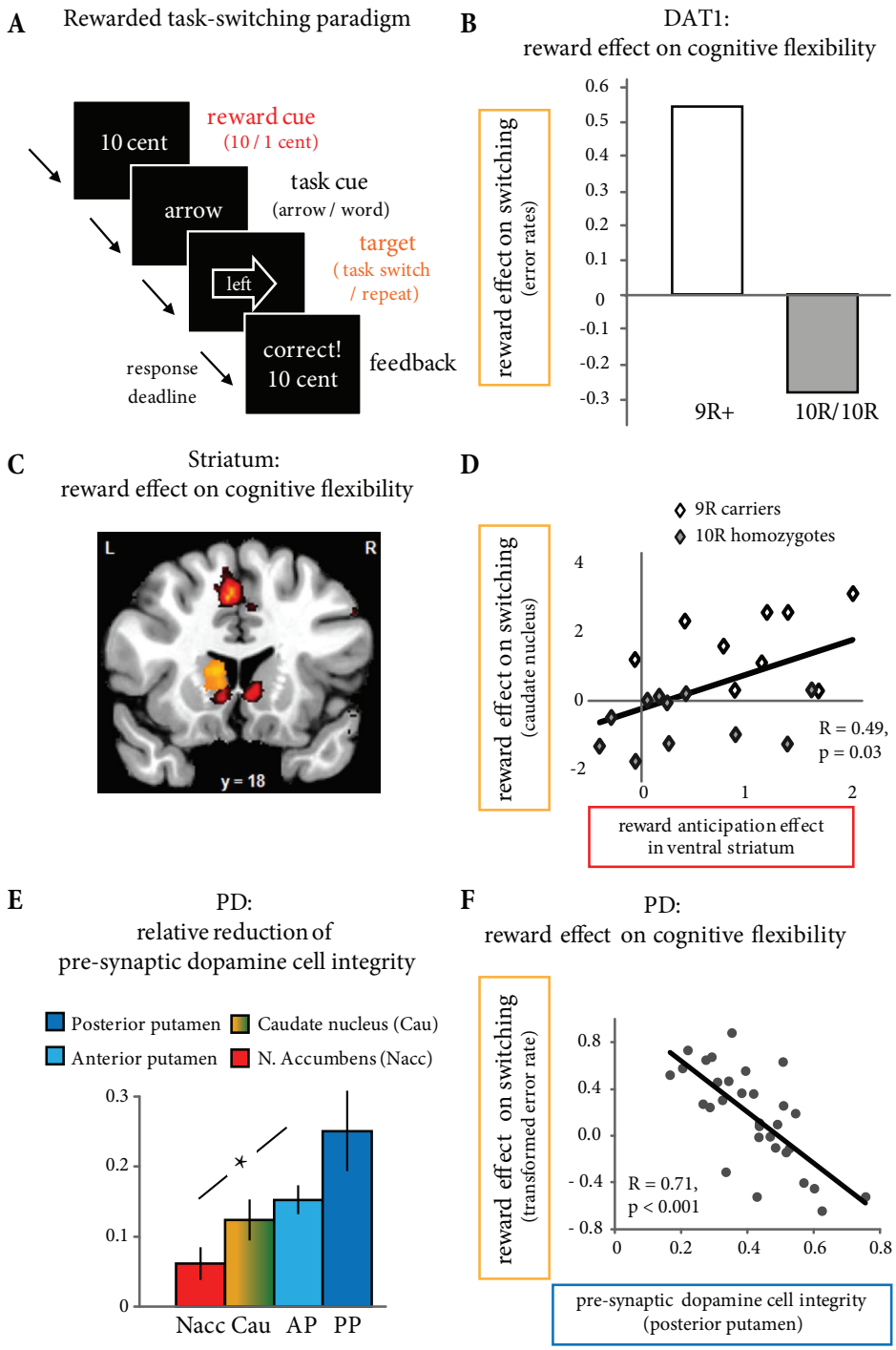

A
Rewarded task-switching paradigm
10 cent
reward cue
(10 / 1 cent)
arrow
task cue
(arrow / word)
left
target
(task switch
/ repeat)
correct!
10 cent
feedback
response
deadline
B
DAT1:
reward effect on cognitive flexibility
reward effect on switching
(error rates)
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
9R+
10R/10R
C
Striatum:
reward effect on cognitive flexibility
L
R
y = 18
D
9R carriers
10R homozygotes
reward effect on switching
(caudate nucleus)
4
2
0
-2
0
1
2
R = 0.49,
p = 0.03
reward anticipation effect
in ventral striatum
E
PD:
relative reduction of
pre-synaptic dopamine cell integrity
Posterior putamen
Caudate nucleus (Cau)
Anterior putamen
N. Accumbens (Nacc)
0.3
0.2
0.1
0
*
Nacc Cau AP PP
F
PD:
reward effect on cognitive flexibility
reward effect on switching
(transformed error rate)
0.8
0.4
0.0
- 0.4
- 0.8
0
0.2
0.4
0.6
0.8
R = 0.71,
p < 0.001
pre-synaptic dopamine cell integrity
(posterior putamen)

Figure 1.2 Experimental evidence for the beneficial effect of motivation on cognitive flexibility in humans

(A) The rewarded task-switching paradigm used in our studies to investigate the motivation–cognition interface. **(B)** In our genetic imaging study (Aarts et al., 2010), participants with genetically determined high striatal dopamine levels benefited more from reward anticipation in terms of task switching than participants with low dopamine levels. **(C)** In our genetic imaging study (Aarts et al., 2010), reward cues elicited activity in VMS (in red), whereas the dopamine-dependent effect of reward prediction on task switching was observed in DMS (in orange). **(D)** Activity in these striatal sub-regions (see **C**) was positively correlated, with high striatal dopamine subjects showing high activity in both VMS and DMS during reward anticipation and rewarded task switching respectively. **(E)** In our SPECT study in Parkinson's disease (Aarts et al., 2012), patients showed the most marked dopamine depletion in the dorsolateral striatum (posterior putamen), whereas the ventromedial striatum (n. accumbens) was least affected. **(F)** Patients with the greatest dopamine depletion (i.e., least dopamine cell integrity) showed the greatest effects of anticipated reward in reducing the switch cost in the dominant arrow task [(switch-repeat)low – (switch-repeat)high]; presumably by increased reward- induced dopamine release in the relatively intact neurons in ventromedial striatum.

to such an extent that the switch cost no longer differed from that of controls on high reward trials. Interestingly, the use of reward was also highly correlated with the amount of dopamine depletion in the most affected striatal sub-region (Aarts et al., 2012). Patients with greater dopamine cell loss made more use of anticipated reward for reducing the switch cost than did patients with less dopamine cell loss (figure 1.2f). Further exploration of this finding demonstrated that this effect of motivation on task switching was driven by two opponent processes: first, patients with more dopamine depletion made more errors on repeat trials under high than under low reward. This detrimental effect of reward on repeat trials could reflect a form of impulsivity, where the current task representation is rendered unstable by reward, leading to reduced cognitive "perseverance" or maintenance (see also Hazy et al., 2006). Controls did not show such detrimental impulsive behaviour on repeat trials under high reward. Second, patients with more dopamine depletion made fewer errors on switch trials under high than under low reward. Thus, anticipated reward proved beneficial for switching to the other task-set, which profits from reduced cognitive perseverance. This effect of reward on switch trials in patients did not differ from that of controls. The beneficial effects of anticipated reward on task switching in the young healthy adults mentioned above (Aarts et al., 2010) was driven by a beneficial effect of reward on switch trials only, instead of opposite effects of reward on repeat and switch trials. In sum, PD patients differed from controls in showing detrimental effects of reward on repeat trials, which were greatest in patients with most dopamine cell loss in the striatum (Aarts et al., 2012). This result fits with previous findings that a low baseline dopamine state contributes to trait impulsivity and addictive behaviour (Cools et al., 2007a; Dalley et al., 2007); presumably due to reduced auto-regulatory mechanisms, resulting in increased dopamine release (Buckholtz et al., 2010). Hence, we speculate that reward-induced impulsivity in our PD group was caused by increased reward-related dopamine release in the relatively intact dopamine cells projecting to the ventral striatum (figure 1.2e). In line with this view are the findings of increased dopamine release in

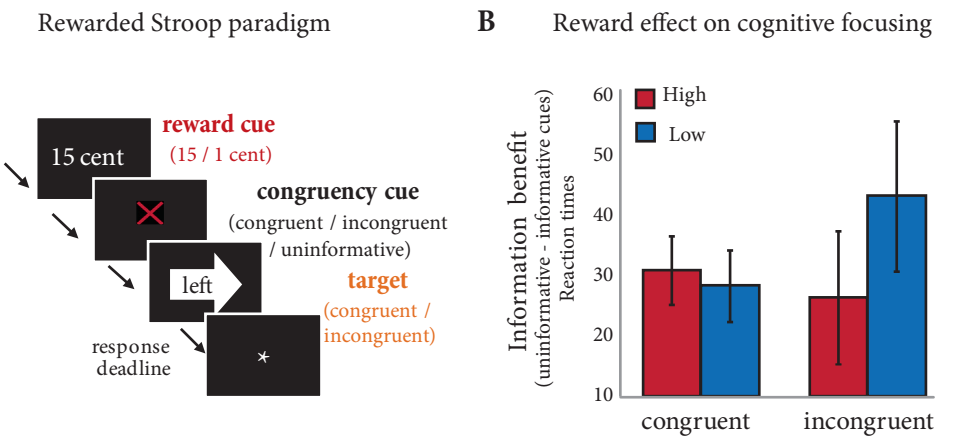


Figure 1.3 Incentive motivation might have detrimental effects on cognitive focusing
(A) The rewarded Stroop paradigm, including a reward cue (1 or 15 cent), an information cue about the upcoming target congruency [informative: incongruent (this example) or congruent (green circle); or uninformative (gray question mark)], and an arrow-word Stroop target. The task was to respond to the direction indicated by the word. **(B)** Reward anticipation had opposite effects on widening and focusing of attention as measured with the information benefit (uninformed–informed) on congruent and incongruent targets respectively; with high anticipated reward particularly impairing proactive focusing on the incongruent trials (M. van Holstein, E. Aarts, R. Cools, unpublished observations).

ventral striatum in PD patients diagnosed with impulsive–compulsive behaviour relative to those without (Evans et al., 2006; Steeves et al., 2009; O'Sullivan et al., 2011). Our PD data are also in accordance with the working hypothesis that striatal dopamine mediates motivational effects on cognition depending on task demands.

Evidence from human studies: functionally specific effects of motivation

Motivation has been shown to improve attentional processes in many perceptual and cognitive control domains (for reviews, see Pessoa, 2009; Pessoa and Engelmann, 2010). Data from a number of human imaging studies have suggested that motivation might have non-specific enhancing effects on cognitive processing. For example, in a functional neuroimaging study, motivational incentives increased PFC activity and connectivity during cognitive control tasks, in a manner that seemed to depend on the cognitive effort (i.e., cost-benefit ratio) rather than on the specific qualitative cognitive demand of the tasks (Kouneiher et al., 2009). Based on these data the authors argued that motivation and cognitive control can be regarded as two separate, additive instead of interactive factors of executive functioning (Kouneiher et al., 2009). However, such an additive view of motivation and cognition contrasts with the conclusion drawn by a different set of recent studies which enabled the disentangling of different cognitive control components. These studies have found that effects of appetitive

motivation and affect may well depend on the type of cognitive processing at hand (Dreisbach and Goschke, 2004; Dreisbach, 2006; Rowe et al., 2007), consistent with our working hypothesis. Before turning to these studies, we will discuss preliminary data from our own lab. So far we have seen that appetitive motivation can potentiate certain forms of task switching to well-established stimulus-response mappings in a dopamine-dependent manner. The observation that these effects were driven by detrimental effects of anticipated reward on repeat trials and beneficial effects on switch trials in the PD group (Aarts et al., 2012) already indicates a level of functional specificity. To test more directly the hypothesis that these beneficial effects of appetitive motivation on some cognitive functions might come at the expense of impairments on other cognitive functions, we designed a Stroop-like conflict task with high and low reward conditions. This task resembled the previously used task-switching paradigm in many ways except that it required cognitive focusing instead of cognitive switching. Seventeen participants performed this Stroop-like task by responding with a left or right button press to the words "left" or "right" in a left or right pointing arrow (figure 3a). The direction denoted by the word was either congruent or incongruent with the direction indicated by the arrow. Similar to the task-switching paradigm discussed above (Aarts et al., 2012), all trials began with a cue predicting high or low reward for correct performance. Critically, following the reward cues, we explicitly informed participants about the (in)congruency of the upcoming Stroop target (see Aarts et al., 2008). In half of the trials, participants were informed about this congruency by informative cues (figure 3a). In the other half of the trials, the targets were preceded by cues that gave no information about the upcoming congruency. The idea here was that incongruency-predictive cues (relative to non-informative cues) would encourage participants to reduce their attentional focus, whereas the congruency-predictive cues would encourage participants to widen their attentional focus. In other words, cues that signalled upcoming incongruent targets would encourage participants to proactively focus on the task-relevant word, preventing distraction by the task-irrelevant arrow, whereas cues that signal upcoming congruent words encouraged participants to proactively widen attention in order to comprise both the task-relevant word as well as the task-irrelevant arrow (see Aarts et al., 2010). The combination of reward and information cues enabled us to determine the effects of appetitive motivation on the cognitive focusing of attention.

Consistent with our previous results (Aarts et al., 2008) we showed that (irrespective of reward condition) participants responded faster and made less errors when informative cues preceded the congruent and incongruent targets relative to uninformed targets (M. van Holstein, E. Aarts, R. Cools. unpublished observations). Importantly, as predicted, appetitive motivation significantly altered the information benefit depending on the congruency of the targets. That is, proactive widening of attention (uninformed-informed congruent targets) benefitted from anticipated reward (15 vs. 1 cent), whereas proactive focusing of attention (uninformed-informed incongruent targets) was hampered by anticipated reward (**figure 1.3b**). Intriguingly, these data show that, depending on the task at hand, appetitive motivation can have both beneficial as well as detrimental effects on cognitive function.

Similar findings have been obtained when studying the effects of positive affect on cognitive control. Thus, positive affect has been shown to increase cognitive flexibility (i.e., decreasing perseveration), while increasing distractibility (i.e., decreasing cognitive stability) on different types of trials in a task switching paradigm (Dreisbach and Goschke, 2004). Similar opposite effects have been observed in an AX continuous performance task: Positive affect increased cognitive flexibility when a maintained goal unexpectedly changed (Dreisbach, 2006; van Wouwe et al., 2009), but, within the same task, positive affect decreased the ability to maintain the goal when nothing changed (Dreisbach, 2006). Functionally specific effects of positive affect have also been demonstrated in conflict paradigms, like the Eriksen flanker task. Some authors have shown that positive affect increased attention towards the distracting flanker arrows, thus, increasing 'the breadth of attentional selection' (Rowe et al., 2007); similarly, others have found that positive affect reduced the ability to focus on the target arrow after experienced conflict (van Steenbergen et al., 2010). Our preliminary results from the rewarded Stroop conflict paradigm extend these effects of positive affect in the flanker conflict task, by revealing contrasting effects of appetitive motivation on the widening and focusing of attention within the same task and within the same participants. In sum, both appetitive motivation and positive affect enhance certain forms of cognitive flexibility at the expense of cognitive focusing. According to our working hypothesis, these effects might reflect dopamine-dependent flow of information processing related to Pavlovian incentives from ventromedial parts of the striatum to more dorsal regions in the striatum, associated with habit-like information processing.

It might be noted here again that multiple mechanisms have been proposed to underlie the motivational control of behaviour (Dickinson and Balleine, 2002). We have highlighted that some motivational influences can be maladaptive, and these might implicate dopamine. However, there is also evidence for motivational influences on goal-direct behaviour, that is, those mediated by instrumental incentive learning and acquisition of action-outcome representations (Dickinson and Balleine, 2002). These alternate mechanisms might account for findings that at first sight seem incompatible with the current working hypothesis. Specifically, appetitive motivation has been shown to increase spatial orienting to a target location in the face of distracters (Engelmann and Pessoa, 2007; Engelmann et al., 2009), or to reduce conflict by biasing visual selection (Padmala and Pessoa, 2011). Furthermore, in young and old adults as well as in medicated patients with Parkinson's disease, motivation increased anti-saccade performance, encompassing incompatible stimulus-response mappings like in Stroop and flanker paradigms (Harsay et al., 2010). The critical question is whether these effects are also dependent on striatal dopamine, or whether they implicate modulation by different neurochemical systems. Addressing this question requires controlled dopaminergic medication withdrawal and/or pharmacological manipulation approaches.

Frontal control of dopamine-dependent striatal processing

The striatum does not act alone and requires interactions with specific frontal regions to operate effectively (Alexander et al., 1986; Passingham, 1993) (**figure 1.1**). Recent neuroimaging work in humans and monkeys has revealed that effects of appetitive motivation on cognitive control are accompanied by modulation of responses in the PFC (Ichihara-Takeda and Funahashi, 2008; Kouneiher et al., 2009; Beck et al., 2010; Ichihara-Takeda et al., 2010; Jimura et al., 2010; Wallis and Kennerley, 2010). For example, functional interactions between the medial and the lateral PFC have been shown to accompany effects of appetitive motivation on the cognitive control processes involved in task switching (Kouneiher et al., 2009). Another functional neuroimaging study concluded that the lateral PFC incorporates reward value in goal-directed control during working memory processes (Jimura et al., 2010).

These data concur with the existence of multiple mechanisms for the motivational control of behaviour, which may interact in multiple ways, either competitively or synergistically. For example, signals in the PFC might control dopaminergic activity in striatal areas in a top-down manner, thus allowing controlled influences on value assignment to states or actions (Daw et al., 2005; Doll et al., 2009) (see **figure 1.1**). Consistent with this hypothesis are observations that stimulation of different parts of the frontal cortex (using transcranial magnetic stimulation) alters focal dopamine release in strongly connected topographically specific parts of the striatum (as measured using [11C]raclopride positron emission tomography) (Strafella et al., 2001; Strafella et al., 2003; Strafella et al., 2005; Ko et al., 2008). The role of the PFC in integrating motivation, cognition and action is also highlighted by anatomical tracer studies in non-human primates showing that value-sensitive regions in ventromedial PFC (i.e., ACC/orbitofrontal cortex) project not only to strongly connected regions in ventromedial striatum, but also diffusely to more dorsal regions in the striatum that receive most projections from the DLPFC (Haber et al., 2006) (**figure 1.1**). Electrophysiological work with rodents has revealed that changes in dopamine release and receptor stimulation in the striatum can alter such PFC input to the striatum (Goto and Grace, 2005). More specifically, changes in tonic dopamine release were shown to modulate PFC inputs into the VMS – and to influence set shifting behaviour - through dopamine D2 receptors (Goto and Grace, 2005). These results show that striatal dopamine can modulate motivated behaviour not only via altering striatal output but also via altering striatal input *from* the PFC.

Conclusions and future directions

There are multiple mechanisms for the control of behaviour and cognition by motivation. This paper focuses on the appetitive motivational system, while recognizing that opponent influences on behaviour are likely seen of the aversive motivational system. In particular we have concentrated on those effects of appetitive motivation that implicate dopamine. These dopamine-dependent effects of motivation likely have both detrimental as well as

beneficial consequences for cognition, via altering information flow from ventromedial to dorsolateral parts of the striatum. This general observation is in line with the observation that motivational influences on behaviour are not necessarily driven by representations of the goals of instrumental behaviour, but might well reflect Pavlovian or habit-like anomalies. This is particularly likely in the case of dopamine, which is recognized to play a special role in Pavlovian and habit systems.

An important implication of this observation is that effects of dopamine on interactions between motivation and cognitive control that appear to be mediated by a modification of motivational influences on cognitively mediated, goal-directed behaviour, like task switching, may in fact reflect modification of motivation influences on habitual behaviour. Findings that the dopamine-dependent effects of motivation on task switching are strongest when participants are required to switch to well-established stimulus-response mappings are in line with this hypothesis, which requires testing in future work.

A further issue to be addressed in future research is the degree to which the contrasting effects of motivation on habit-like switching and on proactive focusing can be understood in terms of competition between a striatal system controlling habit-like processing and a prefrontal system controlling goal-directed behaviour (Dickinson, 1985; Daw et al., 2005). Clearly these questions require a careful integration of traditional psychological approaches, which leverage well-operationalized behavioural definitions of goal-directed and habitual behaviour, with pharmacological studies of cognitive control.

Furthermore given the proposed opponency between appetitive and aversive motivational systems, one might ask what is the effect of punishment-predictive stimuli on cognition? This is particularly interesting in the context of empirical findings that conditioned inhibitors, i.e. stimuli predictive of reward omission do not trigger an increase, but rather if anything a decrease in midbrain dopamine firing (Tobler et al., 2005). Moreover there is increasing speculation about the involvement of the part-opponent system of serotonin (Daw et al., 2002; Dayan and Huys, 2009; Boureau and Dayan, 2011; Cools et al., 2011), an area that is wide open for empirical work.

Finally, progress in the understanding of the motivational control of cognition will depend on the degree to which the balance between transient and sustained, e.g., context effects are taken into account (e.g., Higgins et al., 1997; Maddox and Markman, 2010; Savine et al., 2010). For example, Maddox and Markman (2010) propose that performance does not only depend on local incentives and task demands (as discussed in the current review), but also interacts with global incentives like an overall bonus or punishment at the end of a task. Such advances will no doubt benefit from the recognition that the impact of transient (phasic) changes in neurotransmitter activity depends critically on the tonic neurochemical state of the system.

Chapter 2

General introduction and thesis outline

In the overview in **chapter 1**, a number of hypotheses related to the role of dopamine in motivated cognitive control were proposed. The experiments presented in this thesis aim to address a number of these hypotheses, thereby focusing on the effects of reward motivation on flexible switching between well-established task sets. First, the experiments presented in this thesis speak to a causal role for dopamine in motivated cognitive control and aim to elucidate which dopamine receptor type is involved in this process. In doing so, natural variation in baseline dopamine signalling is taken into account to explain individual differences in task- and drug effects. Second, following previous neuroimaging work that suggests a role for the striatum in mediating the effect of motivation on task switching, the work in this thesis aims to assess the necessity of the striatum. Finally, it aims to test the hypothesis that the prefrontal cortex can alter processing in the striatum during motivated cognitive control.

Genetic differences in dopaminergic drug-response

Chapters 3 and 4 aim to further elucidate the role of dopamine and specific dopamine receptors in motivated cognitive control by assessing the effect of dopaminergic drugs on the integration of motivation and flexible control, both in healthy subjects (**chapter 3**) and patients with ADHD (**chapter 4**).

One challenge with pharmacological studies is that individuals can vary greatly in their response to drugs. This idea is illustrated by a study in which the effect of a dopamine receptor agonist on cognitive functioning was assessed (Kimberg et al., 1997). This work revealed that subjects with low basal memory capacity benefited from bromocriptine (**box 2.2a**) on a range of complex cognitive tasks, whereas already high functioning individuals (with high basal memory capacity) showed detrimental effects of the same drug (Kimberg et al., 1997). This phenomenon can be explained by an inverted U shaped theory, which states that an individual's response to dopaminergic drugs depends on the baseline state of that subject (Cools and Robbins, 2004). Thus, dopamine can have beneficial effects on cognitive functions, but both too low and too high levels of dopamine can impair cognitive functioning (Williams and Goldman-Rakic, 1995; Arnsten, 1998).

One source of individual variation in basal levels of dopamine activity may arise from genetic variation. Numerous pharmacogenetic studies have shown that individual differences in dopamine genes can account for individual differences in response to drugs. For example, Mattay and colleagues (2003) exploited inter-individual differences in natural variation in the gene coding for the catechol-*O*-methyltransferase (COMT) enzyme. COMT is the primary mechanism for terminating the action of dopamine in the prefrontal cortex. Variation in this gene is associated with individual differences in dopamine signalling. Mattay and colleagues showed that individuals with genetically determined low dopamine signalling performed worse on a 'prefrontal' cognitive task than those carrying the allele associated with higher dopamine signalling. However, after the administration of amphetamine, which increases dopamine levels, performance of low baseline subjects improved, while amphetamine had

no effect in the group of subjects with already high dopamine levels. Furthermore, a number of studies have shown that the effects of a dopamine D2 receptor agonist can be explained by natural variation in the gene coding for the dopamine D2 receptor (Kirsch et al., 2006; Cohen et al., 2007). Subjects carrying the *Taq*1A1 variant of the allele (A1+ subjects) have ~30% fewer dopamine D2 receptors in the striatum and exhibit impairments in reward processing, compared with those not carrying this allele (A1- subjects). Cohen and colleagues (2007) assessed whether this genetic predisposition could explain individual responses to a dopamine receptor agonist during reward processing. To this end they used a reversal learning paradigm, which requires flexible adaptation of behaviour when a previously rewarded stimulus is no longer rewarded and a new rule needs to be learned. In the placebo condition, the low dopamine receptor group (A1+ subjects) performed worse than the A1- group. However, administration of the dopamine D2 receptor agonist cabergoline improved rule-learning performance in the subset of subjects with genetically determined low dopamine receptor density (A1+), but the dopamine D2 receptor agonist impaired performance in those already performing well under placebo (the A1- group). This effect was accompanied by opposite effects in reward-related neural responses in regions of the reward network (the medial orbitofrontal cortex and striatum): Administration of the D2 receptor agonist increased activity in these regions in subjects with low reward-related activity under placebo (A1+), while it had the opposite effect in those with already high baseline reward-related activity (A1-).

As was discussed in **chapter 1**, in addition to predicting individual differences in drug response, natural (genetic) variation between individuals can also explain individual differences in task performance (e.g. (Frank et al., 2007; Dreher et al., 2009; Aarts et al., 2010; Colzato et al., 2010a; Stelzel et al., 2010) (**box 2.2c**). In **chapters 3 and 4**, I exploited individual variability in the gene coding for the dopamine transporter (DAT) to account for inter-individual variability in task performance, neural signalling, and drug response. Task-related differences in performance or neural signalling as a function of variation in this genotype can be taken to suggest that dopamine is involved in the studied process.

Evidence for a role for dopamine in the integration of reward motivation and cognitive control has been provided by a number of studies, and much of this evidence is reviewed in **chapter 1** of this thesis. Previous work that also employed the rewarded task-switching paradigm presented in this thesis (**box 2.3**) has shown that reward can modulate flexible control in the context of task switching (Aarts et al., 2010). The anticipation of a reward (i.e. high vs. low reward cue) increased neural responses in the ventral striatum, while the integration between reward and task switching was associated with increased signalling in the caudate nucleus. Interestingly, these signals correlated, suggesting that communication between the ventral and dorsal striatum may mediate the information transfer from reward regions to cognitive control regions (**figures 1.2c, d and 2.1, box 2.1**). Dopamine-dependent effects in this latter study were revealed by showing that inter-individual differences in signalling in the caudate nucleus depended crucially on individual differences in dopamine signalling, measured by exploiting differences in the *DAT1* genotype. Although these results provide

a strong foundation for the hypothesis that dopamine is involved in motivated cognitive control, they do not directly manipulate the dopamine system, nor do they provide evidence for the involvement of any specific dopamine receptor subtype.

Box 2.1 | The striatum and its spiralling striato-nigral-striatal projections

The striatum is the input structure of the basal ganglia, a collection of nuclei located deep in the brain, which are involved in a wide range of behaviours. The striatum can be roughly divided into three parts: the ventral part (VS, **figure 2.1: red**), including the nucleus accumbens, which is primarily involved in Pavlovian processes and the anticipation of rewards, the caudate nucleus (**figure 2.1: orange/green**), which is implicated in instrumental conditioning and goal-directed behaviour, such as the flexible updating of task demands, and the putamen (**figure 2.1: blue**), which is involved in motor processes. The striatum is well-connected to other parts of the brain and thus ideally suited to integrate signals about context and novelty from the hippocampus, affective processes and reward value from the amygdala and top-down processes such as attention, conflict and working memory related signals from the prefrontal cortex (**figure 2.1**).

Approximately 90% of striatal neurons are GABA-ergic medium spiny neurons (MSNs), which express dopamine receptors. Importantly, these inhibitory MSNs cannot generate activity (unlike for example dopamine neurons). Instead, changes in striatal activity modulate signals from other regions, such as excitatory glutamatergic inputs coming from the frontal cortex. Dopamine signals in the striatum are thought to play an important role in how input from other regions, such as the hippocampus and prefrontal cortex, affect signalling in the striatum (Grace et al., 2007). These dopamine signals originate from the midbrain (VTA/SN: ventral tegmental area and substantia nigra) and can modulate the excitability of the striatum, either by facilitating or inhibiting neuronal activity, depending on which dopamine receptors are stimulated (i.e. D1 or D2) and the concentration of dopamine (**box 2.2**). Stimulation of D1 receptors increases the excitability of striatal neurons, whereas dopamine D2 receptor stimulation decreases the responsiveness of these neurons, making the striatum either more or less sensitive to prefrontal input, respectively (**box 2.2**). The striatum in turn sends projections back to the cortex (via other nuclei e.g. the pallidum, subthalamic nucleus and thalamus), forming the so-called corticostriatal circuits (Alexander et al., 1986) and to the midbrain, forming striato-nigral-striatal loops (Haber et al., 2000) (**figure 1.1 and 2.1**). These corticostriatal circuits are organized in functionally specific circuits (**chapter 1**). The segregated nature of the corticostriatal circuits in functionally specific circuits is largely maintained in these striato-nigral connections, but importantly, each region of the striatum projects to the part of the midbrain connected to a slightly more dorsolateral striatal region, allowing the integration of information across circuits. This organization of the striatum and cortex in cortico-striatal-pallidal-thalamus-cortical circuits allows them to work together to enable a broad behavioural repertoire.

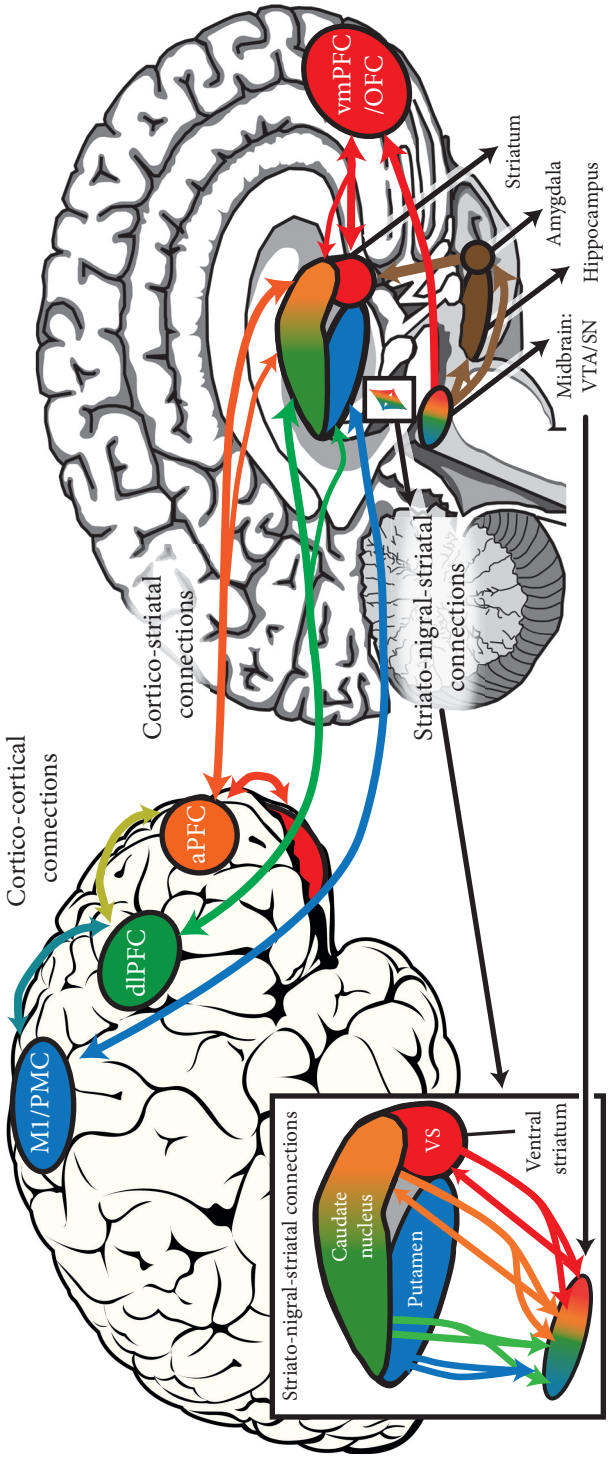


Figure 2.1 The organization of the midbrain, striatum and prefrontal cortex in cortico-striatal-nigral circuits
Three ways by which information about rewards (red /orange), cognitive control (green) and actions (blue) can be integrated. Information can be integrated at the cortical level, by direct cortico-cortical connections, or at the level of the striatum by direct cortico-striatal interactions, e.g. the aPFC projecting to not only to the anterior (orange), but also to posterior parts of the caudate nucleus (green) or by striato-nigral-striatal connections, at the level of the midbrain. Note that the regions in this figure are scaled to relative importance to the work in this thesis, and are not true to anatomical size.

Dopamine receptor specific effects during motivated cognitive control

Optimal cognitive control requires persistence in the face of distracting stimuli when pursuing a goal, and the ability to flexibly adapt behaviour when circumstances change. The dual-state theory provides a mechanism by which these opposing cognitive functions can act together to allow adaptive behaviour (Durstewitz and Seamans, 2008). This theory proposes that the cognitive effects of dopamine and dopaminergic drugs depend on the subtype of dopamine receptor that is activated in the prefrontal cortex (Durstewitz and Seamans, 2008). Two dopamine states are proposed to account for these opponent processes: A D1-dominated state, which is beneficial for robust online maintenance of information, and a D2-dominated state, which is associated with higher flexibility. Although this theory focussed on the prefrontal cortex, it is important to keep in mind that dopamine D2 receptors are abundantly expressed in the striatum, but that the expression of these receptors in the prefrontal cortex is low (Hurd et al., 2001). D2 receptors in the striatum might be especially important for the flexible updating of task representations, whereas prefrontal dopamine D1 receptor stimulation is beneficial when a task requires stable representations. Experimental- and computational work indeed showed that the striatum is especially important when the updating of prefrontal representations is required (Frank et al., 2001; van Schouwenburg et al., 2010). More specifically, the striatum is thought to act as a gating mechanism, which updates and stabilizes active maintenance in the prefrontal cortex. Interestingly, it was proposed that this gating mechanism is driven by (reward-related) midbrain dopamine (Cohen et al., 2002). The idea that dopamine D2 receptor stimulation plays an important role in flexible behaviour has further been evidenced by pharmacological experiments in rodents (Floresco et al., 2006b; Kellendonk et al., 2006) and humans (Mehta et al., 2004; Stelzel et al., 2010). In terms of reward processing, both dopamine D1 and D2 receptor stimulation play a role (Ikemoto et al., 1997; Koch et al., 2000; Cohen et al., 2007). However, the mechanism by which dopamine modulates motivated cognitive control so far remains elusive.

In **chapter 3**, I aimed to assess whether dopamine D2 receptor stimulation modulates task switching, or the interaction between reward and task switching. To this end, I analyzed the results of an experiment in which the dopamine D2 receptor agonist bromocriptine was administered and compared performance on the rewarded task-switching paradigm (**box 2.3**) in a placebo session with performance after subjects received a dose of bromocriptine (**box 2.2a**). However, bromocriptine does not act exclusively on the dopamine D2 receptor, but also has some affinity for dopamine D1 receptors. To confirm that the effects of bromocriptine were indeed associated with dopamine D2 receptor stimulation, a pre-treatment approach was used (**box 2.2a**). Further, building on previous work (Aarts et al., 2010; Cools and D'Esposito, 2011), we took into account the genetically determined state of the dopamine system for two reasons. First, we aimed to explain inter-individual differences in responses to dopaminergic drugs and on task performance. Second, we exploited variation in the *DAT1* genotype because the DAT is most abundant in the striatum. Therefore, it is conceivable that

any effects dependent on the *DAT1* are associated with the striatum. The previous observation that motivated cognitive control depends on striatal dopamine signalling (**chapter 1**) was replicated in **chapter 3**, by showing that the effect of reward on task switching depended on individual differences in the *DAT1* genotype. Although the administration of bromocriptine affected task switching, it had no effect on the interaction between reward and task switching. Thus, the work in **chapter 3** revealed a role for dopamine in motivated cognitive control. However, evidence for the involvement of dopamine D2 receptors in motivated cognitive control was not provided. Given previous evidence for a role of dopamine D1 and D2 receptors (Koch et al., 2000), or even combined dopamine D1 and D2 receptor stimulation (Ikemoto et al., 1997) in reward motivation, we aimed to manipulate the dopamine system in a more general manner in **chapter 4**. To this end we administered the rewarded task-switching paradigm in patients with attention deficit hyperactivity disorder (ADHD) after intake and withdrawal of methylphenidate, a non-selective catecholamine reuptake blocker (**box 2.2b**), and compared their performance and brain activity to that of a group of subjects without ADHD.

Clinical relevance: Neuropsychiatric deficits in motivated cognitive control

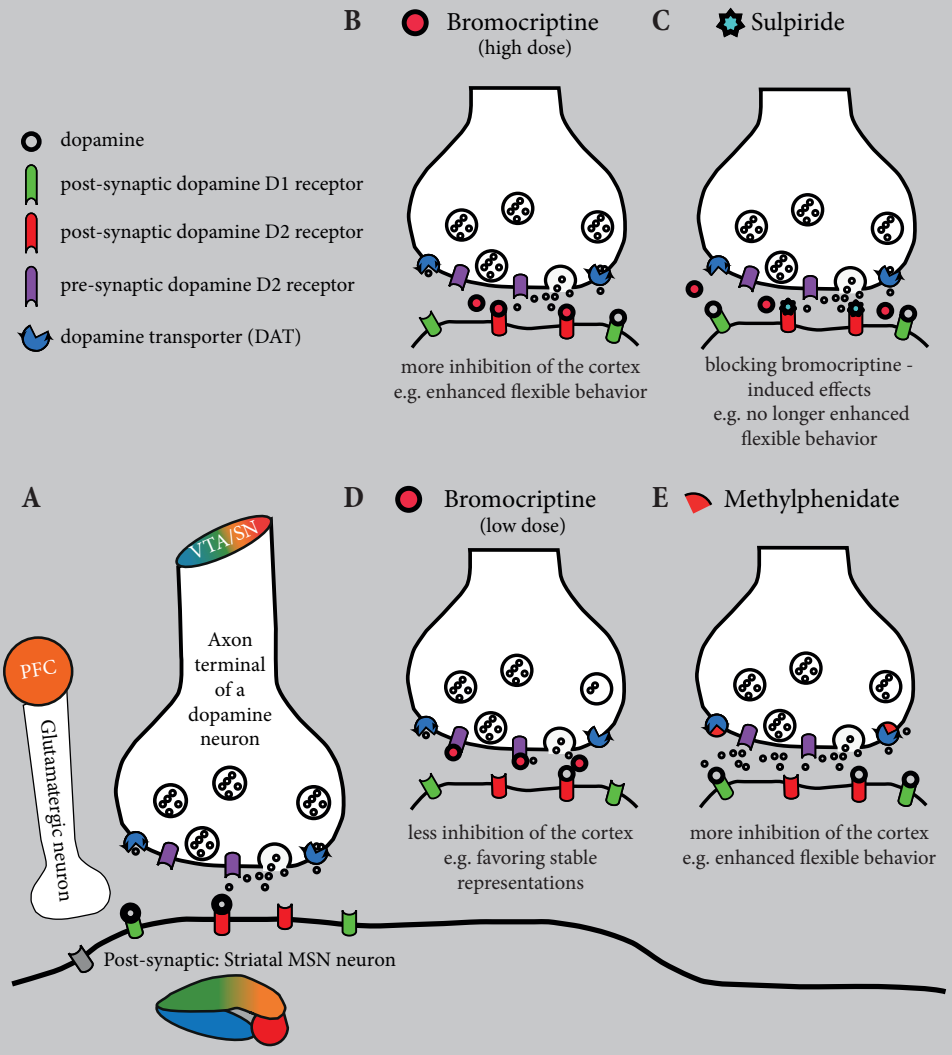
ADHD is a neuropsychiatric disorder with symptoms related to hyperactivity, inattention and/or impulsivity, which start in childhood (American Psychiatric Association, 1994, 2013). ADHD is not exclusively a childhood disorder, but it continues to affect`~2.5% of adults (Simon et al., 2009). Deficits in flexible, adaptive control have been reported in ADHD (Sonuga-Barke, 2003; Dibbets et al., 2010), but also in other neuropsychiatric disorders such as schizophrenia (Ravizza et al., 2010), Parkinson's disease (Cools et al., 2001a), and obsessive compulsive disorder (OCD) (Meiran et al., 2011). Interestingly, deficits in these disorders are not restricted to the cognitive domain, but often extend to reward processing deficits, at least in ADHD (Plichta and Scheres, 2014), schizophrenia (Strauss et al., 2014) and OCD (Figee et al., 2010). Combined with the abundance of evidence above showing that motivation can indeed change cognitive processing, it is conceivable that at least some of these cognitive deficits may actually stem from deficits in the motivational domain.

Previous work has indeed shown that motivation can improve cognitive control in children with ADHD (Konrad et al., 2000), but studies on motivated cognitive control are thus far absent in this group. Previous attempts to elucidate the neural mechanism underlying aberrant neural processing in ADHD often focused on deficits in dopamine signalling in the prefrontal cortex, but deficits in reward-related striatal dopamine have also been suggested in ADHD (Tripp and Wickens, 2009). We hypothesized that ADHD would be accompanied by aberrant integration of reward and cognitive neural signalling and that *striatal* dopamine would be involved in this process. **Chapter 4** addresses this issue by assessing, in adults with ADHD compared with healthy individuals, how reward motivation can alter neural

processing during the execution of the rewarded task-switching paradigm (**box 2.3**). To this end, I compared a group of adults who were diagnosed with ADHD with a group of subjects without ADHD while they performed the rewarded task switching paradigm in a functional MRI environment (**box 2.4**). Effects of dopamine in these patients were assessed by testing the patients both after their normal dose of methylphenidate (i.e. after Ritalin®, or an equivalent dose of Ritalin for those usually taking Concerta®; **box 2.2b**) and after withdrawal from their normal medication (**box 2.2b**). This enabled me to assess whether ADHD medication affects the integration of motivation and cognitive control signals. Further, to account for inter-individual differences in task performance and neural processing during this task (Aarts et al., 2010), individual variability in the dopamine transporter genotype was taken into account (**box 2.2c**). The results revealed that ADHD was accompanied by excessive signalling in the striatum when patients had not taken their medication. However this effect depended on the *DAT1* genotype, and was only present in a subset of patients. In addition, this excessive striatal response was normalized after intake of methylphenidate. Surprisingly however, we did not replicate the previous observation that motivated cognitive control varies according to the *DAT1* genotype in healthy subjects ((Aarts et al., 2010) and **chapter 3**). One major difference between these studies was the age of the subjects: those in **chapter 3** were ~22 years old, whereas the control group in **chapter 4** was on average 38 years old. In **chapter 5** I therefore aimed to assess whether the age of the participants could indeed explain the differences between these studies.

Box 2.2 | Dopamine

Neuroimaging tools (e.g. functional MRI (fMRI); **box 2.4** and TMS; **box 2.5**) provide valuable insight in the brain regions involved in the execution of tasks or in the connectivity between regions. Although fMRI BOLD might correlate with changes in dopamine (Knutson and Gibbs, 2007) and TMS can induce changes in dopamine release in the striatum (Strafella et al., 2003), these methods alone do not provide direct evidence for the involvement of any given neurotransmitter system. Ideally then, to assess the involvement of dopamine in the anticipation of reward, one would want to administer a drug that manipulates the dopamine system.



This figure was inspired by: Marieke van der Schaaf (2014)
Dopaminergic modulation of reward and punishment learning (PhD thesis)

2.2a Dopamine receptor agonist / antagonist

In **chapter 3**, I used the dopamine receptor agonist, bromocriptine to assess the role of the dopamine system, in particular the dopamine D2 receptor, in rewarded task switching. One problem with human pharmacology is that many of the pharmacological agents lack receptor specificity. Bromocriptine for example, binds primarily, but not exclusively, to the dopamine D2 receptor (**figure b and d**). However, it also acts on the dopamine D1 receptor and it can even exert its action via the noradrenaline and serotonin systems. To strengthen the claim of the involvement of dopamine D2 receptors when observing an effect of bromocriptine, a pre-treatment approach was used. To this end, bromocriptine was co-administered with sulpiride, a D2 receptor antagonist, which does not bind to dopamine D1 receptors (**figure c**). The rationale behind this design is as follows: If the effect observed after bromocriptine treatment was indeed mediated by dopamine (D2) receptor stimulation, then blocking the dopamine (D2) receptors (i.e. by means of co-administration of bromocriptine and sulpiride) should 'undo' the effect of bromocriptine. However, if the behavioural effects were mediated by another neurotransmitter system or D1 receptor stimulation, then blocking dopamine (D2) receptors should not affect the results obtained after bromocriptine treatment alone.

2.2b Methylphenidate

Once dopamine has been released into the synapse, it binds to dopamine receptors, but its action is quickly terminated by reuptake, allowing it to modulate goal-directed and reward-related behaviour on a relatively fast time scale (Floresco et al., 2003; Grace et al., 2007) (**figure a**). The dopamine transporter (DAT) is the primary mechanism for terminating the action of dopamine in the striatum. Methylphenidate (e.g. instant release: Ritalin®, slow release: Concerta®) is a drug that blocks the DAT, thereby increasing dopamine levels (Volkow et al., 2001) (**figure e**). Methylphenidate is the most commonly prescribed pharmacological treatment for ADHD. In **chapter 4**, I tested patients with ADHD twice, once after intake of their normal dose of Ritalin® (or after an equivalent dose of Ritalin® for those usually taking Concerta®) and once after patients had refrained from taking their medication for 24 hours. To account for individual differences to drug responses, we took into account inter-individual variability in the *DAT1* genotype. When interpreting the effects of methylphenidate it is important to keep in mind that it not only blocks the dopamine transporter, but also exerts its action by blocking noradrenaline transporters, primarily in the prefrontal cortex.

2.2c The dopamine transporter genotype (DAT1/SLC6A3)

One way to account for inter-individual differences in dopamine function is by taking into account natural variation in the dopamine transporter (DAT) genotype (*DAT1/SLC6A3)*. Within this gene, short sequences of DNA are repeated (in tandem), and the number of times this repetition occurs varies across participants (i.e. is polymorphic). When assessing variation in the variable number of tandem repeats (VNTR) in a particular part of the DAT gene, the 3'untranslated region (UTR), people can have between 3 and 11 repeats of the gene, but the 9-repeat (9R) and 10-repeat (10R) are most common and thus often the focus of research.

Variation in this polymorphism has been used to assess whether drug and/or task effects are dopamine-dependent. However, the effect of having either of the VNTRs on the baseline levels of dopamine is still under debate. *In vitro* studies have shown that the VNTR has an effect on DAT expression and that the 10R allele is associated with higher expression (Fuke et al., 2001). A number of *in vivo* studies have used single photon emission computed tomography (SPECT) to assess DAT-density in human subjects. The results are inconsistent (**table**), but those with the largest sample of healthy subjects suggest that (healthy) humans carrying the 9R allele may have upregulated DAT. However, the next question then is how these inter-individual differences in DAT expression relate to differences in dopamine signalling. The SPECT studies measure DAT binding, reflecting how much DAT is present, and do not measure any differences in dopamine levels or dopamine release. The DAT is highly adaptive to homeostatic needs; it is thus possible that subjects with higher phasic dopamine levels will have upregulated DATs to terminate dopamine's action after it has been released.

Although the effects of either carrying at least on 9-repeat allele (9R+), of two 10-repeat alleles (10R/10R) *DAT1* genotype are to be determined, we do consistently see effects of the *DAT1* on behaviour and neural responses. For example, variability in the *DAT1* gene predicted reward-related activity in ventral striatum (Dreher et al., 2009; Forbes et al., 2009; Aarts et al., 2010). In line with the hypothesized increase in phasic dopamine signalling in individuals who carry at least one 9 repeat allele, these studies revealed increased neural activity (measured with fMRI) in the ventral striatum in individuals carrier 9 repeats of the allele (compared with 10R homozygotes) during reward processing.

DAT expression	Study	Sample	N: total (age)	N: 9/9; 9/10; 10/10	SPECT Ligand	ROI
9R+ > 10/10	van de Giessen 2009	Healthy	79 (18-35)	5;27;45	ß-CIT	9R/9R vs. 10/10 sign in P 9R/10R vs. 10/10 in striatum, CN and P
9R+ > 10/10	van Dyck 2005	Healthy	96 (18-88)	5;36;53	ß-CIT	Both in CN and P
9R+ > 10/10	Jacobsen 2000	Healthy	27 (37 ± 9.3)	2;7;18	ß-CIT	Striatum
9/10 < 10/10	Heinz 2000	AA and H	14 AA (37 ± 7) 11 H (34 ± 11)	0;10;15	ß-CIT	P (CN is not significant)
9/10 & 10/11<10/10	Cheon 2005	ADHD	11 (9.82 ± 1.33)	4x 9/10, 10/11; 7x 10/10	[^{123}I]IPT	BG
No effect	Martinez 2001	H and SZ	31 H (~40.5) 29 SZ (~39)	23x 9/9 9/10, 9/11; 36x 10/10	ß-CIT	No effects
No effect	Lafuente 2007	SZ	62 SZ (~30)	5;30;25	[^{123}I] FP-CIT	No effects (CN, aP, mP, pP)
No effect	Lynch 2003	H and PD	66 H: 46 (18-83) 95 PD: 60.8 (37-84)	14;68;74; other:7	^{99}Tc-TRODAT-1	No effects

SZ = schizophrenia patients, H = healthy subjects; AA = abstinent alcoholics; PD = Parkinson's disease; ADHD = attention deficit hyperactivity disorder (Korean children); CN = caudate nucleus; P = putamen (aP, mP and pP refer to anterior, medial or posterior putamen); β-CIT = ^{123}I-(2- β -carbomethoxy-3-β(4-iodophenyl)-tropane; [^{123}I]IPT = I-123-N-(3-iodopropen-2-yl)-2h-carbomethoxy-3beta-(4-chlorophenyl)tropane

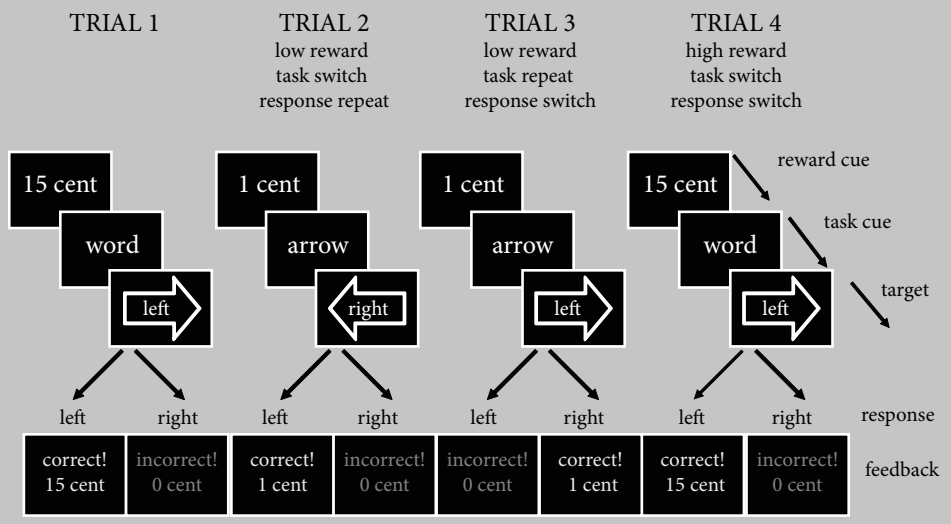
Box 2.3 | Cued task-switching paradigm with a reward manipulation

Subjects were presented with response-incongruent arrow-word combinations (targets), to which they had to respond by pressing a left or right button. There were two possible targets: a left-pointing arrow with the word 'right' in it (e.g. trial 2), and a right-pointing arrow with the word 'left' in it. A task cue preceding the target indicated according to which task (arrow or word) the subject had to respond on the current trial. Compared with the previous trial, the task could either switch (e.g. from word to arrow or vice versa) or remain the same (i.e. repeat). Switch and repeat trials occurred in random order. In addition to such task switches, the paradigm allows us to look at response switches (**chapter 7**), i.e. whether the correct response (left or right button), remained the same

compared with the previous trial, or switched. Finally, a reward cue at the start of each trial indicated whether €0.01 or €0.15 (or sometimes €0.10; **chapter 5**) could be earned after a correct and sufficiently fast response. Immediately following the response, feedback was given (e.g., "correct! 1 cent").

Responses (both behaviourally and neurally) on this task can be used to assess switching (by comparing switch to repeat trials), reward anticipation (by comparing high with low reward trials) and their interaction (i.e. low reward (switch – repeat) – high reward (switch – repeat). In addition, in chapter 7 this paradigm is used to assess the integration between reward, task switching and motor switching.

This paradigm is used throughout this thesis to assess the effects of a dopamine receptor agonist (**chapter 3**) on behaviour and to assess differences in neural signalling (**box 2.4**) between patients with ADHD and the effects of methylphenidate (**box 2.2; chapter 4**). Subsequently, it was used to investigate whether performance on this task changes across the life span (**chapter 5**). In **chapter 6** I present a version of this paradigm designed for rodents to assess the causal role for the striatum (**box 2.5**) in successful motivation-cognition integration. Finally, in **chapter 7** I used non-invasive brain stimulation (**box 2.5**) in human subjects to perturb activity in the neural circuitry involved in reward processing to gain insight in the neural mechanism underlying the reward, cognition, action integration.



Box 2.4 | Functional magnetic resonance imaging

Functional magnetic resonance imaging (fMRI) is a non-invasive imaging technique used to measure neural activity. Neural activity is accompanied by an increase in oxygen and glucose consumption. Functional MRI allows the mapping of brain function by making use of differences in magnetic properties between oxygenated and de-oxygenated blood. This difference is captured in the blood oxygen level dependent signal, or BOLD signal, which is used as a proxy for neural activity (Logothetis et al., 2001). FMRI offers good spatial resolution (~3 mm in this thesis), but blood flow changes are slow and delayed compared to when the neural activity took place. Therefore, changes in BOLD response start approximately 2 seconds after the neural activity took place and peak after 6 – 12 seconds. Nevertheless, with the help of modelling techniques, which use the shape and delay of the BOLD response, we can implement rapid event-related fMRI.

I am interested in brain activity associated with specific functions. Therefore, in the work described in this thesis, fMRI scanning took place while subjects performed a computer task (**box 2.3**). To assess neural responses associated with a specific function, I compared different conditions on a task. For example, to assess which parts of the brain are activated when a reward is anticipated, I assessed the BOLD response when people expect to earn a high reward, and compared this to their BOLD response when they expect to earn only a small reward. All other things being equal, the difference in BOLD response between these conditions is then due to changes in the reward prospect. However, and crucial to keep in mind when using fMRI, is that this co-occurrence of changes in BOLD and task-related processing does not imply causality. If we want to assess whether a region is *crucial* for a certain function, we will need to perturb activity in this region (e.g. using TMS; **box 2.5; chapter 7**) or apply lesions to a region (**box 2.5**; **chapter 6**).

Aging and cognitive control

Aging is accompanied by a range of cognitive deficits and diminished striatal processing which are, at least partly, due to changes in the dopamine system. These changes in the dopamine system occur gradually across the life span and start early in adulthood (Backman and Farde, 2001). In **chapter 5** I explored how integration of reward with cognitive control information changes across the life span, from adolescence to senescence. The results presented in **chapter 5** show that aging is indeed accompanied by diminished integration between reward and task switching: younger subjects showed a reward-based adaptation of cognitive control, whereas responding in older adults did not vary with changing reward conditions.

In summary, the *DAT1*-depencency and BOLD fMRI work in **chapters 3 and 4** suggest that striatal dopamine is involved in motivated cognitive control. In addition, previous work has shown age-related reductions in striatal dopamine. In chapter 5 I observed age-related changes in motivation-cognition integration (**chapter 5**). Together these results suggest a role for the striatum in mediating this interaction. However, changes in BOLD response (**chapter 4** and **box 2.4**), *DAT1* genotype-dependent effects (**chapter 3 and 4**) or the correlation between aging and motivated cognitive control (**chapter 5**) do not provide evidence for a causal role. When one wants to assess whether a region is crucial for a given function, the consequences of manipulating this region or its associated circuit is required. To assess whether the striatum was indeed crucial for successful integration of reward and task-switching signals, I aimed to disrupt processing in the ventral striatum in rodents. One challenge was the absence of a suitable paradigm to measure this effect in rodents. Paradigms in rodents often assess whether they can learn to flexibly adapt their behaviour, based on trial-and-error learning (i.e. without the use of cues) (Ragozzino et al., 1999). Further, although rewards are generally used to reinforce behaviour, the amount of reward an animal anticipates is often not directly manipulated, at least not on tasks measuring behavioural flexibility. To overcome this issue, I first developed a rodent homologue of the rewarded task-switching paradigm (**chapter 6**). Next, I applied excitotoxic lesions (**box 2.5**) to the rodent striatum (i.e. the nucleus accumbens core) to assess whether it is crucial for optimal integration of reward information and cognitive processes (**chapter 6**). The results in **chapter 6** showed reward-related improvements in cognitive flexibility in animals with an intact striatum, but not in those with lesions of the striatum. Together the results so far are in line with the role for striatal dopamine in motivated cognitive control. However, in chapter 1 we hypothesized that communication between the prefrontal cortex and the striatum may also be important for motivated cognitive control. More specifically, we hypothesized that signals in the prefrontal cortex might control activity in the striatum in a top-down manner.

Prefrontal control of striatal processing

In **chapter 7** this idea was tested by assessing whether processing in the prefrontal cortex can alter processing of motivated cognitive control in the striatum (**chapter 1**).

In humans, we can manipulate neural signalling by using non-invasive brain stimulation (transcranial magnetic stimulation; TMS; **box 2.5**). This technique can only target regions near the skull, but previous work has shown that neuronal excitability in regions connected to the stimulated region can also be affected. For example, stimulation of the motor cortex can alter dopamine signalling in the putamen (**figure 2.1: blue**) (Strafella et al., 2003; van Schouwenburg et al., 2012), and this technique thus provides a way by which we can target the striatum after stimulation of a cortical region in human subjects. Using this technique in healthy young human subjects, I aimed to assess the nature of the interactions between the cortex and the striatum. In **chapter 7**, I therefore used TMS to temporarily decrease neural signalling in three regions of the cortex (**figure 2.1**). More specifically, I used this technique to target the cortical regions involved in reward processing, cognitive control (task switching) and action (response switching) (**figure 2.1**). Combined with fMRI (box 2.4), this enabled me to assess whether stimulation of the cortex could indeed modulate processing in the striatum in a task-specific way. Based on anatomical work (**chapter 1**), we hypothesized that changing the excitability of the part of the prefrontal cortex involved in reward processing (the anterior prefrontal cortex; **figure 2.1: orange**) would affect processing in the part of the striatum implicated in reward processing (**figure 2.1: orange**). In addition, in line with the idea that information transfer between corticostriatal circuits is crucial for adaptive behaviour, we hypothesized that changing processing in the anterior prefrontal cortex could change processing.

Box 2.5 | Revealing causal effects

One way to alter neuronal excitability in humans is by means of applying non-invasive brain stimulation, or transcranial magnetic stimulation (TMS) (**chapter 7**). TMS uses electromagnetic induction to generate electrical currents in the brain to alter neuronal excitability. Applying TMS over a cortical region can either increase or decrease neuronal excitability, depending on a number of factors. One important factor is the type of protocol used for stimulation. While single-pulse TMS depolarizes neurons under the coil, causing single action potentials, repetitive TMS (rTMS) can have longer-lasting excitatory (e.g. 5Hz, 10Hz, or intermittent theta burst stimulation; iTBS) or inhibitory (e.g. continuous theta burst stimulation; cTBS) effects (Huang et al., 2005; Wischnewski and Schutter, 2015). Previous work using neurochemical positron emission tomography (PET) imaging has shown that applying rTMS over the frontal cortex can cause changes in dopamine release in the striatum (Strafella et al., 2003; Ko et al., 2008). Subsequent work has shown effects of frontal rTMS in the amygdala, striatum, and cortical regions distant from the stimulation site, using fMRI (e.g. (Volman et al., 2011; van Schouwenburg et al., 2012; Hanlon et al., 2013; Zandbelt et al., 2013). Work in rodents has confirmed that stimulation of the cortex can increase dopamine release in the striatum by directly measuring dopamine concentrations using microdialysis (Taber and Fibiger, 1993). Importantly, rodent work has shown that the effects of iTBS crucially depend on midbrain dopamine (Hsieh et al., 2015). This was revealed by showing that the excitatory effects of iTBS (reflected by increased motor evoked potentials) are blocked in animals with dopamine lesions in the substantia nigra.

Another way to assess whether a region is necessary for a given function is by studying subjects with brain lesions. Overstimulation of the glutamatergic N-methyl-D-aspartate (NMDA) receptor can induce cell death. NMDA lesions are therefore commonly used to apply excitotoxic lesions (**chapter 6**) of a given brain region in rodents. Using stereotaxic surgery, we can lower an injection needle into the striatum and infuse the excitotoxic into the brain (Kirby et al., 2012). Next, we can compare animals with lesions to those without any damage (i.e. typically the animals in this group will undergo sham surgery, whereby saline instead of the excitotoxic compound is infused during surgery).

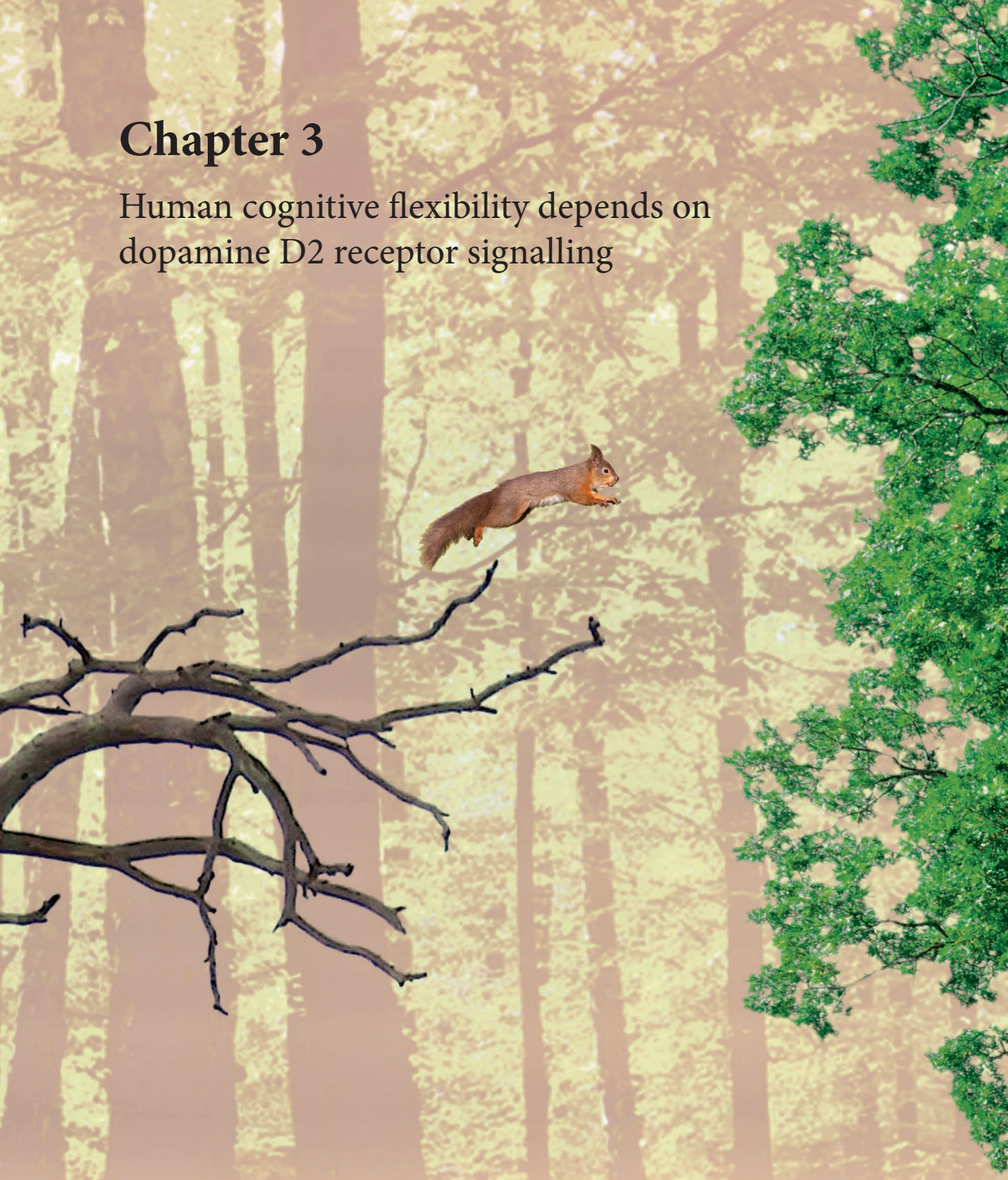
In summary, genetic imaging work and work in patients with Parkinson's disease (**chapter 1**) has suggested a role for striatal dopamine in motivated cognitive control. A role for the dopamine D2 receptor in flexible updating of task demands has been suggested while reward processing has been associated with both dopamine D1 and D2 receptor signalling. In addition, inter-individual differences in response to pharmacological manipulations can be explained by taking into account the baseline state of the dopamine system. The role of specific dopamine receptor-types in motivated cognitive control has thus far not been assessed, nor have dopamine or the striatum been directly manipulated to assess their role in motivated cognitive control. One way by which reward may influence motivated cognitive control is by modulating the mechanism by which the prefrontal cortex and striatum communicate.

The work presented in this thesis aimed to address three primary questions. First, it aims to elucidate which specific dopamine receptor is involved in motivated cognitive control. Second, the role of the striatum is further assessed by directly manipulating the striatum and testing whether it is crucial for motivated cognitive control. Third, I aimed to provide evidence for the idea that prefrontal modulation can change striatal processing during motivated cognitive control. Finally, in **chapter 8** I will recap the results and provide an interpretation of the finding presented in this thesis.

In short, the aim of the studies presented in this thesis was to increase our understanding of the neural mechanisms that allow prospective rewards to alter our ability to exert cognitive control. More specifically, the experiments in this thesis aim to elucidate the role for striatal dopamine and the corticostriatal network during the integration of reward and flexible cognitive control.

Chapter 3

Human cognitive flexibility depends on dopamine D2 receptor signalling



Based on: van Holstein M.*, Aarts E.*, van der Schaaf M.E., Geurts D.E., Verkes R.J., Franke B., van Schouwenburg M.R., Cools R. (2011) Human cognitive flexibility depends on dopamine D2 receptor signaling. Psychopharmacology (Berl) 218:567-578. * = shared 1st author

Abstract

Accumulating evidence indicates that the cognitive effects of dopamine depend on the subtype of dopamine receptor that is activated. In particular, recent work with animals as well as current theorizing has suggested that cognitive flexibility depends on dopamine D2 receptor signalling. However, there is no evidence for similar mechanisms in humans. We aim to demonstrate that optimal dopamine D2 receptor signalling is critical for human cognitive flexibility. To this end, a pharmacological pre-treatment design was employed. This enabled us to investigate whether effects of the dopamine receptor agonist bromocriptine on task-set switching were abolished by pre-treatment with the D2 receptor antagonist sulpiride. To account for individual (genetic) differences in baseline levels of dopamine, we made use of a common VNTR polymorphism in the 3'-untranslated region of the dopamine transporter gene, *DAT1*. Bromocriptine improved cognitive flexibility relative to placebo, but only in subjects with genetically determined low levels of dopamine (n = 27). This beneficial effect of bromocriptine on cognitive flexibility was blocked by pre-treatment with the selective dopamine D2 receptor antagonist sulpiride (n = 14). These results provide strong evidence in favour of the hypothesis that human cognitive flexibility implicates dopamine D2 receptor signalling.

Introduction

Adequate adaptation to our environment requires a range of behavioural control processes, such as reinforcement learning, incentive motivation, working memory, and task switching. Brain dopamine has been most commonly implicated in working memory (Lyon and Robbins, 1975; Cools, 1980; Oades, 1985) and in reward-related processes, including reinforcement learning and incentive motivation (Berridge and Robinson, 1998; Schultz, 2002; Daw et al., 2005; Baldo and Kelley, 2007). However, there is considerable evidence that dopamine is also critical for other control processes, such as task switching. This evidence comes mainly from work with experimental animals (Cools, 1980; Floresco et al., 2006b; Haluk and Floresco, 2009) (for a review, see Oades, 1985; Redgrave et al., 1999; Floresco and Magyar, 2006), drug administration and candidate gene studies in healthy volunteers (Mehta et al., 1999; Cools et al., 2007a; Stelzel et al., 2010) as well as medication withdrawal studies in patients with Parkinson's disease (Cools et al., 2001a, b, 2003).

Accumulating evidence indicates that these cognitive effects of dopamine depend on the subtype of dopamine receptor that is activated (Seamans and Yang, 2004; Frank and O'Reilly, 2006; Frank and Fossella, 2011). In particular, recent *in vivo* work with animals (Floresco et al., 2006b; Floresco and Jentsch, 2011) as well as *in vitro* and theoretical work (Bilder et al., 2004; Durstewitz and Seamans, 2008) implicates the dopamine D2 receptor family in task switching. For example, in rodents, blockade of dopamine D2 receptors in the prefrontal cortex (PFC) impaired strategy set shifting, while leaving unaltered performance on working memory tasks (Floresco et al., 2006b). According to the dual-state theory put forward recently by Durstewitz and Seamans (Seamans and Yang, 2004; Durstewitz and Seamans, 2008), PFC networks can be either in a D1-dominated state, which is characterized by a high energy barrier favouring robust stabilization of representations, or in a D2-dominated state, which is characterized by a low energy barrier favouring fast flexible switching between representations. Consistent with this proposal are findings that dopamine D2 receptor agonists act in opposite ways to dopamine D1 receptor agonists, at least *in vitro*, on NDMA and GABA currents, neuronal excitability as well as on cyclic AMP production (Durstewitz and Seamans, 2008) with dopamine D2 receptor stimulation inducing reduction in NMDA currents and GABAergic inhibition.

The hypothesis that dopamine D2 receptor stimulation is important for task switching is corroborated by findings in humans that the dopamine D2 receptor antagonist sulpiride impaired performance on task-set switching (Mehta et al., 2004). However, according to current standards in animal pharmacology (Feldman et al., 1997), more direct claims about the receptor mechanisms of drug effects can be made based only on the observation that the action of a receptor agonist is blocked by pre-treatment with a receptor antagonist; an approach that has been rarely adopted in human research. Here, we provide stronger evidence for a role of dopamine D2 receptor action in cognitive flexibility by adopting such a pre-treatment design in young healthy volunteers. Specifically we demonstrate that an effect of

the dopamine receptor agonist bromocriptine on cognitive flexibility was abolished by pre-treatment with the dopamine D2 receptor antagonist sulpiride.

Cognitive flexibility was assessed using the task switching paradigm (Rogers and Monsell, 1995). Unlike traditional measures of cognitive flexibility, such as the Wisconsin Card Sorting Test (Grant and Berg, 1948) or indeed any other set switching paradigm with a rule learning component, this paradigm minimizes demands for learning and working memory. It requires the ability to switch rapidly, based on external cues, between already well-established task-sets (stimulus-response mappings). Adequate performance does not depend on feedback or trial-and-error learning, and the acquisition of task-sets is a rapid learning process, where the formation of associations between stimuli (i.e. the word 'left') and responses (i.e. a left button press) does not require extensive training. After the acquisition of task-sets in practice blocks, switches can be rapidly performed and measured under time-pressure. Moreover, task switches are externally cued, which reduces the load on working memory. Therefore, the task-switching paradigm is relatively specific for measuring task switching.

One challenge to dopaminergic drug research is that there is large variability across different individuals, with only some people benefiting from the drug, thus obviating an effect across the population as a whole (Cools and Robbins, 2004; Cools and D'Esposito, 2011). We know that at least some of this variability reflects variation in baseline levels of dopamine (Mattay et al., 2003; Cohen et al., 2007; Cools et al., 2009b). For example, high-impulsive subjects (who likely exhibit low baseline dopamine function (Dalley et al., 2007; Buckholtz et al., 2010)) are more sensitive to the beneficial effect of dopaminergic drugs on task switching and reversal learning than are low-impulsive subjects (Cools et al., 2007a). Moreover, dopaminergic drugs like bromocriptine, amphetamine and methylphenidate have diametrically opposite, beneficial and detrimental effects in subjects with low and high working memory capacity respectively (Mattay et al., 2000). The hypothesis that this individual variability reflects variation in baseline levels of dopamine was strengthened by three recent observations. First, working memory capacity correlates positively with dopamine synthesis capacity in the striatum, as measured with neurochemical positron emission tomography (Cools et al., 2008). Second, dopaminergic drug administration was shown to have opposite effects in individuals with high and low dopamine synthesis capacity (Cools et al., 2009b). Finally, dopaminergic drug administration was shown to have opposite effects as a function of individual genetic variation in dopamine transmission (Cohen et al., 2007; Mattay et al., 2003). Based on these observations, we predicted that the dopamine receptor agonist bromocriptine would improve task switching, but only in those individuals with low baseline levels of dopamine.

One way to assess differences in baseline levels of dopamine is by taking into account individual genetic differences. For example, using the same task-switching paradigm, we previously showed that performance and task-related striatal BOLD responses depended on individual variability in the dopamine transporter (DAT) gene, which has been associated with differences in gene expression in the striatum (e.g., Heinz et al., 2000; Fuke et al., 2001; Mill et al., 2002; VanNess et al., 2005) (but see van Dyck et al., 2005). Moreover, these effects

were independent of the catechol-*O*-methyltransferase *(COMT)* gene (Aarts et al., 2010), which codes for the enzyme that degrades DA primarily in the PFC. Therefore, we took into account individual differences in baseline dopamine function by making use of a common variable number of tandem repeat (VNTR) polymorphism in the 3'-untranslated region of the DAT gene (*DAT1*/*SLC6A3*).

We anticipated that subjects with genetically determined lower levels of dopamine as measured with the *DAT1* genotype would show the greatest effect of bromocriptine on task switching. Finally, we predicted that an effect of bromocriptine would be blocked by pre-treatment with the selective dopamine D2 receptor antagonist sulpiride.

Materials and methods

Subjects

Initially, 55 subjects were recruited through advertisements on the campus. *DAT1* genotype was available for 49 subjects, and one subject was excluded because of an ADHD diagnosis. The resulting 48 subjects were right-handed, speaking Dutch fluently and European Caucasians (24 male and 24 female, mean age 21.58 years, range 18-27). They were compensated for participation and gave written informed consent in a manner approved by the local ethics committee on research involving human subjects.

Screening and inclusion

All subjects were screened before inclusion by a medical doctor and a research nurse; this included the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998) and a physical examination for weight, heart rate, blood pressure, and an electroencephalogram, to exclude major psychiatric, neurological or medical illness including substance abuse at the time of testing. One subject had a history of anorexia nervosa, but was treated successfully three years prior to this study and was therefore not excluded.

General procedure

Subjects were asked to abstain from alcohol and nicotine 24 hours before testing and from caffeine on the day of testing. All subjects consumed a light breakfast before ingestion of the drugs. At the start of each session, subjects were asked about their current medical status and their compliance with the above mentioned restrictions.

Experimental Design

Subjects performed a pre-cued task-switching paradigm (**figure 3.1**) with a reward manipulation. The task is described extensively elsewhere (Aarts et al., 2010).

Subjects had to respond to incongruent arrow-word combinations, either by responding to

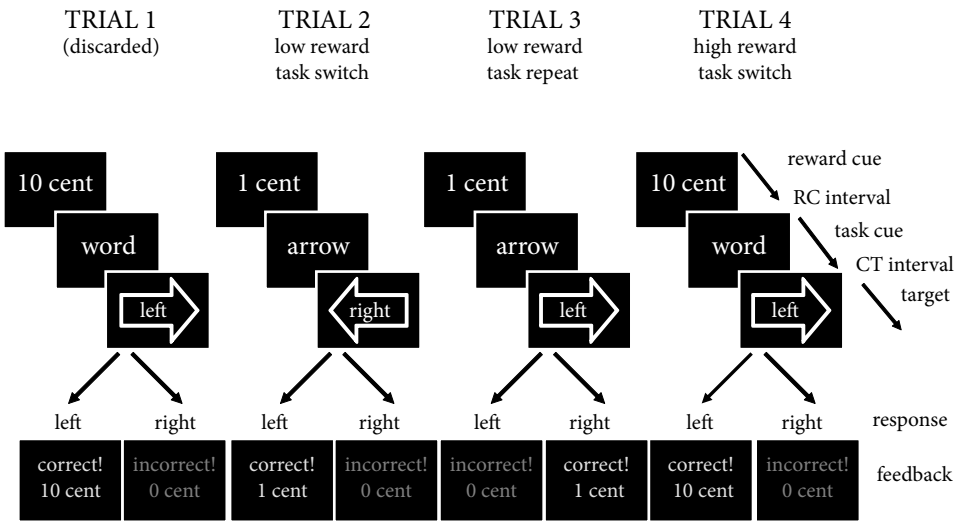


Figure 3.1 Example trials from the experimental paradigm
In the first trial, the reward cue indicated that the subject could earn 1 cent with a correct and sufficiently quick response (as opposed to 10 cents in the second trial). The task-cue indicated that the subject should respond to the arrow of the incongruent arrow-word Stroop-like target in the first trial, but to the word of the incongruent arrow-word Stroop-like target in the second trial. Hence, the second trial is an example of a switch of the task relative to the previous trial.

the direction of the arrow or the direction indicated by the word ("left" or "right"). As in previous work (Aarts et al., 2010), we included only incongruent trials because the switch cost is largest in the presence of response conflict, which is evoked more by incongruent than congruent targets (Aarts et al., 2009). Before each trial, a task-cue appeared indicating according to which task (arrow or word) the subject had to respond. Compared with the previous trial, the task either changed unpredictably (from arrow to word or vice versa; switch trial), or remained the same (repeat trial). The critical measure of interest, the switch cost, was calculated by subtracting performance [error rate (%) and response time (ms)] on repeat trials from that on switch trials.

Given our prior observation that effects of individual variability in striatal dopamine on task switching are potentiated under conditions of high incentive motivation (see also Baldo and Kelley, 2007; Aarts et al., 2010), we also manipulated reward anticipation by presenting high and low reward cues prior to the task cue. The reward-cue informed the subjects whether 1 cent (low reward) or 10 cents (high reward) could be earned with a correct and quick response. Immediately following the response, feedback was given (e.g., "correct! 10 cents"). There was a variable interval between the reward-cue and the task-cue of 1 to 2 seconds. Subjects responded with their index fingers on a left or right button box.

The main experiment consisted of 160 trials and lasted ~ 30 minutes with a 30 second break

after every 32 trials. In the break, the amount of money the subject earned thus far was displayed on the screen and subjects were told in advance the total amount would be added to their financial compensation as a bonus.

Pharmacological procedure

All 48 subjects were tested at least twice: once after an oral dose of the dopamine receptor agonist bromocriptine (Parlodel ®, Novartis; 1.25 mg) and once after a placebo. In addition, a subgroup (n = 14) received placebo or bromocriptine after pre-treatment with placebo or the dopamine D2 receptor antagonist sulpiride (Dogmatil ®, Sanofi – Aventis; 400 mg) on two other occasions. The order of administration of the two or four sessions was randomized according to a double-blind, placebo-controlled crossover design. The sessions were always separated by at least one week. The doses described here have been used before in similar psychopharmacological studies and have been shown to be well tolerated by subjects (Mehta et al., 2004; Cools et al., 2007a). Sulpiride or placebo was administered 30 minutes prior to bromocriptine or placebo.

The task was performed ~4 hours after sulpiride or placebo intake and ~3.5 hours after bromocriptine or placebo intake. Time of dosing was optimized for detecting drug effects during functional Magnetic Resonance Imaging (fMRI) that took place immediately prior to the experiment reported here (data to be published elsewhere). The timing of the fMRI sessions was based on prior studies showing behavioural effects at similar doses and at similar time points in healthy volunteers (Luciana et al., 1992; Kimberg et al., 1997; Luciana and Collins, 1997; Mehta et al., 2001; Mehta et al., 2003; Mehta et al., 2004; Gibbs and D'Esposito, 2005b, a; Cools et al., 2007a; Mehta et al., 2008). Mean time to maximal plasma concentration of sulpiride is about 3 hours, with a plasma half-life of about 12 hours (Mehta et al., 2003), while mean time to maximal plasma concentration of bromocriptine is about 2.5 hours with a plasma half-life of about 7 hours (Deleu et al., 2002). The combination of plasma kinetics and physiological effects shows that the time of testing coincided with high plasma concentrations of both bromocriptine and sulpiride (**supplementary results: table S3.1**).

A session started either at 8.00, 8.30 or 10.30 AM and starting time was kept identical between each subject's two or four sessions. Blood pressure, heart rate, mood measures [visual analogue scales; 16 ratings on a scale of 0-100 (Bond and Lader, 1974)] and blood samples (6 ml) were taken immediately after arrival of the subject and on average 73.1 (sd: 45.4) min minutes before the task was performed. Blood samples were used to determine the change in prolactin levels due to dopamine D2 receptor binding (Fitzgerald and Dinan, 2008) (**supplementary material and methods**).

Neuropsychological assessment

On the day of screening, subjects completed a number of questionnaires, including the Beck Depression Inventory (BDI; (Beck et al., 1961), Barratt Impulsiveness Scale (BIS-11; (Patton

et al., 1995), State-Trait Anxiety Inventory (STAI; (Spielberger et al., 1970)), and Listening span (Daneman and Carpenter, 1980; Salthouse et al., 1991) (**supplementary materials and methods**). Verbal IQ was determined using Dutch Adult Reading Test, (DART) the Dutch version of the National Adult Reading Test (Schmand et al., 1991).

Genotyping

All molecular genetic analyses were carried out in a CCKL-certified laboratory at the department of Human Genetics of the Radboud University Nijmegen Medical Centre. DNA was isolated from saliva samples using Oragene kits (DNA Genotek Inc, Ottawa, Ontario, Canada). Genotyping of the 40 base pair variable number of tandem repeats (VNTR) polymorphism in the 3' untranslated region of the *SLC6A3/DAT1* gene encoding the DAT was performed as follows. Genomic DNA (100 ng) was amplified with 0.2 µM fluorescently labelled forward primer (5'-Ned-TGTGGTGTAGGGACGGCCTGAGAG-3') and 0.2 µM reverse primer (5'-CTTCCTGGAGGTCACGGCTCAAGG-3') with PIG tail, 0.25 mM dNTPs, 0.4 U AmpliTaq Gold DNA polymerase (Applied Biosystems, Nieuwerkerk a/d Ijssel, The Netherlands) in an PCR Optimized buffer D, (Invitrogen, Breda, The Netherlands) containing 10% DMSO (v/v). Cycling conditions were 12 min 95 °C followed by 35 cycles of 1 min 94°C, 1 min 58°C and 1 min 72°C, and a final 5 min at 72°C. PCR products were diluted 10 times and 1 µl of the diluted PCR product together with 9.7 µl formamide and 0.3 µl GeneScan-600 Liz Size StandardTM (Applied Biosystems) was analyzed on an 3730 Genetic Analyzer (Applied Biosystems) according to the protocol of the manufacturer. Analysis of the length of the PCR products was performed with Genemapper software. To investigate the random genotyping error rate, the lab included 5% duplicate DNA samples, which had to be 100% consistent. In addition, 4% blanks were included, which were required to be negative.

Most of the participants (except three) took part in the study before their genotype was determined. After their participation, three groups of genotypes were established: a group homozygous for the common 10-repeat allele (10R/10R) (n = 27, mean age: 21.7 $\pm$ 2.2, 12 female), a group homozygous for the 9-repeat allele (9R/9R) (n = 7), and a group of 9R/10R heterozygotes (n = 14). The 9R/9R and 9R/10R subjects were combined into one group of 9R carriers (n = 21, mean age: 21.4 $\pm$ 1.9, 12 female). Three 10R homozygotes of this sample were selected from an existing genetic database at the centre. Of the subgroup of participants who received four instead of two drug sessions, we only included data from the 10R homozygotes (n = 14; mean age: 21.9 $\pm$ 2.4, 6 females), because these were the participants showing an effect of bromocriptine in the larger sample.

The DAT removes dopamine from the synapse into the pre-synaptic neuron (Willeit and Praschak-Rieder, 2010), thereby terminating its action. The 10-repeat allele has been associated with increased gene expression and presumably lower levels of synaptic dopamine in the striatum relative to the 9-repeat allele (e.g., Heinz et al., 2000; Fuke et al., 2001; Mill et al., 2002; VanNess et al., 2005) (but see van Dyck et al., 2005).

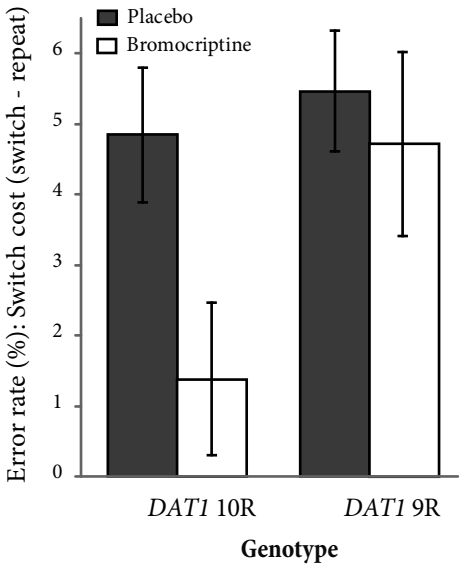


Figure 3.2 Bromocriptine improved task switching in 10R homozygotes
The switch cost (switch – repeat) in terms of error rate (percent) differed between the two genotype groups: Bromocriptine reduced the switch costs in the 10R homozygotes (n = 27; with relatively lower levels of striatal dopamine), but not in the 9R carriers (n = 21). These results indicate that the effect of bromocriptine on task switching depends on baseline levels of striatal dopamine. Error bars represent the standard error of the difference between switch and repeat trials.

Statistical analyses

The mean latencies of the correct responses and the proportion of errors were analyzed using a repeated-measures general linear model (GLM) with the within-subjects factors Reward, Switching, Drug and the between-subjects factor *DAT1* genotype group. A similar ANOVA with Order (of drug administration: the order of bromocriptine and placebo in the large sample, or the order of all four drug sessions in the subgroup) as a covariate of no interest revealed no relevant interaction effects with Order (i.e., Order x Drug x Switching: $F(1, 25) < 1$; $F(1, 12) < 1$) for any of the reported Drug -by- Switching interactions. Accordingly, the ANOVA was run without this additional factor. Effects of sulpiride (pre)treatment were assessed for the group that showed an effect of bromocriptine (i.e. the 10R homozygotes). The first trial of each block was eliminated from analyses as they were neither switch nor repeat trials (five trials per subject).

To investigate whether drug effects reflected a form of learning rather than task switching, we also assessed learning curves for each subject, i.e. switch costs as a function of time (**supplementary results: learning effect**).

Prolactin and mood ratings (three factors: contentedness, alertness, and calmness, according

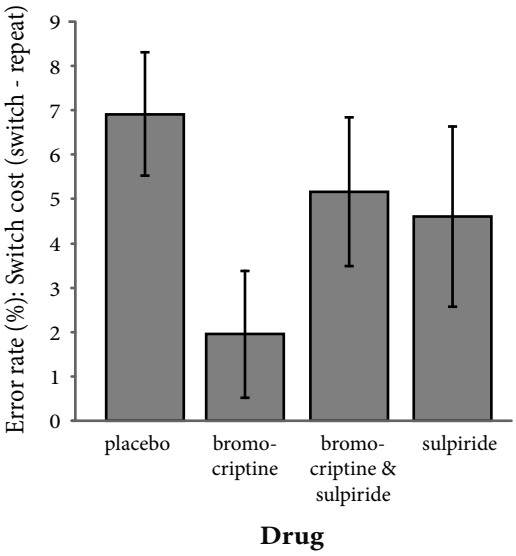


Figure 3.3 Sulpiride abolished the effect of bromocriptine
Shown is the switch cost (switch – repeat) in error rate (percent) for the 10R homozygotes (n = 14) who received pre-treatment with sulpiride, as well as bromocriptine and sulpiride alone. In this smaller group, bromocriptine also reduced the switch cost relative to placebo. However, when the same subjects received sulpiride pre-treatment, bromocriptine no longer facilitated task switching. Error bars represent the standard error of the difference between switch and repeat trials.

to Bond and Lader (1974) **see supplementary results)** were available for 46 subjects. For each session we calculated the drug-induced change in prolactin and mood ratings (after - before drug intake) and compared this with the placebo-induced change [difference score = (drug session (Time2 –Time1)) – (placebo session (Time2 – Time1))] **(supplementary results: table S3.1 + mood measures).** Pearson correlations were calculated, in the 10R homozygotes, between trait anxiety (STAI), trait impulsivity (BIS-11), depression (BDI), listening span scores, bromocriptine-induced mood changes, bromocriptine-induced prolactin changes and bromocriptine-induced changes in task switching.

Results

Genetic variation predicts the effect of bromocriptine on task switching

All 48 subjects performed the pre-cued task-switching paradigm after receiving a placebo or the dopamine receptor agonist bromocriptine (1.25 mg).

Under placebo, there was no difference in terms of task switching between the *DAT1* genotype groups [error rates; Switching x *DAT1*: $F(1,46) < 1$]. However, consistent with our

prediction, bromocriptine improved task switching: The proportion of errors on switch trials relative to repeat trials (i.e. the error switch cost) was reduced after bromocriptine relative to placebo in subjects with genetically determined low striatal dopamine levels (i.e. the *DAT1* 10R homozygotes; n = 27) [Drug x Switching: $F(1,26) = 5.4$, $p = .028$]. This effect was driven by a combination of improvement on switch trials and impairment on repeat trials (**supplementary results: table S3.2b**). By contrast, there was no effect of bromocriptine on task switching in the *DAT1* 9R carriers (n = 21), who presumably have higher levels of striatal dopamine [Drug x Switching: $F(1,20) < 1$] (**figure 3.2; supplementary results: table S3.2a**). None of these effects were found in terms of response times (all $p > .2$) (**supplementary results: table S3.2a; supplementary discussion**).

Effect of bromocriptine on task switching is blocked by sulpiride pre-treatment

To investigate whether the beneficial effect of bromocriptine on task switching in the 10R homozygotes was mediated by stimulation of dopamine D2 receptors, we assessed the effect of bromocriptine after blocking the dopamine D2 receptors with sulpiride (400 mg) in a subgroup of the 10R homozygotes (n = 14). First we tested whether the reduced switch cost after bromocriptine administration was still present in this smaller group. Again, we found that bromocriptine reduced the error switch cost relative to placebo [Drug x Switching: $F(1,13) = 5.6$, $p = .034$], an effect that again reflected a combination of improved switching and impaired repeat performance (**supplementary results: table S3.2c**)**.** As anticipated, blocking the dopamine D2 receptors by pre-treatment with sulpiride abolished the effect of bromocriptine relative to placebo [Drug x Switching: $F(1,13) < 1$]. Sulpiride by itself, relative to placebo, had no effect on task switching [$F(1,13) < 1$] (**figure 3.3; supplementary results: table S3.2c and figure S3.2;** [Bromocriptine (on/off) × Sulpiride (on/off) × Switching: $F(1, 13)=3$, $p = .1$]. None of these effects were present in the response times (all $p > .3$) (**supplementary results: table S3.2c; supplementary discussion**).

Effects of motivation on task switching vary as a function of genetic variation, but are not modulated by bromocriptine

Our previous study (Aarts et al., 2010) revealed beneficial effects of incentive motivation on task switching. Specifically, switch costs were reduced when subjects anticipated high reward, relative to when they anticipated low reward. However, this effect was restricted to subjects with genetically determined high levels of striatal dopamine (i.e., the 9R carriers). Here we replicate this effect in an independent sample: irrespective of drug, task switching varied as a function of anticipated reward and *DAT1* genotype. The 9R carriers showed a larger response time benefit of anticipated reward on switching than did the 10R homozygotes (**supplementary results: figure S3.1 and supplementary discussion**) [Reward x Switching x *DAT1*: $F(1,46) = 5.3$, $p = .026$].

However, contrary to our expectations, we observed no difference in terms of this effect

between the bromocriptine and placebo session. [Reward x Switching x *DAT1* x Drug: $F(1,46) = 1.5$, $p > .1$], [Reward x Switching x Drug: $F(1,46) < 1$]. The degree to which reward affected performance irrespective of task switching [main effect Reward: response time: $F(1,46) = 19.4$, $p < .001$; error rate: $F(1,46) = 20.6$, $p < .001$] was also not modulated by bromocriptine (error rate and response time: [Reward x Drug: $F(1,46) < 1$], [Reward x Drug x *DAT1*: $F(1,46) = 1.6$, $p > .2$]).

Neuropsychological assessments

There were no differences between the two *DAT1* genotype groups in term of age, gender, IQ, trait impulsivity (BIS-11), depression (BDI), trait anxiety (STAI) or working memory capacity (listening span; all $p > .2$) (**supplementary results: table S3.3a**), and there were no significant correlations between any of these trait measures and drug-induced changes in performance (all $p > .2$).

Listening span

Working memory capacity (measured with listening span; Daneman and Carpenter 1980, Salthouse and Babcock 1991) has been associated with striatal dopamine synthesis capacity (Cools et al., 2008) Moreover, previous studies have shown that dopaminergic drug effects can be predicted from working memory capacity (Luciana et al., 1992; Kimberg et al., 1997; Luciana and Collins, 1997; Mehta et al., 2001; Mehta et al., 2003; Mehta et al., 2004; Gibbs and D'Esposito, 2005b, a; Cools et al., 2007a; Mehta et al., 2008). Accordingly, we assessed drug effects as a function of listening span. To this end, we divided the group into low-span participants ($n = 23$) and high-span participants ($n = 25$), using a median-split analysis (**supplemental table S3.3b**). Consistent with prior work, and like the 10R *DAT1* genotype group, the low-span group was sensitive to the beneficial effects of bromocriptine on task-switching (Drug x Switching: $F(1,22) = 4.457$, $p = .046$). Conversely, the high-span group was not sensitive to the effect of bromocriptine (Drug x Switching: $F(1,24) < 1$), similar to the *DAT1* 9R group (Drug x Switching x Span: $F(1, 46) = 1.2$, $p > .2$). Moreover, in the subgroup of low-span participants that took part in all four drug sessions, bromocriptine also reduced the switch cost (Drug x Switching $F(1,9) = 5.466$, $p = .044$), an effect that was not present after pre-treatment with sulpiride (Drug x Switching: $F(1,9) < 1$) nor after sulpiride alone ($F(1,9) = 1.06$, $p = .33$).

Effects of drugs on mood ratings and prolactin levels

Participants reported no drug-induced changes in mood in the large sample (all $p > .3$) or in the subgroup (all $p > .05$). There were also no significant correlations between drug-induced changes in task performance and drug-induced changes in mood (all $p > .3$)

Furthermore, bromocriptine decreased plasma prolactin levels relative to placebo, whereas

sulpiride increased plasma prolactin levels relative to placebo (**supplementary results: table S3.1**). These data evidence the opposite effects of the two drugs in vivo. The finding that the prolactin response was not nullified in the combined sulpiride and bromocriptine session (sulpiride versus sulpiride and bromocriptine: $t(21) = -.279$, $p = .783$) likely reflects the fact that sulpiride was administered prior to bromocriptine. The effect of sulpiride was disproportionately large, thus masking any subsequent effect of bromocriptine.

Discussion

The present results show that the dopamine receptor agonist bromocriptine improved task switching by stimulating dopamine D2 receptors. Specifically, bromocriptine reduced the error switch cost in individuals with genetically determined low dopamine levels, and this beneficial effect of bromocriptine on task switching was abolished by pre-treatment with the selective dopamine D2 receptor antagonist sulpiride. This finding significantly strengthens prior evidence (Mehta et al., 2004; Floresco et al., 2006b; Cools et al., 2007a; Durstewitz and Seamans, 2008; Stelzel et al., 2010) for a role of dopamine D2 receptor signalling in task switching, thus further establishing a role for dopamine outside the domains of working memory and learning in humans. In particular, the data concur with the dual-state theory put forward recently by Durstewitz and Seamans (Seamans and Yang, 2004; Durstewitz and Seamans, 2008), which is grounded in *in vitro* neurophysiology and biophysically realistic computational modelling work (see introduction). According to this theory, dopamine D2 receptor stimulation favours fast flexible switching between different task-relevant representations, by allowing multiple inputs to impinge simultaneously on the PFC. It also fits with data from animal studies showing that genetic over-expression of striatal dopamine D2 receptors (Kellendonk et al., 2006) and abnormal increases in dopamine D2 receptor activity in the rodent striatum alters strategy set shifting in rodents (Haluk and Floresco, 2009).

It might be noted that the present finding that the beneficial effect of bromocriptine on task switching was blocked by pre-treatment with sulpiride highlights the role of dopamine D2 receptor signalling in task switching, but does not directly rule out the involvement of dopamine D1 receptor signalling or the importance of synergistic action between dopamine D1 and D2 receptor signalling in task switching. Indeed rodent work suggests that both dopamine D1 and D2 receptor signalling are important for cognitive flexibility (Floresco et al., 2006b). The conclusion that task switching implicates dopamine D2, *but not D1* receptor signalling would require demonstration that effects of bromocriptine were not blocked by a dopamine D1 receptor antagonist. Unfortunately, there is a relative lack of dopamine D1 selective drugs available for human research, and accordingly, such a demonstration will have to await future developments.

An interesting feature of current dual-state theory is that the beneficial effect of dopamine D2 receptor stimulation on task switching might be accompanied by a detrimental effect on the stabilization of current task-relevant representations. This hypothesis is corroborated here by

the observation (as well as our prior observation; (Cools et al., 2007a)) that the drug effect on the switch cost was driven by a combination of better performance on switch trials, and poorer performance on repeat trials (**supplementary results: table S3.2a and b**). Indeed performance on repeat trials would suffer from poor stabilization of task-relevant representations. It also concurs with previous findings in humans that the dopamine D2 receptor antagonist sulpiride impaired performance on task-set switching, but, by contrast, improved performance on a delayed response task that required the stabilization of representations in the face of task-irrelevant distraction (Mehta et al., 2004).

Unlike this prior study (Mehta et al., 2004), we here failed to uncover a significant task-switching impairment after administration of sulpiride. This is surprising, not only given that prior finding, but also given our observation that sulpiride *did* block the beneficial effect of bromocriptine on task switching. There are a number of possible explanations for this discrepancy. First, there might have been a difference between the two studies in terms of the time of testing after drug intake. Our task switching data were acquired approximately four hours after drug intake, while (Mehta et al., 2004) started testing already 90 minutes after drug intake. Dopamine D2 receptor occupancy after sulpiride administration, measured approximately two hours after intake is relatively modest (Mehta et al., 2008). Accordingly dopamine D2 receptor occupancy after four hours might have been insufficient to exert an effect on its own, even though it was clearly sufficient to block the effects of bromocriptine. A second possibility is that it is particularly difficult to demonstrate impairment using the present version of the task-switching paradigm, where subjects were constantly encouraged and motivated to perform as well as they could by means of monetary incentive. Thus the paradigm might simply not have been sensitive to detecting impairment (as opposed to improvement). In any case, there is one major interpretational advantage of our failure to find an impairment after administration of sulpiride by itself; indeed, this feature of the data implies that the effect of bromocriptine was blocked rather than masked (or averaged out) by an effect of sulpiride, thus strengthening our conclusion that dopamine D2 receptor stimulation is essential for bromocriptine to enhance task switching performance.

The baseline-dependent effects of bromocriptine on task switching resemble previously observed effects of bromocriptine on reward learning and working memory (Cools et al., 2007a; Cools et al., 2009b). For example, we have previously shown that beneficial effects of bromocriptine on reward learning are greatest in subjects with low dopamine synthesis capacity (Cools et al., 2009b). Similarly, we have also shown that beneficial effects of bromocriptine on task switching were restricted to high-impulsive subjects (Cools et al., 2007a), with impulsivity being associated with low baseline dopamine function (Dalley et al., 2007; Buckholtz et al., 2010).

One possible mechanism underlying this enhanced beneficial effect of dopamine receptor stimulation in low dopamine subjects is enhanced postsynaptic receptor function. Indeed the dopamine system is highly plastic and regulates itself to maintain equilibrium, partly through changes in transporter and receptor density/function. The *DAT1* 10R subjects are thought to

be characterized by high dopamine transporter density, which is associated with enhanced uptake of dopamine from the synapse and thus reduced remaining levels of dopamine in the synapse. Following the rules of homeostasis, such low synaptic dopamine levels might well be accompanied by increased postsynaptic dopamine receptor function. Increased postsynaptic receptor function would compensate for the reduced synaptic dopamine levels, thus contributing to the maintenance of equilibrium in overall dopamine function. In other words, enhanced receptor function might represent a self-regulatory or compensatory mechanism aimed at maintaining homeostasis, i.e. optimal functioning of the low-dopamine system. In this context, the lack of a *DAT1* effect on task switching at baseline (under placebo) is not surprising, because any dopamine-dependent function including task switching should depend on a combination of synaptic dopamine levels and receptor function. Indeed high- and low dopamine groups have been observed to perform similarly under placebo in a number of previous studies (Kimberg et al., 1997; Cools et al., 2007a). Critically, this enhanced postsynaptic receptor function might underlie the disproportional response of low dopamine subjects to dopamine receptor stimulation. Thus the significant effect of dopamine receptor stimulation with bromocriptine in the 10R, but not the 9R group is not surprising, given these presumed hyper-functioning dopamine receptors.

Our finding that bromocriptine did not impair subjects with higher baseline levels of dopamine (i.e. the 9R carriers) was somewhat surprising given prior observations that subjects with already optimized levels of dopamine can be impaired by dopaminergic drug administration (although see Cools et al., 2007a; e.g. Cools et al., 2009b). Such detrimental effects of dopaminergic drug administration have been accounted for by inverted-U shaped relationships between dopamine receptor stimulation and cognitive performance, whereby both too much as well as too little dopamine leads to poor performance. Our finding that the 9R carriers were not impaired accordingly might reflect their positioning near, but not quite yet at the optimum of the so-called inverted-U shaped curve (Cools and Robbins, 2004; Cools and D'Esposito, 2011). However, the obvious alternative hypothesis relates to our failure to obtain an effect of sulpiride; the paradigm might simply not be sensitive to detecting impairment, perhaps due to high levels of incentive motivation induced by the reward cues that preceded each trial. According to this alternative hypothesis, subjects with high basal levels of dopamine will exhibit impairment after bromocriptine on a task that does not involve monetary reward.

Task switching has most often been associated with the PFC (Monsell, 2003; Aron et al., 2004; Derrfuss et al., 2005; Sakai, 2008) and traditionally, cognitive effects of dopamine are ascribed to modulation of the PFC. However, recent theories as well as empirical data have highlighted a complementary role for (dopamine in) the *striatum* (Braver and Cohen, 2000; Frank et al., 2001; Cools et al., 2004; Lewis et al., 2004; Leber et al., 2008; McNab and Klingberg, 2008). Specifically, recent computational work has emphasized the role of dopamine in the *striatum* in the updating of current task-relevant representations (Hazy et al., 2006). The suggestion that the striatum is well suited to serve the gating mechanism that updates

current task-relevant representations in the PFC concords with a rapidly growing body of data from functional neuroimaging and animal studies on working memory (Collins et al., 2000; Dahlin et al., 2008; McNab and Klingberg, 2008; Dodds et al., 2009; Marklund et al., 2009). Furthermore, it also concurs with empirical data from human imaging and animal studies showing (effects of dopamine D2 receptor manipulations on) striatal involvement during shifting (Lyon and Robbins, 1975; Oades, 1985; Collins et al., 1998; Cools et al., 2003; Cools and Robbins, 2004; Floresco and Magyar, 2006; Kellendonk et al., 2006; Cools et al., 2007b; Cools et al., 2007a; Dodds et al., 2008; Leber et al., 2008; Clatworthy et al., 2009; Haluk and Floresco, 2009; Aarts et al., 2010; van Schouwenburg et al., 2010). For example, we have recently shown, using dynamic causal modelling of fMRI data that activity in the striatum may regulate task switching by modulating (or 'gating') connectivity between the PFC and task-relevant representations in posterior cortex (van Schouwenburg et al., 2010). While we do not rule out the involvement of the PFC in the present study (see e.g. Stelzel et al., 2010), both the DAT and dopamine D2 receptors are most abundant in the striatum (Camps et al., 1989; Ciliax et al., 1999; Hurd et al., 2001). However, the finding that effects of bromocriptine are DAT- and dopamine D2-dependent, strongly implicates the striatum. This observation also concurs with previous work with patients with Huntingon's disease (Aron et al., 2003b), Parkinson's disease (Cools et al., 2001b, a) and focal basal ganglia lesions (Cools et al., 2006).

In sum, our findings strengthen evidence in favour of the hypothesis that dopamine D2 receptor signalling is important for task switching, with prior evidence suggesting that this effect is mediated by the striatum. The data also illustrate the need to take into account genetic variation in baseline levels of striatal dopamine when predicting drug effects. Finally, although the sample size was rather small, this study emphasizes the value of employing the pre-treatment approach in humans and future studies might adopt this approach to enable replication and extension of the present results.

Supplementary material

Supplementary materials and methods

Blood samples for prolactin

Secretion of the hormone prolactin is inhibited by dopamine D2 receptor stimulation in a dose dependent manner. In order to measure the level of prolactin in blood plasma and thereby ascertain the effects of the drugs, we drew blood twice during each of the sessions. After centrifugation, the sample concentrations were labelled with a participant code, study day number, state monitoring number, date and time of blood sampling and stored. Plasma prolactin levels were determined by an electrochemiluminescence immunoassay on a Modular E170 Analyzer (Roche Diagnostics) by Prof Fred Sweep and Rob van den Berg at the Laboratory for Endocrinology of the UMC Nijmegen.

Neuropsychological assessment

Working memory capacity was measured using the Dutch version of the listening span task (Salthouse et al., 1991). Subjects listened to sets of two to seven sentences while answering written questions about the content of each sentence. They then turned the page and wrote down the last word of each sentence. There are three trials at each level and the span represents the maximum number of last words that were remembered correctly on at least two out of three trials (for more details, see (Salthouse et al., 1991)). In this case, recall of final words was scored irrespective of recall-order.

Supplementary discussion

There was no effect of bromocriptine as a function of reward (see **main results**). At first sight, this might seem surprising given current literature about dopamine's role in reward processing. However, bromocriptine has particularly high affinity for the dopamine D2 receptor (Deleu et al., 2002). Accordingly, it remains possible that dopamine D2 receptor signalling is not critical for the effects of motivation in the present task. This hypothesis is in keeping with current theorizing implicating primarily the dopamine D1 receptor in reward processing (Frank, 2005).

In order to stress subjects to respond as fast as possible, the response deadline was very strict, possibly causing a floor effect. This might have hampered the improvement of performance in terms of response times on bromocriptine vs. placebo, explaining the absence of any drug-effects on response times.

Supplementary results

Table S3.1 Effects of drugs on prolactin levels

Blood samples were used to determine prolactin values before drug intake and approximately 2.25 hours after bromocriptine intake and 2.75 hours after sulpiride intake (see methods). All drug-induced changes in prolactin values were significantly different from that during the placebo session. Moreover, we observed no correlations between drug -induced prolactin levels and drug-induced switching performance (all $p > .7$)

	Drug		
	Bromocriptine	**Sulpiride & Bromocriptine**	**Sulpiride**
Mean (s.e.d.) difference from placebo (df = 45)	- 130.9 (19.9) **		
Mean (s.e.d.) difference from placebo (df= 13)	-99.6 (24) *	2010 (259) **	1964.3 (259.3) **

* = $p < .002$, ** = $p < .001$

s.e.d. = standard error of the difference between drug and placebo

Sulpiride & bromocriptine versus sulpiride: $t(13) = -0.27$, $p = .79$

Table S3.2a Mean response times and error rates on reward and switching for the *DAT1* 9R carriers ($n = 21$)

		High reward		Low reward	
		Repeat	**Switch**	**Repeat**	**Switch**
Placebo	Errors (%) (s.e.m.) *, 1	8.27 (1.45)	12.21 (1.52)	9.29 (1.58)	16.28 (2.06)
	RT (ms) (s.e.m.) +, 2	344.17 (11.58)	348.6 (12.59)	350.78 (14.25)	358.97 (13.58)
Bromocriptine	Errors (%) (s.e.m.) *, 3	7.52 (1.5)	12.25 (1.61)	11.22 (1.96)	15.93 (1.69)
	RT (ms) (s.e.m.) +	361.3 (11.82)	356 (11.9)	360.21 (11.83)	368.97 (14.97)

s.e.m. = standard error of the mean

Significant effects:

* Main effect of reward: $F(1,20) = 19$, $p < .001$], main effect of switching: $F(1,20) = 32.3$, $p < .001$

1 switching: $F(1,20) = 40.7$, $p < .001$; reward: $F(1,20) = 5.1$, $p < .04$; 2 switching: $F(1,20) = 7.4$, $p < .02$

3 switching: $F(1,20) = 13.1$, $p < .002$; reward: $F(1,20) = 14.9$, $p < .001$

+ Main effect of reward: $F(1,20) = 6.4$, $p < .02$

Table S3.2b Mean response times and error rates on reward and switching for the *DAT1 10*R homozygotes (n = 27)

		High reward		Low reward	
		Repeat	**Switch**	**Repeat**	**Switch**
Placebo	Errors (%) *, 1	8	11.8	8.21	14.1
	(s.e.m.)	(1.20)	(1.38)	(1.23)	(1.74)
	RT (ms) +, 3	320.89	325.36	327.2	329.88
	(s.e.m.)	(6.4)	(6.81)	(6.85)	(7.45)
Bromocriptine	Errors (%) *, 2	9.95	11.12	11.71	13.30
	(s.e.m.)	(1.46)	(1.42)	(1.53)	(1.83)
	RT (ms) +, 4	319.36	322.97	330.93	328.75
	(s.e.m.)	(8.91)	(9.85)	(9.79)	(10.07)

s.e.m. = standard error of the mean

Significant effects:

* Main effect of switching: $F(1,26) = 19.9$, $p < .001$; main effect of reward: $F(1,26) = 4.9$, $p < .04$; drug*switching: $F(1,26) = 5.4$, $p < .0.3$

1 main effect of switching: $F(1,26) = 25.5$, $p < .001$; 2 main effect of reward: $F(1,26) = 6.9$, $p < .02$

3 main effect of reward: $F(1,26) = 6.4$, $p < .02$; main effect of switching: $F(1,26) = 4.4$, $p <. 05$

4 main effect of reward: $F(1,26) = 13.7$, $p < .002$; + main effect of reward: $F(1,26) = 15.1$, $p<.001$

Table S3.2c Mean response times and error rates on reward and switching for the subgroup of 10R homozygotes who received sulpiride (pre)-treatment (n = 14)

		High reward		Low reward	
		Repeat	**Switch**	**Repeat**	**Switch**
Placebo	Errors (%) (s.e.m.) *, 1	9.66 (1.58)	15.68 (1.74)	9.59 (1.82)	17.41 (2.37)
	RT (ms) (s.e.m.) +	319.14 (10.17)	320.42 (11.24)	323.25 (10.4)	327.7 (12.03)
Bromocriptine	Errors (%) (s.e.m.) *	12.09 (2.11)	13.32 (1.63)	13.39 (2.16)	16.06 (2.32)
	RT (ms) (s.e.m.) +, 2	305.36 (8.39)	310.98 (9.29)	316.62 (10.32)	317.95 (10.58)
Sulpiride	Errors (%) (s.e.m.) 3	9.29 (1.76)	13.14 (1.87)	13.37 (2.53)	18.73 (2.64)
	RT (ms) (s.e.m.)	323.67 (12.73)	329.18 (14.88)	326.08 (12.47)	335.54 (15)
Sulpiride - bromocriptine	Errors (%) (s.e.m.) 4	13.69 (2.61)	17.21 (2.82)	15.39 (2.91)	22.19 (3.04)
	RT (ms) (s.e.m.)	310.61 (11.39)	312.35 (10.47)	316.71 (11.98)	315.77 (12.04)

s.e.m. = standard error of the mean

Significant effects:

* Main effect of switching: $F(1,13) = 22.1$, $p < .001$], drug * switching: $F(1,13) = 5.6$, $p < .04$

+ Main effect of reward $F(1,13) = 7.6$, $p < .02$;

1 main effect of switching $F(1,13) = 24.4$, $p < .001$;

2 Main effect of reward $F(1,13) = 7.8$, $p < .02$;

3 main effect of switching: $F(1,13) = 5.1$, $p < .05$; main effect of reward: $F(1,13) = 19.7$, $p < .001$;

4 main effect switching $F(1,13) = 9.6$, $p < .009$

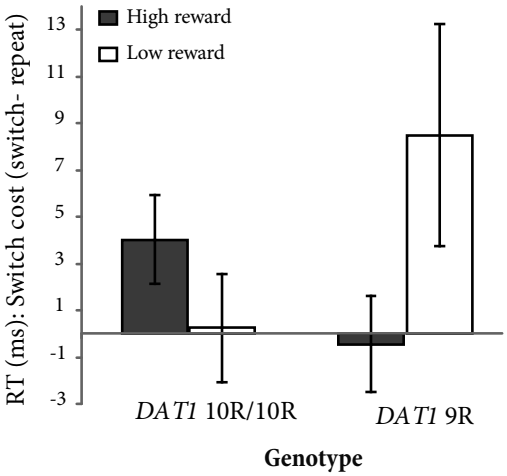


Figure S3.1 Dopamine-dependent motivation-cognition interaction
Shown here is the switch cost (switch – repeat) in terms of response times for the two genotype groups. In contrast to the 10R homozygotes (n = 27), the 9R carriers (n = 21; with relatively higher levels of striatal dopamine) exhibited decreased switch costs under high relative to low reward [Reward x Switching x DAT1: $F(1,46) = 5.3$, $p = .026$]. Bars represent the standard error of the difference between switch and repeat trials. We did not find these effects in the error rates [Reward x Switching x DAT1: $F(1,46) < 1$].

Learning effect

This paradigm was designed to measure set switching and effects of incentive motivation by monetary reward. To assess whether the observed drug effects on set switching reflect a form of learning, we analyzed drug effects as a function of time. Specifically, we binned the data in eight successive bins of 20 trials each, and looked at the interaction between Switching, Drug and Time. We found no learning effects across the two *DAT1* genotype groups [Switching x Drug x Time: $F(7,40) < 1$], in the 10R homozygotes [Switching x Drug x Time: $F(7,19) < 1$], or in the 9R carriers [Switching x Drug x Time: $F(7,14) = 1.74$, $p > .1$].

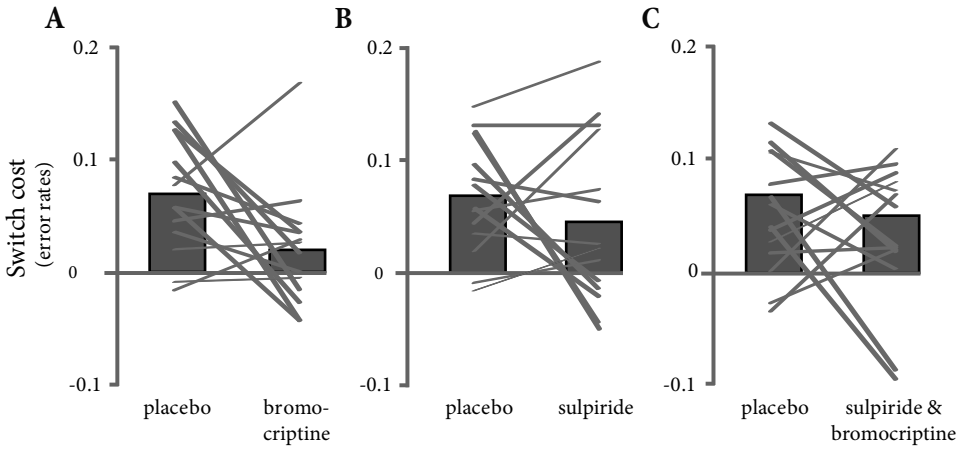


Figure S3.2 a-c
Shown are mean and individual switch costs (switch - repeat) in terms or error rates, from a) the placebo compared with the bromocriptine session, b) the placebo compared with the sulpiride session, and c) the placebo compared with the bromocriptine after sulpiride pre-treatment session.

Table S3.3a Neuropsychological assessment for two *DAT1* genotype groups

	***DAT1* genotype**	
	9R Carriers	**10R Homozygotes**
n	21	27
Age (mean ± s.d.) [a]	21.4 ± 1.9	21.7 ± 2.2
DART*-score (mean ± s.d.) [a]	104.1 ± 8.8	104.1 ± 10.2
Females: n (%) [c]	12 (57.1 %)	12 (44.4 %)
BIS-11 total (mean ± s.d.) [b]	64.5 ± 10.4	64.3 ± 7.5
BDI (mean ± s.d.) [a]	2.5 ± 2.3	2.3 ± 2.7
Listening span (mean ± s.d.) [a]	5.5 ± 1.2	5.4 ± 1.3
STAI (mean ± s.d.) [a]	32.1 ± 5.7	29.9 ± 6.5

a) $F(1,46) < 1.2$, $p > .2$; b) $F(1,43) < 1$, $p > .9$; c) $\chi^2(1) < 1$, $p > .3$
* DART = Dutch Adult Reading Test, verbal IQ measure.
The two genotype groups did not differ in terms of age, IQ, gender, Barratt Impulsiveness Scale (BIS-11), Beck Depression Inventory (BDI), listening span and State-Trait Anxiety Inventory (STAI).

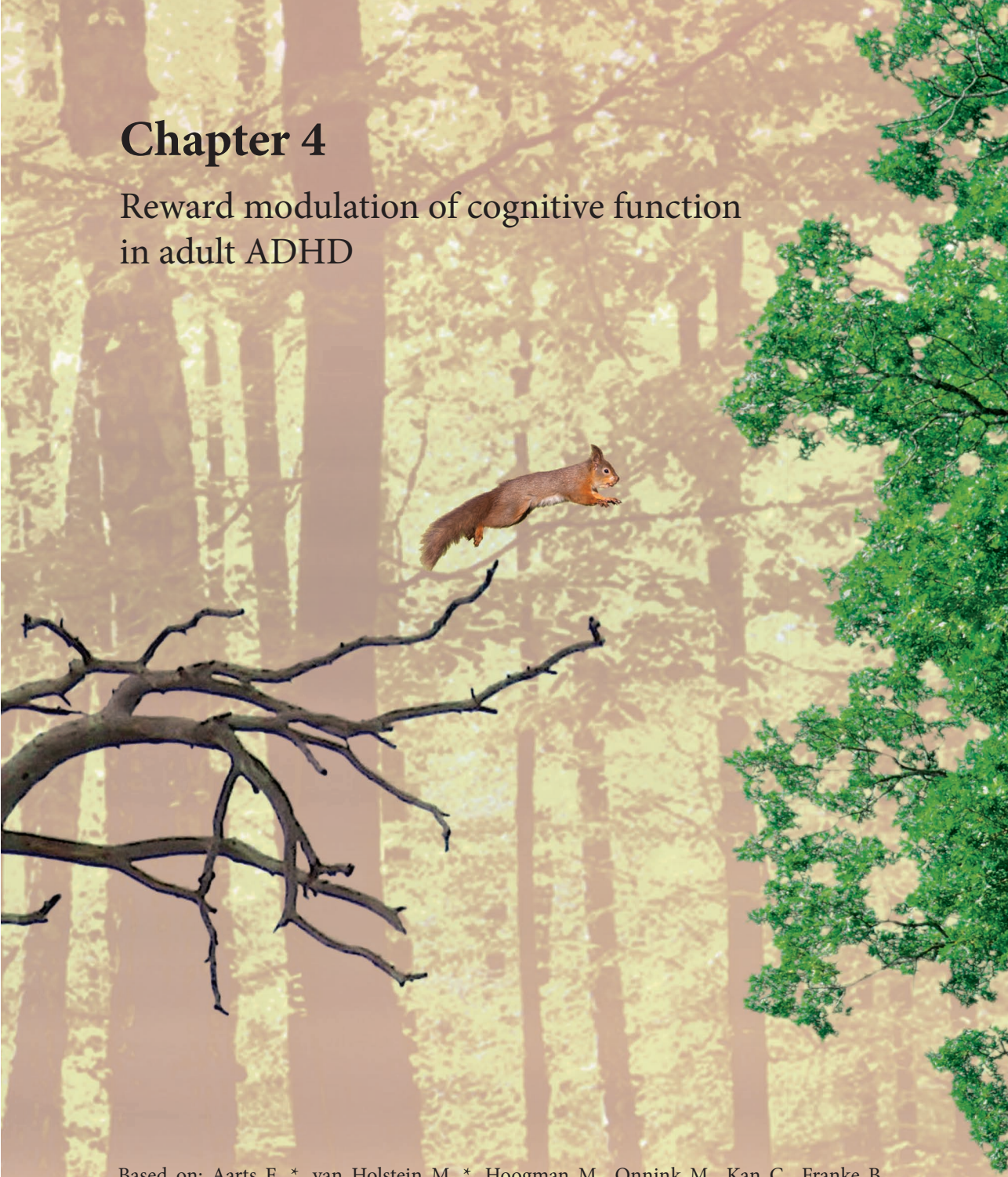
Table S3.3b Demographics in low and high listening span groups

	Listening Span	
	Low	**High**
n	23	25
Age (mean ± s.d.) [a]	21.5 ± 1.8	21.6 ± 2.3
DAT1 10R genotype: n (%) [c]	11 (47.8 %)	16 (64 %)
DART*-score (mean ± s.d.) [a]	104.8 ± 9.9	103.4 ± 9.4
Females: n (%) [c]	12 (52.2 %)	12 (48 %)
BIS-11 total (mean ± s.d.) [b]	65.6 ± 9.8	63.2 ± 7.7
BDI (mean ± s.d.) [a]	2.6 ± 2.4	2.2 ± 2.6
STAI (mean ± s.d.) [a]	30.8 ± 5.3	30.8 ± 7
Listening span score	≤ 5	> 5

a) $F(1,46) < 1$; b) $F(1,43) < 1$; c) $\chi^2(1) < 1.3$, $p > .3$; * DART = Dutch Adult Reading Test, verbal IQ measure. The two listening span groups did not differ in terms of age, *DAT1* genotype, IQ, gender, Barratt Impulsiveness Scale (BIS-11), Beck Depression Inventory (BDI), and State-Trait Anxiety Inventory (STAI).

Chapter 4

Reward modulation of cognitive function in adult ADHD



Based on: Aarts E. *, van Holstein M. *, Hoogman M., Onnink M., Kan C., Franke B., Buitelaar J., Cools R. (2015) Reward modulation of cognitive function in adult attention-deficit/hyperactivity disorder: a pilot study on the role of striatal dopamine. Behav Pharmacol 26:227-240.

* = shared 1st author

Abstract

Attention-deficit/hyperactivity disorder (ADHD) is accompanied by impairments in cognitive control, such as task-switching deficits. We investigated whether such problems, and their remediation by medication, reflect abnormal reward motivation and associated striatal dopamine transmission in ADHD. We employed functional genetic neuroimaging to assess effects of dopaminergic medication and reward motivation on task switching and striatal BOLD signal in 23 adults with ADHD ON and OFF methylphenidate and 26 healthy controls. Critically, we took into account inter-individual variability in striatal dopamine by exploiting a common genetic polymorphism (3'-UTR VNTR) in the DAT1 gene coding for the dopamine transporter. Results revealed a highly significant group by genotype interaction in the striatum. This was due to a subgroup of patients with ADHD exhibiting greatly exaggerated effects of reward on striatal BOLD signal during task switching when they were OFF their dopaminergic medication. Specifically, patients carrying the 9R allele showed greater striatal signal than healthy controls carrying this allele, while no effect of diagnosis was observed in 10R homozygotes. Aberrant striatal responses were normalized when 9R-carrying patients with ADHD were ON medication. These pilot data demonstrate an important role for aberrant reward motivation, striatal dopamine and inter-individual genetic differences in cognitive processes in adult ADHD.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is characterized by symptoms of inattention, impulsivity and/or hyperactivity (American Psychiatric Association, 1994, 2013). Although originally considered a childhood disorder, ADHD persists into adulthood in quite a number of cases, and affects between 2.5 and 4.9% of the adult population (Kooij et al., 2005; Kessler et al., 2006; Polanczyk et al., 2007; Simon et al., 2009). A first-line treatment option for ADHD is prescription of psychostimulant medication, primarily the dopamine and noradrenaline transporter blocker methylphenidate.

ADHD is associated with a wide range of cognitive control deficits that span the domains of attention, response inhibition, working memory and task switching (Barkley, 1997; Bush et al., 1999). Such cognitive control deficits have been attributed most commonly (albeit not exclusively; see Cortese et al., 2012) to (dorsal) prefrontal cortex dysfunction (Dickstein et al., 2006; Cubillo et al., 2010; Dibbets et al., 2010; McCarthy et al., 2014). And accordingly, effects of methylphenidate on cognitive control deficits in ADHD are thought to reflect action (i.e. increasing synaptic levels of dopamine and noradrenaline) in the prefrontal cortex (Aron et al., 2003a; Berridge et al., 2006; Schmeichel et al., 2013) (for a review see Arnsten and Li, 2005). In addition to cognitive control deficits, ADHD is accompanied by processing deficits in the domains of reward and motivation (Sergeant et al., 2003; Sonuga-Barke, 2003; Scheres et al., 2007; Furukawa et al., 2014). Unlike the cognitive control deficits, these reward-related deficits are often attributed to changes in the ventral striatum (Ströhle et al., 2008; Plichta et al., 2009; Hoogman et al., 2011; Carmona et al., 2012; Volkow et al., 2012; Hoogman et al., 2013; Plichta and Scheres, 2014), as is the modulation of reward-related processing by methylphenidate (Dodds et al., 2008). Indeed, besides acting on noradrenaline transporters, methylphenidate acts by blocking dopamine transporters, which are more abundant in the striatum than in the prefrontal cortex (Volkow et al., 1995; Ciliax et al., 1999).

The observation that both cognitive control deficits and reward-related deficits contribute to ADHD concurs with the dual pathway model of AHD, according to which two subtypes of ADHD exist with different developmental pathways, underpinned by different neural circuits and modulated by different branches of the dopamine system (Sonuga-Barke, 2002, 2003, 2005; for more recent models see Durston et al., 2011; de Zeeuw et al., 2012). More specifically, disturbances in the executive mesocortical dopamine circuit, encompassing the dorsal striatum, dorsomedial thalamus and dorsolateral prefrontal cortex, underlie cognitive deficits in ADHD whereas motivational deficits are grounded in disturbances in the mesolimbic reward circuit, including the ventral striatum and orbitofrontal cortex. Here we approach the issue from a different angle by asking whether cognitive task-related processing deficits and their remediation by methylphenidate reflect indirect modulation of motivation and reward-related processing in the striatum rather than direct modulation of prefrontal processing. This question is grounded in current neuroanatomical and neurochemical models that emphasize a hierarchical arrangement of spiraling striatonigrostriatal loops

allowing directional interaction between motivational and cognitive circuits (Haber et al., 2000; Haber, 2003; Ikeda et al., 2013). Furthermore, it concurs generally with a large body of work showing that striatal dopamine is important not just for motor control but also for cognitive functioning (e.g. Cools et al., 1984). Moreover, it follows directly from work showing that methylphenidate-induced changes in striatal dopamine release can contribute to cognitive (attentional) symptoms in ADHD (Glow and Glow, 1979; Volkow et al., 2012). The hypothesis also concurs with observations that cognitive deficits in children with ADHD can be remediated by increases in motivation (Konrad et al., 2000; Slusarek et al., 2001; Uebel et al., 2010), although inconsistent findings have been reported as well (Oosterlaan and Sergeant, 1998; Desman et al., 2008; Shanahan et al., 2008; Karalunas and Huang-Pollock, 2011). None of these studies, however, speak to the neural mechanisms of such motivational effects and their modulation by methylphenidate.

Here we aimed to assess whether cognitive task-related processing deficits in adult ADHD can be a function of reward-related striatal functioning by using functional magnetic resonance imaging (fMRI). To index reward effects on cognitive task-related processing, we employed a rewarded task-switching paradigm that we previously established to be sensitive to - and reveal its effect only when taking into account - changes in striatal dopamine transmission (Aarts et al., 2010; for a review see Aarts et al., 2011; Aarts et al., 2012; Aarts et al., 2014a; see also Aarts et al., 2014b).

One major challenge for studies aiming to isolate dopaminergic drug effects is that such dopaminergic drug effects vary greatly across different individuals as a function of (genetically determined) baseline levels of dopamine (Verheij and Cools, 2008; Cools and D'Esposito, 2011; van Holstein et al., 2011). Prior work suggests the possibility that the effects of methylphenidate surface *only* by taking into account such inter-individual differences (Clatworthy et al., 2009), for example by exploiting known common polymorphisms in dopamine genes. Here we stratify our sample by inter-individual variation in the 40-bp variable number of tandem repeats (VNTR) polymorphism in the 3' untranslated region (3'-UTR) of the dopamine transporter (DAT) gene (*DAT1, SLC6A3*). This is based on several lines of evidence, suggesting an important role for the dopamine transporter in the pathophysiology of ADHD. The dopamine transporter is the main mechanism responsible for clearing extracellular dopamine in the striatum. Genetic variation of the *DAT1* gene might lead to inter-individual variation in the availability of dopamine transporters and subsequently in dopamine levels. Although it has remained inconclusive in the literature which allele leads to decreased dopamine transporter availability (Costa et al., 2011; Faraone et al., 2013), genetic fMRI studies have consistently demonstrated the 9-repeat allele to be associated with increased striatal reward responses (Dreher et al., 2009; Forbes et al., 2009; Aarts et al., 2010). Furthermore, methylphenidate exerts its action in the striatum by blocking the dopamine transporter (Volkow et al., 1998; Volkow et al., 2002), mice that lack the DAT (i.e. *DAT1* knock-out mice) exhibit ADHD-like behavior (Giros et al., 1996; Gainetdinov et al., 1999), and several dopaminergic genes, including the *DAT1* genotype have been implicated in

ADHD (Faraone et al., 2005; Brookes et al., 2008; Franke et al., 2008; for a review, see Durston et al., 2009; Gizer et al., 2009; Franke et al., 2010).

In summary, in this pilot study we tested the hypothesis that effects of reward motivation on task switching and striatal BOLD signal vary as a function of *DAT1* genotype adult patients with ADHD, when they were ON relative to OFF their methylphenidate regimen, compared with healthy controls.

Methods

Participants

We present data from 23 patients with ADHD (mean ± SE age 35.74 ± 2.36; 14 men) and 26 healthy control participants (mean ± SE age 38.08 ± 2.00; 11 men). Patients visited our centre on two occasions, once after intake of methylphenidate and once after withdrawal from methylphenidate. Healthy controls were also tested on two occasions, without any methylphenidate (**procedure**).

Initially we recruited 57 participants (29 patients with ADHD and 28 healthy controls) from an ongoing study on ADHD and genetics, IMpACT-NL (Hoogman et al., 2011; Hoogman et al., 2013; Onnink et al., 2014; www.impactADHDgenomics.com), in which they were tested extensively, genotyped, and diagnosed (**table 4.1**). Patients were included if they met DSM-IV-TR criteria for ADHD in childhood as well as adulthood. All participants were assessed using the Diagnostic Interview for Adult ADHD (Kooij and Francken, 2007). The Structured Clinical Interviews for DSM-IV (SCID-I and SCID-II) were administered. Assessments were carried out by trained professionals (psychiatrists or psychologists). In addition, a quantitative measure of clinical symptoms was obtained using the ADHD rating scale-IV (Kooij et al., 2005). Exclusion criteria for participants were alcohol or substance addiction in the last 6 months, current psychosis, manic episodes, obsessive compulsive disorder or eating disorders (assessed using SCID-I), full-scale IQ estimate < 70 (assessed using the Wechsler Adult Intelligence Scale-III), neurological disorders, sensorimotor disabilities, and non-Caucasian ethnicity. An additional exclusion criterion for healthy comparison subjects was a current or past neurological or psychiatric disorder according to SCID-I.

Three patients did not complete the testing sessions. Two patients were excluded because they did not follow instructions regarding methylphenidate withdrawal and/or intake (**procedure**) and one because of excessive head movement. One healthy control participant was excluded from analysis due to suboptimal quality of the structural data leading to normalization difficulties, and one for meeting the criteria for an ADHD diagnosis according to the ADHD rating scale-IV (Kooij et al., 2005) (**neuropsychological assessment**). Hence, 23 patients with ADHD and 26 healthy controls were included in the final analyses.

Table 4.1 DeAmographics, impulsivity and diagnostic interview for DIAGNOSIS x *DAT1* group

	ADHD (N= 23)		HC (N= 26)		Univariate GLM / Chi-Square / Fisher's Exact Test		
	9R carriers	**10R/10R**	**9R carriers**	**10R/10R**	**ADHD vs. HC**	**9R carriers vs. 10R/10R**	**Diagnosis x *DAT1***
Demographics							
N	12	11	10	16			ns
Age mean (SE) [a]	36.25 (3.78)	35.18 (2.91)	41.1 (2.79)	36.25 (2.70)	$F(1,45) < 1$	$F(1,45) < 1$	$F(1,45) < 1$
IQ (WAIS III) mean (SE) [*, a]	11.58 (0.66)	12.72 (0.54)	12 (0.91)	12.31 (0.80)	$F(1,45) < 1$	$F(1,45) = 1.05$; $p > .1$	$F(1,45) < 1$
Gender: males N / % [b]	7 / 58%	7 / 64%	4 / 40%	7 / 44%	$p > .1$	$p > .1$	$p > .1$
Education level mean (SE) [*, c]	4.75 (0.22)	5.00 (0.30)	5.10 (0.23)	5.00 (0.26)	$Chi^2 (3) = 1.77$; $p > .1$	$Chi^2 (3) = 5.03$; $> .1$	$Chi^2 (1) < 1$
Handedness: right handed N / % [*, c]	12 /100%	9 / 82 %	8 / 80%	15 / 94%	$Chi^2 (2) = 2.25$; $p > .1$	$Chi^2 (2) < 1$	$Chi^2 (1) < 1$
Smokers N / % [b]	6 / 50%	6 / 55%	3 / 30%	5 / 31%	$p > .1$	$p > .1$	$p > .1$

BIS-11 impulsivity score [a]	74.75 (2.74)	71.09 (4.58)	58.9 (3.00)	59.5 (1.75)	$F(1,45) = 20.78$; $p < .001$	$F < 1$	$F < 1$
SCID-Axis I Current co-morbidities *				Chi-Square: Fisher's Exact Test			
Depressive	0/10	1/11	0/9	0/15	ns	ns	ns
Dysthymic	0/10	1/11	0/9	0/15	ns	ns	ns
Anxiety	1/10	1/11	0/9	0/15	ns	ns	ns
SCID-Axis II Personality *							
Borderline	2/10	0/10	0/9	0/15	ns	ns	ns
Antisocial	1/10	0/10	0/9	0/15	ns	ns	ns
Obsessive-compulsive	2/10	0/10	0/9	0/15	ns	ns	ns

* = administered during IMpACT-NL study, values indicate number of participants meeting the criterion / total number of participants in which the SCID-I or SCID-II was administered; 10R/10R = 10R homozygotes; a = Univariate GLM; b = Chi-Square: Fisher's Exact Test; c = Chi-Square Test

All patients had a current prescription of methylphenidate [either immediate-release (Ritalin®; N = 5; mean ± SD 44 ± 22.74 mg per day), or sustained release (Concerta®; N = 18; mean ± SD 48.5 ± 21.19 mg per day), three of them occasionally took Ritalin® in addition to Concerta®]. All participants were native speakers of Dutch. Participants were compensated for participation and gave written informed consent in a manner approved by the local ethics committee on research involving human participants (CMO Arnhem-Nijmegen 2009/058, NL27180.091.09).

Procedure

All participants were asked to abstain from alcohol on the day of testing and from nicotine and caffeine at least one hour before arriving at the centre. The patients were tested once OFF (i.e. withdrawn from Ritalin® for 24 hours and from Concerta® for 48 hours before testing) and once ON methylphenidate, (i.e. after intake of (mean ± SD) 13.15 mg ± 5.55 of Ritalin®, the equivalent of (mean ± SD) 0.16 ± 0.05 mg/kg body weight of Ritalin®, half an hour before arriving at the centre). Patients using sustained-release methylphenidate were prescribed an equivalent dose (instant dose (mg) = sustained dose (mg) * 0.278) of immediate-release methylphenidate by the psychiatrist (JB) for one day (3 doses a day). Three patients using additional medication (one antihistamine, and two SSRI's) were asked to take the same dose on both sessions. The order of the ON and OFF session was approximately counterbalanced across participants (**table 4.2**). The healthy control group did not take methylphenidate, but was nevertheless tested twice to rule out order effects. Control data were averaged across the two sessions. Sessions were separated by at least one week and both sessions took place at approximately the same time of day. With the exception of medication state, the procedure was identical for both groups and both sessions.

Cognitive task with reward manipulation

Participants were scanned while performing an established pre-cued task switching paradigm (**figure 4.1, box 2.3**) with a reward manipulation (Aarts et al., 2010; van Holstein et al., 2011; Aarts et al., 2012; Aarts et al., 2014a). The paradigm started approximately 60 minutes after arrival (mean ± SD 91.8 ± 16.1 minutes after drug intake). The task was programmed and presented using Presentation® 13 (Neurobehavioral Systems, Inc.).

Participants had to respond to incongruent arrow-word combinations, either by responding to the direction of the arrow or the direction indicated by the word ("left" or "right"). A task-cue appeared 400 ms before the target indicating the task (arrow or word) that the participant had to perform on the current trial. Relative to the previous trial, the task either changed unpredictably (from arrow to word or vice versa; switch trial), or remained the same (repeat trial). The critical measure of interest, the switch cost, was calculated by subtracting performance on repeat trials from that on switch trials. In addition, we manipulated reward motivation by presenting high and low reward cues prior to the task cue to assess the effect

Table 4.2 ADHD characteristics

	ADHD		Statistics
	9R carriers	**10R/10R**	***DAT1* effect**
First session ON MPH	6 / 50%	6 / 55%	ns
Ritalin dose ON	14.38 (1.80)	11.82 (1.39)	ns
Ritalin [a]	1 / 9%	4 / 33%	ns
Concerta dose	53.18 (6.91)	36.63 (7.20)	ns
Subtypes: DIVA [b]			ns
Combined	11	6	
Inattentive	0	3	
Hyperactive / impulsive	0	1	

a) Three of the Concerta® users (one 9R carrier) occasionally took 15 mg Ritalin® in addition to Concerta®; b) DIVA was not administered for one patient in each *DAT1* group; 10R/10R = 10R homozygotes

of reward on task switching. The reward-cue informed the participants whether 1 cent (low reward) or 15 cents (high reward) could be earned with a correct and sufficiently quick response. Immediately after the response, feedback was given (e.g., "correct! 15 cents"). There was a variable interval between the reward-cue and the task-cue of 2 to 6 seconds. Participants used their right index and middle fingers to respond with a button box.

On both sessions, the task was practiced twice outside the scanner and once inside the scanner. The first practice block contained 24 trials with the task cue, target and feedback ("correct" / "incorrect"). As soon as participants succeeded to complete this block with less than 5 errors, the second practice block of 24 trials was performed, in which the reward cues were included. The third and final practice block was performed during the acquisition of the anatomical scan. The mean response times (RT) of the correct trials per trial-type (arrow-repeat, arrow-switch, word-repeat, word-switch trials) in this third practice block were used as the response deadline in the main experiment. This ensured equal difficulty across participants and sessions.

The main experiment consisted of 160 trials and lasted ~ 35 minutes with a 30 second break after every 32 trials. In the break, the amount of money the participant had earned thus far was displayed on the screen and participants were told in advance that the total amount would be added to their financial compensation as a bonus.

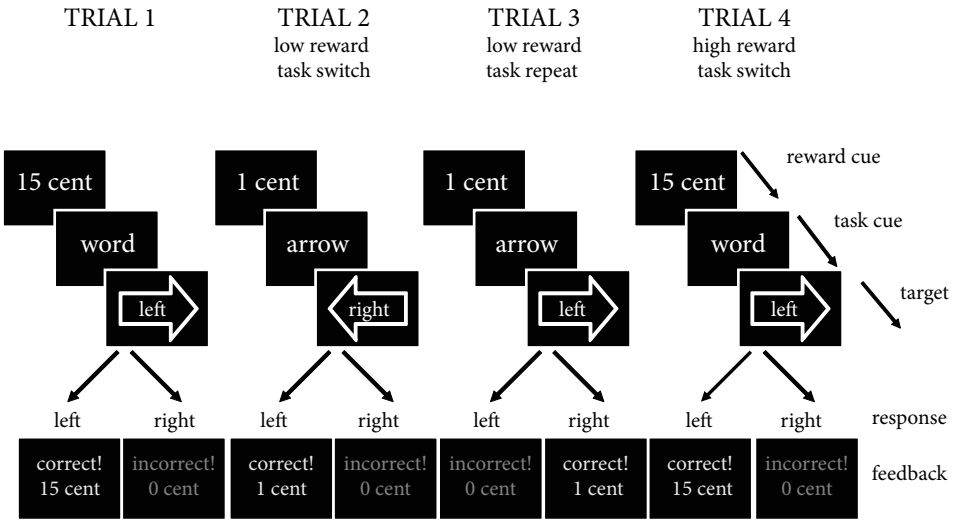


Figure 4.1 Task-switching paradigm with reward manipulation
Participants were instructed to respond either to the direction indicated by the arrow (i.e. -> or <-) or to the direction indicated by the word (i.e. 'left' or 'right') with a left or right button press. The task performed on a particular trial either changed compared with the preceding trial (i.e. switch trial; arrow - word or word - arrow) or remained the same (i.e. repeat trial; arrow-arrow, word-word). In addition we manipulated the amount of anticipated reward (e.g. 1 Eurocent vs. 15 Eurocent) on a trial-by-trial basis by means of a reward anticipation cue. At the start of each trial this cue indicated the amount of reward on that trial providing a correct and sufficiently fast button press (see also Aarts et al. 2010 and box 2.3).

Neuropsychological assessment

During the first session, participants completed the Barratt Impulsiveness Scale (BIS-11a; Patton et al., 1995), a self-report trait measure of impulsivity. At the beginning of both sessions, participants completed the Bond and Lader (1974) visual analogue scale for a comparison of mood between sessions (16 moods rated on scale 0-100, resulting in 3 mood categories) and an ADHD symptom rating scale (Kooij et al., 2005) to assess self-reported ADHD symptoms. Motor speed was measured using the box completion task (Salthouse, 1996), sustained attention with the digit vigilance or number cancellation task (Lewis and Kupke, 1977), and verbal fluency with the begin letters D, A, and T (Spreen and Benton, 1977).

Genotyping

DNA was isolated from EDTA blood samples. Genotyping of the 40-bp VNTR in the 3'-UTR of SLC6A3/DAT1 was carried out as described before (Hoogman et al., 2013) at the department of Human Genetics of the Radboud university medical center. In line with previous studies reporting the effect of this variant, we established a group of carriers of the 9-repeat (9R) allele

(i.e. the risk factor for adult ADHD) and a group homozygous for the 10R allele (Colzato et al., 2010b; Rokem et al., 2012) (table 4.1). We preselected our participants from a previous sample (Hoogman et al., 2013) to homogenize sample numbers per group (diagnosis x genotype) as much as possible. Therefore, Hardy-Weinberg equilibrium was not considered.

In the ADHD group, 12 individuals were carriers of the 9R allele and 11 individuals were homozygous for the 10R allele (table 4.1). In the healthy control group, 10 individuals were carriers of the 9R allele and 16 individuals were homozygous for the 10R allele. We performed a power calculation in G*Power (http://www.gpower.hhu.de) based on the effect sizes obtained in an independent dataset using a similar rewarded task-switching paradigm and the same VNTR in the DAT1 gene in healthy volunteers (Aarts et al., 2010). The power calculation revealed that we would need at least 8 participants per group (four groups: genotype x diagnosis) to obtain significant effects of genotype on striatal BOLD responses during rewarded task switching (effect size = 0.78; $\alpha = 0.05$; power $(1 - ß) = 0.8$). Currently, our smallest group consists of 10 participants.

Functional MRI data acquisition

Participants were scanned in a 3T MR scanner (Magnetom TrioTim, Siemens Medical Systems, Erlangen, Germany), using an 8-channel head coil. T2*-weighted images were acquired with a gradient echo planar imaging (EPI) sequence (30 axial slices, repetition time = 2020 ms, echo time = 30 ms, voxel size = 3.5 x 3.5 x 3 mm, field of view = 224 mm, flip angle = 80°). All functional images were acquired in a single run. Stimuli were presented on a computer display projected onto a mirror attached to the head coil. The first 4 volumes were discarded to allow for T1 equilibrium. Before the acquisition of the functional images, a high-resolution T1-weighted MP-RAGE anatomical scan was obtained (192 sagittal slices, repetition time = 2300 ms, echo time = 3.03 ms, voxel size = 1 x 1 x 1 mm, field of view = 256 mm).

fMRI statistical analyses

Data were pre-processed and analyzed using SPM5 (Wellcome Dept. of Cognitive Neurology, London). First, functional EPI images were spatially realigned and corrected for differences in slice acquisition timing. Structural and functional data were co registered and normalized to a standard anatomical space (Montreal Neurological Institute) using a unified segmentation procedure (Ashburner and Friston, 2005). The normalized images were smoothed with an isotropic 8 mm full-width-at-half-maximum (FWHM) Gaussian kernel.

The pre-processed fMRI time series were analyzed at the first level using an event-related approach in the context of the GLM. Our statistical model on the first (subject-specific) level considered the factors Reward (high, low), Task (arrow, word), Task-switching (repeat, switch), and Feedback (correct-1cent, correct-15cents, error-0cents, too late-0cents). This resulted in 21 regressors of interest: 2 regressors for Reward-cues, 8 regressors for Targets (Reward x Task x Task switching), and 4 regressors for Feedback. All regressors of interest were modeled as

a stick function (duration = 0) convolved with a canonical hemodynamic response function. Additionally, breaks (duration of 30 seconds), 6 motion parameters, and their derivatives were modeled as regressors of non-interest. Finally, we included 3 regressors of non-interest to account for movement-induced intensity changes by using the mean time series from the segmented white matter, cerebral spinal fluid and out of brain signals (Majdandzic et al., 2007; Verhagen et al., 2008). High-pass filtering (128 seconds) was applied to the time series of the functional images to remove low-frequency drifts.

At the second level, the Reward x Task switching contrast images from the first level were used in three GLMs to assess the effects of Reward during Task switching: two models to assess the interaction with DAT1 Genotype and Diagnosis (HC versus ADHD OFF and ADHD ON versus HC), and one model to test the interaction with DAT1 genotype and Medication (ADHD ON versus ADHD OFF). Statistical inference ($p < .05$) was performed at the cluster level, correcting for multiple comparisons over the search volume (the whole brain). The intensity threshold necessary to determine the cluster-level threshold was set at $p < .001$, uncorrected. For each effect we report the t-values (t) at the voxel-level, the whole-brain corrected p-values for the cluster (pcluster), and the size of the cluster (k). In addition, supplementary exploratory analyses were performed for which the uncorrected threshold was set to $p < .001$, and we report the t-values (t) and p-values (puncorr) at the voxel level.

Behavioral statistical analyses

We excluded the first trial of each block (5 trials in total), because these cannot be considered as either repeat or switch trials. All trials to which subjects responded (i.e. all trials except response omissions) were included in the analysis, even if the response was too late for a reward to be obtained. For the analysis of the mean RTs, we excluded the responses faster than 200ms. For each participant, we calculated the mean RTs for all the correct responses and the proportion of errors for each of the four conditions, i.e. Reward (high - low) x Task switching (switch - repeat). To maximize homogeneity of variances between groups and to assure normal distribution of the data, a natural logarithm (LN) transformation was applied to the mean RTs. The mean proportions of incorrect responses were transformed with the following formula: $2*\arcsin\sqrt{x}$ (Sheskin 2003). Levene's tests of homogeneity of variances and Shapiro-Wilk tests of normality revealed that this transformation was successful in improving variance between groups and the distribution of the data.

Proportions or errors and mean RTs were analyzed using a repeated-measures general linear model (GLM) with the within-subjects factors Reward (high, low), Task switching (repeat, switch), the between-subject factor DAT1 genotype (9R carriers, 10R homozygotes), and either the between-subject factor Diagnosis (ADHD or healthy control) or within-subject factor Medication (ON, OFF). Effects were considered significant when $p < .05$.

Statistical analysis of mood measures and neuropsychological tests

Mood values were calculated for each session and reduced to three factors: contentedness, alertness, and calmness, according to Bond and Lader (1974). Neuropsychological and demographic differences between groups or medication states and their interaction with the DAT1 genotype were tested using SPSS 21 with univariate or repeated measures GLM's or their non-parametric counterparts (Wilcoxon signed rank or Mann-Whitney U tests, respectively; table 4.3). Non-parametric DAT1 Genotype x Medication interactions were assessed with a Mann-Whitney U test of the difference between the score OFF and ON Medication. Non-parametric DAT1 Genotype x Diagnosis effects were assessed using the Kruskal-Wallis test (**table 4.3**). An effect was considered significant when $p < .05$.

Results

Functional MRI effects

Main task effects

Across groups and sessions, the cue indicating a high reward compared with the cue indicating a low reward elicited a robust response in regions in the striatum, in the frontal cortex and the occipital cortex (**table 4.4**). There was also a strong main effect of task switching during the targets, as evidenced by a greater response in frontal and parietal regions on switch compared with repeat trials (**table 4.4**).

ADHD OFF versus healthy controls:

BOLD signal in the dorsal striatum varied highly significantly as a function of ADHD diagnosis (patients with ADHD OFF their medication versus healthy controls), DAT1 genotype (9R carriers vs. 10R homozygotes) and task (Reward x Task switching) (x, y, z = -20, 4, 16; t = 4.92; p cluster < .001; k = 324; figure 4.2A-I). This finding concurs with our hypothesis that the effect of Reward on Task switching in the striatum would vary as a function of DAT1 Genotype and Diagnosis (healthy controls compared with patients with ADHD). The striatal effect was due to greater task-related signal in patients with ADHD carrying the 9R allele compared with 9R carriers in the healthy control group (Reward x Task switching x Diagnosis in 9R carriers: x, y, z = -18, 2, 16; t = 4.90; p cluster = .001; k = 333) and greater task-related signal in the 9R carrying patients with ADHD compared with the 10R homozygous patients with ADHD (Reward x Task switching x DAT1 in patients with ADHD OFF Medication: x, y, z = -12, -4, 6; t = 4.96; p cluster = .002; k = 295). To illustrate this effect, we extracted the beta values from the cluster in the left dorsal striatum depicted in figure 4.2A-I and plotted the results in figure 4.2B. The only other significant neural difference between the ADHD group OFF Medication and the healthy control group was observed in the posterior cingulate cortex (Reward x Task switching x Diagnosis x DAT1: x, y, z = -6, -12, 46; t = 5.56; p cluster < .001; k = 338).

Table 4.3 Mood and neuropsychological assessment

	ADHD OFF		ADHD ON		HC		Univariate or repeated measures GLM (unless noted otherwise)				
	9R carriers	**10R/10R**	**9R carriers**	**10R/10R**	**9R carriers**	**10R/10R**	**ADHD OFF vs. HC**	**ADHD ON vs. HC**	**ADHD ON vs. ADHD OFF**	**DIAGNOSIS x *DAT1***	**MPH x *DAT1***
Bond & Lader mood scales							F(1,44)	F(1,45)	F(1,20)	F(1,44)	F(1,20)
Contentedness	67.42 (4.58)	66.91 (7.15)	76.86 (3.84)	76.82 (4.63)	84.69 (3.50)	77.05 (2.82)	F = 8.78; $p < .005$	MWU =336.5; $p > .05$	Wc= 50; $p = .013$	F < 1	F < 1
Alertness	49.36 (4.19)	57.15 (5.90)	71.79 (3.99)	69.38 (4.66)	78.52 (5.15)	69.74 (2.62)	F = 22.74; $p < .001$	F =1.42; $p > .05$	F =22.73; $p < .001$	F = 3.58; $p > .05$	F = 1.96; $p > .05$
Calmness	59.73 (4.44)	49.46 (7.75)	58.91 (6.07)	62.00 (6.91)	83.40 (4.56)	74.72 (3.52)	F = 22.46; $p < .001$	F = 13.26; $p < .001$	F = 1.14; $p > .05$	F < 1	F = 1.485, $p > .05$
Neuropsychological assessment											
Motor speed (RT, sec)	54.09 (2.60)	54.27 (3.44)	55.18 (3.32)	53.36 (2.34)	69.67 (8.51)	64.31 (6.05)	MWU = 355.5; $p > .05$	MWU = 356; $p > .05$	F<1	F < 1	*MWU = 230;* $p > .05$
Vigilance (RT)	219.64 (13.65)	204.46 (10.39)	222.00 (10.36)	199.73 (9.79)	204.67 (8.41)	210.09 (9.23)	F < 1	MWU =289; $p > .05$	Wc = 122; $p > .05$	F < 1	F < 1
Vigilance (misses)	5.09 (1.42)	5.00 (1.05)	2.46 (0.64)	3.82 (1.12)	2.72 (1.12)	2.78 (0.61)	MWU = 177.5; $p = .024$	MWU = 256; $p > .05$	Wc = 150; $p = .026$	*KW (3) = 5.418;* $p > .05$	*MWU = 311;* $p > .05$
Verbal fluency (no. of words)	37.55 (3.82)	42.27 (3.21)	38.18 (3.48)	43.36 (3.48)	46.89 (3.66)	42.16 (2.11)	F = 1.42; $p > .05$	F<1	F < 1	F = 1.51; $p > .05$	F < 1

KW = Kruskal-Wallis test; MWU = Mann Whitney U test;
Wc = Wilcoxon paired rank test; MPH = methylphenidate; 10R/10R = 10R homozygotes

Table 4.4 BOLD maxima across all subjects

Main effect of Reward anticipation during cues and main effect of Task switching during targets at a whole-brain cluster-level corrected threshold of p < .05.

Label	Brodmann	Side	MNI coordinates			Cluster size	Significance	t-value
		L/R	x	y	z	(No. voxels)	Cluster level	peak
Main effect Reward: high > low reward								
Superior parietal lobe (B7) *	7	L	-16	-68	56	3126	$p < .001$	7.38
Insular cortex (B13) * Extending into the striatum, pallidum and thalamus	13	L+R	30	26	0	3468	$p < .001$	6.56
Cingulate gyrus (B32) *	32	L+R	-4	12	40	3171	$p < .001$	6.24
Occipital lobe (B16) *	16	L	-26	-94	12	352	$p < .002$	5.81
Cingulate gyrus (B23) *	23	L+R	-4	-30	28	283	$p < .005$	5.43
Main effect Reward: low > high reward								
Inferior frontal gyrus	10	R	48	46	8	368	$p < .002$	6.29
Posterior Cingulate: Precuneus	31	L+R	-6	-56	20	460	$p < .001$	4.76
Superior temporal gyrus	39	R	50	-60	26	248	$p < .01$	4.42
Superior frontal gyrus	9	L	12	56	26	228	$p < .02$	4.06
Main effect Task switch: switch > repeat								
precuneus (B7) *	7	L	-24	-66	34	3289	$p < .001$	6.89
inferior frontal gyrus (B9) *	9	L	-48	12	28	1675	$p < .001$	6.02
middle frontal gyrus (B11) *	11	L	-24	48	-10	221	$p < .018$	5.43
Main effect Task switch: repeat > switch								
Superior Temporal gyus	41	R	56	-28	12	694	$p < .001$	4.72
Occipital lobe (cuneus)	19	R	14	-88	34	180	$p < .04$	3.94
Superior temporal gyrus	41	L	-44	-32	14	617	$p < .001$	3.90

* also significant after FWE correction at the voxel level (p FWE < .05)

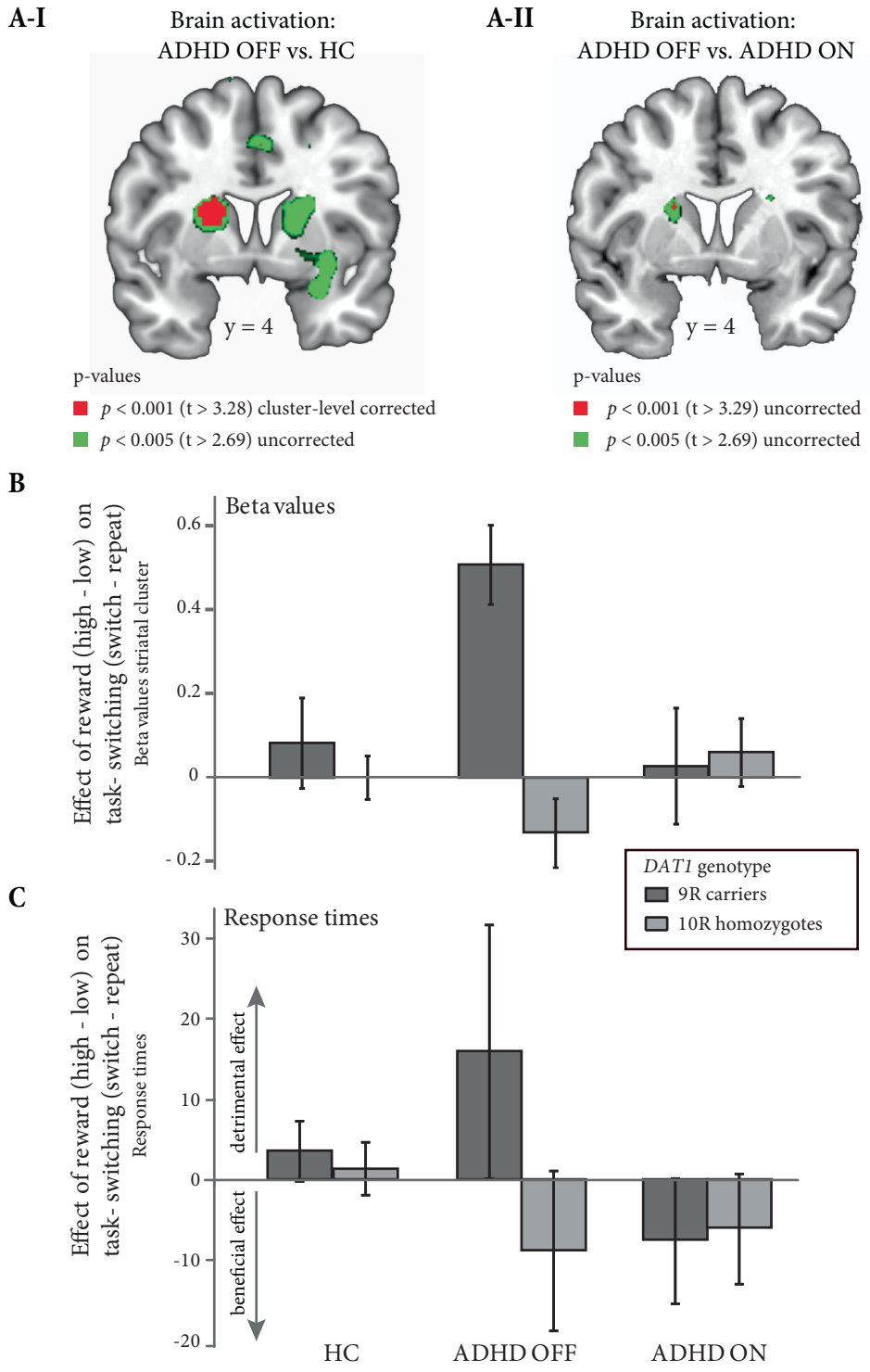

A-I
Brain activation:
ADHD OFF vs. HC
y = 4
p-values
p < 0.001 (t > 3.28) cluster-level corrected
p < 0.005 (t > 2.69) uncorrected
A-II
Brain activation:
ADHD OFF vs. ADHD ON
y = 4
p-values
p < 0.001 (t > 3.29) uncorrected
p < 0.005 (t > 2.69) uncorrected
B
Beta values
Effect of reward (high - low) on task- switching (switch - repeat)
Beta values striatal cluster
0.6
0.4
0.2
0
- 0.2
DAT1 genotype
9R carriers
10R homozygotes
C
Response times
Effect of reward (high - low) on task- switching (switch - repeat)
Response times
detrimental effect
beneficial effect
30
20
10
0
-10
-20
HC
ADHD OFF
ADHD ON

Figure 4.2 Rewarded task switching as a function of DAT1 genotype in patients with ADHD ON and OFF their methylphenidate medication, relative to healthy controls (HC)
A-I: Increased dorsal striatal responses during rewarded task switching for patients with ADHD OFF methylphenidate relative to healthy controls, as a function of DAT1 genotype; **A-II:** Increased dorsal striatal responses during Rewarded Task switching for patients with ADHD OFF methylphenidate relative to when ON methylphenidate, as a function of DAT1 Genotype; **B:** The beta values from the whole-brain cluster-corrected cluster in the left striatum depicted in A-I, illustrating the direction of the effect; **C:** The response times during Rewarded Task switching. Positive values reflect an increased switch cost (i.e. slower on switch than on repeat trials) for high reward relative to low reward trials, i.e. a detrimental effect of reward on the switch cost. Error bars represent the standard errors of the difference between high reward (switch - repeat) - low reward (switch - repeat).

ADHD ON versus healthy controls & ADHD OFF versus ADHD ON:

There was no longer an effect of diagnosis when comparing patients with ADHD ON medication with healthy controls, suggesting that the aberrant striatal response was restored by Medication. Although a direct comparison of the ON and OFF session (ADHD ON vs. ADHD OFF Medication) did not reach significance at our stringent threshold, exploratory analyses confirmed that task-related responses in the same region in the striatum were diminished for patients ON relative to OFF Medication, depending on *DAT1* Genotype (Reward x Task switching x *DAT1* x Medication: x, y, z = -20, 4, 16; t = 3.63; *p* uncorr < .001; **figure 4.2A-II and 4.2B**). This is generally in line with the hypothesis that the effect of methylphenidate and Reward motivation on Task switching would vary as a function of *DAT1* Genotype and Medication status (patients with ADHD ON compared with OFF their Medication).

Behavioral effects

Main task effects:

Participants responded more quickly after a high than a low reward (i.e. across groups, irrespective of diagnosis and genotype), as evidenced by a main effect of reward in terms of response times (RTs) ($F(1,48) = 24.36$; $p < .001$). Participants also responded more quickly on repeat than switch trials (main effect of task switching: $F(1,48) = 24.91$; $p < .001$). In addition, participants made more errors on switch than repeat trials (main effect of Task switching $F(1,48) = 28.67$; $p < .001$; **table 4.5**).

ADHD OFF versus healthy controls

There were no differences between the ADHD group OFF Medication and healthy controls in terms of RTs (**figure 2C**). However, the groups did differ in terms of the Reward effect (i.e. low - high reward) on error rates, across switch and repeat trials. This effect depended on *DAT1* genotype (Reward x Diagnosis x *DAT1*: $F(1,45) = 5.56$; $p = .023$): irrespective of task switching, the 10R homozygotes in the ADHD group made less errors on high than low reward trials

Table 4.5 Means (standard errors) for response times and error rates (% errors)
Data are shown for the ADHD group for each medication state (ON or OFF methylphenidate) and by *DAT1* genotype group (9R+ or 10R homozygotes) for both the ADHD and healthy control group (HC)

	Mean response times: ms (SE)				Error rates: % (SE)			
	9R carriers		**10R homozygotes**		**9R carriers**		**10R homozygotes**	
	Repeat	**switch**	**repeat**	**switch**	**repeat**	**switch**	**repeat**	**switch**
HC								
low	411.36 (8.44)	421.48 (10.70)	406.81 (19.05)	413.57 (21.14)	2.68 (0.62)	3.19 (0.72)	1.67 (0.34)	2.44 (0.45)
high	402.51 (8.23)	416.24 (10.68)	397.51 (19.05)	405.75 (20.62)	2.55 (0.49)	2.36 (0.43)	1.65 (0.39)	2.82 (0.45)
ADHD OFF								
low	426.90 (21.15)	431.03 (24.37)	409.45 (24.13)	427.54 (29.15)	3.39 (0.58)	4.84 (0.94)	2.36 (0.33)	3.76 (0.67)
high	421.97 (20.68)	442.20 (21.51)	404.46 (23.52)	413.80 (25.62)	3.44 (0.64)	5.16 (0.88)	1.83 (0.62)	3.42 (0.68)
ADHD ON								
low	417.99 (26.71)	424.03 (27.82)	395.13 (19.94)	405.49 (21.80)	3.17 (0.61)	3.98 (0.77)	1.59 (0.35)	3.28 (0.42)
high	415.29 (27.24)	413.85 (27.25)	387.27 (18.22)	391.64 (21.66)	2.85 (0.70)	3.98 (0.79)	1.53 (0.45)	3.23 (0.55)

relative to the 10R homozygotes in the healthy control group (Reward x Diagnosis in 10R homozygotes: $F(1,25) = 7.03$; $p = .014$; **table 4.5**), while there was no difference between the 9R carriers in the ADHD group and the healthy 9R group. The critical effect of Reward on Task switching errors did not differ between the patients with ADHD OFF Medication and the healthy control group, also not as a function of *DAT1* Genotype (the critical Reward x Task switching x Diagnosis x *DAT1* interaction: error rates $F(1,45) < 1$; response times $F(1,45) = 1.92$; $p > .1$).

ADHD ON versus healthy controls

There were no differences between the ADHD group ON Medication and healthy controls in terms of RTs. Switch costs in error rates were significantly greater in the ADHD group ON Medication than in the healthy control group (Task switching x Diagnosis: $F(1,45) = 6.44$; $p = .015$). The critical effect of Reward on Task switching did not differ between the patients with ADHD ON Medication and the healthy control group, also not as a function of *DAT1* Genotype (the critical interaction between Reward x Task switching x Diagnosis x *DAT1*: error rates $F(1,45) = 1.37$; $p > .1$; response times $F(1,45) < 1$).

ADHD OFF versus ADHD ON

There was no significant difference between the two medication sessions in terms of RTs or errors rates. The critical *DAT1* by Medication interaction in terms of Reward Task switching only trended towards significance for RTs (Reward x Task switching x Medication x *DAT1*: $F(1,21) = 3.23$; $p = .087$; **figure 2C**), and was absent for error rates (Reward x Task switching x Medication x *DAT1*: $F(1,21) < 1$).

In summary, unlike the brain data, the behavioral data did not reveal any significant effects of diagnosis or medication status and/or genotype on how anticipated reward influences task-switching performance (i.e. Reward x Task switching effects). To assess whether the increased BOLD signal in the striatum of 9R-carrying patients with ADHD was accompanied, if anything, by behavioral impairment or improvement, we inspected the numerical (marginal trend) pattern in RTs (**figure 2C**). Disentangling this marginally significant effect (Reward x Task switching x Medication x *DAT1*: $F(1,21) = 3.23$; $p = .087$) revealed that 9R carrying patients OFF Medication tended to show a greater switch cost on high than low reward trials compared with these patients ON their Medication (Reward x Task switching x Medication in 9R carriers: $F(1,11) = 4.40$; $p = .06$; **figure 2C**). These data suggest that the increased dorsal striatal responses in patients with ADHD carrying the 9R allele are accompanied, if anything, by a detrimental effect of reward on Task switching that can be remediated by methylphenidate (**figure 2B + 2C**).

Demographic and neuropsychological data

Table 4.1 summarizes the demographic and neuropsychological data of the patients with ADHD and healthy controls for the two *DAT1* Genotype groups. There was no difference between patients and healthy controls, or between the 9R-carrying and 10R-homozygous group in terms of age, IQ, gender, handedness, smoking status and education level (Table 1), nor an interaction between Diagnosis and *DAT1* Genotype. As expected, the patients with ADHD scored higher on the Barratt Impulsiveness Scale (mean $\pm$ SE: 73.00 $\pm$ 2.58), i.e. they were more impulsive than the healthy controls (mean $\pm$ SE: 59.27 $\pm$ 1.54; t (47) = 4.70; p <.001). There were no differences in current SCID Axis I disorders or SCID Axis II personality traits as a function of Diagnosis, *DAT1* genotype, or Diagnosis x *DAT1* Genotype.

Counterbalancing of the ON and OFF sessions within the two *DAT1* Genotype patient groups was successful: there was no difference between the two *DAT1* groups in the number of subjects being ON Medication during the first session. Furthermore, there were no differences in the dose of Ritalin or Concerta between the *DAT1* Genotype groups, nor in the number of patients usually taking either form of methylphenidate, or in their ADHD subtype (i.e. combined, inattentive or hyperactive/impulsive) (**table 4.2**).

Table 4.3 summarizes the mood scores and neuropsychological tests. Most importantly, there were no interactions between *DAT1* genotype and either medication state (ON or OFF) or diagnosis on mood measures or on the neuropsychological tests. However, patients OFF medication were reportedly less content and less alert than healthy controls and compared with when they were ON medication (**table 4.3**; contentedness: ADHD ON median 83, range 41.6 - 95.2; ADHD OFF median 67.16, range 23.2 - 97.6). In addition, healthy controls reported more calmness than the patients, both ON and OFF Medication (**table 4.3**). There were no differences in terms of motor speed (box completion task), on the time to complete the vigilance test (number cancellation RT) or in verbal fluency. We did observe a difference between the ADHD group OFF Medication and the healthy control group for missed items on the vigilance test, i.e. the ADHD group OFF their Medication missed more numbers (median 4, range 0 - 17) relative to the healthy control group (median 2, range 0 - 11) and relative to when ON Medication (median 3, range 0 - 13). This difference was no longer present when comparing the ADHD group ON Medication to the healthy control group (**table 4.3**).

As expected, methylphenidate ameliorated symptom severity (**table 4.6**) both on attentive and hyperactive symptoms. We did not observe effects of *DAT1* Genotype, nor an interaction between *DAT1* Genotype and Medication status on symptom severity (**table 4.6**).

Table 4.6 Self-reported symptom severity

	ADHD ON		ADHD OFF		Statistics		
	9R carriers	**10R/10R**	**9R carriers**	**10R/10R**	**Drug effect**	***DAT1* effect**	**Drug * *DAT1***
Symptom severity							
Attentive	2.67 (0.66)	3.18 (1.11)	7.25 (0.46)	5.64 (0.83)	$t(22) = 5.92$; $p < .001$	ns	$F(1,21) = 3.47$; $p > .05$
Hyperactive	2.67 (0.66)	2.36 (0.75)	5.33 (0.68)	5.09 (0.72)	$t(22) = 5.15$; $p < .001$	ns	ns

10R/10R = 10R homozygotes

Discussion

We investigated the effects of reward motivation on task switching in adult patients with ADHD, ON and OFF methylphenidate, relative to a matching healthy control group. Task-related BOLD responses were assessed as a function of inter-individual variability in the *DAT1* gene. When OFF medication, adults with ADHD demonstrated greater effects of reward on dorsal striatal BOLD responses during task switching than healthy controls. Critically, this effect was only seen when taking *DAT1* genotype into account, resulting in a strong genotype by diagnosis interaction. Specifically, patients carrying the 9R allele showed exaggerated striatal responses relative to healthy controls carrying the same allele, as well as relative to patients homozygous for the 10R allele. These aberrant striatal responses were normalized when patients with ADHD were ON medication, such that they no longer differed from those of controls. In short, the present pilot study reveals a dysfunctional influence of reward motivation on task switching in the dorsal striatum of adult patients with ADHD, but only in those carrying the 9R risk allele. These findings, albeit preliminary due to the small sample size, suggest that abnormal cognitive task-related processing in adult ADHD depends critically on inter-individual trait differences in striatal dopamine transmission as well as on the motivational state of the individual patient.

The present results demonstrate the importance of taking into account inter-individual variability, as for example indexed by the *DAT1* genotype, when assessing task-related BOLD effects in ADHD. This generally concurs with previous fMRI studies in youth with ADHD, which have found that striatal responses during reward anticipation (Paloyelis et al., 2012) as well as striatal responses during more cognitive tasks, i.e. Go/No-Go paradigms (Durston et al., 2008; Bedard et al., 2010) depend on variation in *DAT1* genotype. A recent study in adults with ADHD failed to extend the effect of *DAT1* genotype on striatal reward responses during reward anticipation, observed in youth (Paloyelis et al., 2012), to adult ADHD (Hoogman et al., 2013). In the current sample with ADHD adults, *DAT1* effects on reward-related striatal responses did surface, but only as a function of *cognitive task*-related processing. This suggests that, in adults with ADHD, the translation of reward information into (effortful) cognitive processing might be more strongly dependent on variability in the *DAT1* gene than reward anticipation itself.

Our study shows that patients with ADHD OFF medication demonstrate abnormal BOLD responses in the caudate nucleus during rewarded task switching, an effect that relied on striatal dopamine signaling as indexed by *DAT1* genotype. In accordance, the caudate nucleus – known to be involved in cognitive flexibility (Cools, 1980; Aarts et al., 2011) – is well-positioned to incorporate motivational influences from more ventral regions in the striatum through feedforward dopaminergic projections (Haber et al., 2000; Grahn et al., 2008; Ikeda et al., 2013). The finding is also remarkably consistent with our previous work using genetic fMRI and positron emission tomography (PET) imaging in healthy volunteers, showing that effects of reward motivation on cognitive control are altered by dopaminergic transmission

in the left caudate nucleus (Aarts et al., 2010; Aarts et al., 2014b). In ADHD, Volkow and colleagues have shown that dopaminergic transmission in reward-related brain regions is associated with symptoms of inattention (Volkow et al., 2009b), and that connectivity between neural reward and attention networks is impaired (Tomasi and Volkow, 2012). Here, we demonstrate that cognitive *task-related* processing deficits in the striatum (i.e. during task switching) are modulated by motivation as well as *DAT1* genotype in ADHD. Unlike suggested previously (Sonuga-Barke, 2002, 2003; de Zeeuw et al., 2012), ADHD might not be accompanied by isolated deficits in either motivational or cognitive/executive processing pathways, but rather by deficits in the integration between these pathways.

The present finding extends to ADHD our previous work in young healthy volunteers showing that effects of reward motivation on task switching and associated striatal signal depend on the *DAT1* genotype (Aarts et al., 2010; see supplement van Holstein et al., 2011). Unlike that previous study, however, the present study did not reveal any *DAT1* genotype effects on rewarded task switching in healthy controls, in neural or behavioral terms. We are puzzled by this lack of effect, but think that it might reflect a difference in the demographics between the current control group that was matched to the ADHD group and the groups in our previous studies that primarily included university students. The most obvious difference is in terms of age, with the current control group being older (mean 38.12 years, SD 10.20) than the healthy volunteers in our previous studies (mean 21.58 years, SD 2.06; and mean 22 years, SD 2.32, for Aarts et al., 2010; van Holstein et al., 2011, respectively). Indeed, studies have consistently observed a reduction in dopamine signaling starting in young adulthood (e.g. Volkow et al., 1996a; Reeves et al., 2002). Importantly, the increases in striatal BOLD in the 9R-carrying patients OFF medication were, if anything, accompanied by impaired performance (i.e. increased RT switch cost for high versus low reward trials, relative to when ON medication). These results contrast with our findings in younger 9R-carrying healthy volunteers who showed increased striatal responses as well as better task switching performance following high versus low reward cues relative to 10R-homozygotes (Aarts et al., 2010). This suggests that the hyperactivation in the dorsal striatum during rewarded task switching in the 9R-carrying patients OFF medication is maladaptive for behavior. The notion of maladaptive striatal hyper activation in 9R-carrying patients with ADHD is in line with the finding that the 9R-allele is the risk allele in adult ADHD (Franke et al., 2010). However, the absence of significant behavioural differences relative to healthy controls precludes statements of normality in terms of performance.

The aberrant striatal responses during rewarded task switching in patients with ADHD (specifically 9R carriers) relative to controls were absent when patients were ON medication. This suggests that methylphenidate normalized striatal responses, although we only obtained trend effects (i.e. at $p < .001$ uncorrected for multiple comparisons) when directly comparing patients ON versus OFF methylphenidate. Our findings suggest that effects of methylphenidate on cognitive task-related processing are accompanied by modulation of the striatum. This generally concurs with prior work showing that methylphenidate can

normalize striatal responses during cognitive processes such as response inhibition (Vaidya et al., 1998; Shafritz et al., 2004; Epstein et al., 2007; Rubia et al., 2009; Rubia et al., 2011). Here, we demonstrate that such normalization of task-related dorsal striatal responses and performance by methylphenidate depends both on *DAT1* genotype and on reward motivation. This suggests that reward motivational factors interact with the effects of *DAT1* genotype to bias the cognitive response to methylphenidate. Future work should address the obvious next question, that is, whether discrepancy in the extant literature regarding the effects of *DAT1* genotype on the clinical response to medication (Kambeitz et al., 2014) also reflects variability in the patient's reward motivational state. Cognitive neuroimaging measures of task-related (motivational) processing might be particularly sensitive to detecting *DAT1*-dependent effects of methylphenidate in ADHD.

It might be noted that the effects in the OFF state could reflect rebound effects due to short-term medication withdrawal. Future studies, with a longitudinal design or comparing medication-naive patients with medicated patients, will need to determine whether the current findings reflect rebound or withdrawal effects rather than an un-medicated ADHD state.

Our findings were obtained with a sample of 23 patients with ADHD and 26 healthy controls. This limited sample size calls for caution when generalizing to the population (Munafo and Gage, 2013) and precludes definitive conclusions. The findings should therefore be considered preliminary and in need of replication, as was recently also explicitly highlighted (Button et al., 2013). Nevertheless, we believe that our findings are robust, given extensive convergent evidence. Indeed, we have previously observed effects of *DAT1* genotype on BOLD signal during rewarded task switching in the same striatal region (i.e. left caudate nucleus) as we report here (Aarts et al., 2010). Moreover, we have previously seen that striatal dopamine synthesis capacity in the (left) caudate nucleus predicted the effects of reward on cognitive performance during a focused attention task (Aarts et al., 2014b). It is unlikely that our whole-brain corrected results represent a false positive effect as our power calculation based on an independent dataset (Aarts et al., 2010; Button et al., 2013) confirmed that our sample should be large enough to obtain significantly meaningful effects (see Methods). Replication of the effect in independent larger samples in future studies will further increase confidence in the reliability of the effect.

Previously, we have obtained similar results in a PET study in healthy volunteers, showing that dopaminergic transmission in the left caudate nucleus altered the effects of reward motivation on cognitive control (Aarts et al., 2014b). In that study, we employed a Stroop interference paradigm instead of a task-switching paradigm, suggesting that our present results can be extended to other domains of cognitive control. However, future work should confirm whether our findings in ADHD can be generalized to domains other than task switching. Moreover, future studies should also examine variation in other dopaminergic genes, like *COMT* (Bilder et al., 2004), to investigate whether the current findings are limited to *striatal* dopamine processing.

To conclude, our data suggest a dysfunctional influence of reward motivation on cognitive

processing (i.e. task switching) in the dorsal striatum of adult patients with ADHD, who carry the 9R ADHD risk allele. This deficit is remediated when patients are tested ON methylphenidate. These findings demonstrate an important role for both reward motivation as well as inter-individual trait differences in striatal dopamine transmission in cognitive processing deficits in adult ADHD.

Chapter 5

Reduced effects of reward motivation on flexible cognitive control across the life span

Based on: Mieke van Holstein, Ili Ma, Esther Aarts, Roshan Cools (in preparation). Reduced effects of reward motivation on flexible cognitive control across the life span

Abstract

Flexible cognitive control refers to the ability to adapt to our ever changing environment and is a hallmark of human cognition. It is well known that optimal flexible cognitive control is sensitive to reward motivation and that the promise of a reward can improve performance on tasks of flexible cognitive control, such as task-switching paradigms. Healthy aging is accompanied by impairments in flexible cognitive control, but also in reward-related processes and changes in processing speed. Here we test the hypothesis that changes in task-switching ability across the life span are a function of promised reward. We tested 118 participants (14-69 years old) on a task-switching paradigm with a reward motivation manipulation. Results revealed that increasing age is associated with reduced influence of a promised reward on flexible cognitive control, in terms of speed-accuracy strategy. These findings indicate that healthy aging across the life span is accompanied by diminished reward-related adaptation of cognitive strategy during task-switching.

Introduction

The world around us is changing constantly, imposing on us an overwhelming amount of information, choices and temptations. The ability to adapt behavior flexibly to these constant changes is a hallmark of human cognition and requires flexible cognitive control. This is a complex, multifactorial construct, but generally refers to the ability to inhibit impulses, set, maintain and update goals and pursue them without being distracted. Failures in the ability to exert flexible cognitive control can have vast consequences, leaving our economies a wreck and our traffic deadly.

Aging is one of today's grand societal challenges. The current proportion of people aged 60 and older is 23% in developed countries and still increasing (United_Nations, 2012). As people age, their ability to look after themselves decreases and most people will eventually require assistance or permanent care. Many of the day-to-day tasks that are required to live independently have a cognitive component. It is well established that older participants are impaired in several aspects of cognition, including memory, speed of processing, task switching (Salthouse, 1996; West, 1996; Kray et al., 2002; Park et al., 2002), and interference- and inhibitory control (i.e. stopping automatic tendencies or motor impulsivity) (Rush et al., 2006; van de Laar et al., 2011). At least some aspects of age-related cognitive decline may begin already early in adulthood (i.e. from 20 years onwards) (Salthouse, 2009)

Task switching, which is considered an important aspect of flexible cognitive control (Monsell et al., 2003), encompasses the ability to quickly update current task demands and to adapt behavior accordingly. It is this cognitive ability that is the focus of the current paper, given accumulating evidence that it is particularly sensitive to aging (Van Asselen and Ridderinkhof, 2000; Kray et al., 2002), (but see Wasylyshyn et al., 2011). However, in addition to cognitive deficits, aging is also accompanied by reward and motivational anomalies. For example, studies have shown age-related deficits in reward-related processing and reward learning (Marschner et al., 2005; Mell et al., 2005; Schott et al., 2007; Chowdhury et al., 2013), (but see Samanez-Larkin et al., 2007).

Although often studied as separate entities, reward and cognition interact closely: Adaptive behavior becomes more important when higher rewards are at stake. Indeed, several studies have shown that reward motivation can improve cognitive performance (e.g. Locke and Braver, 2008; Aarts et al., 2010; Pessoa and Engelmann, 2010; van Holstein et al., 2011; Braver et al., 2014). In fact, reward-related deficits have been argued to underlie at least some of the cognitive processing deficits observed in psychiatric disorders, such as attention deficit hyperactivity disorder (ADHD) and schizophrenia (Velligan et al., 2006; Aarts et al., 2015). This might also be true for cognitive deficits in aging.

In the current study, we used a task-switching paradigm in which we manipulated the amount of reward participants could earn on each trial to test the hypothesis that aging across the life span is accompanied by reduced impact of reward motivation on flexible cognitive control. Given the hypothesis that age-related decreases in cognitive functioning may start early in

Table 5.1 Characteristics of participants and studies

	Study A	Study B	Study C	Study D	Study E	Total
N	32	24	27	9	26	118
Age mean	15.44	21.92	38.78	58	59.58	35.03
Age range	14-17	18-27	24-65	29-67	42-69	14-69
Gender (% men)	59.4 %	41.67 %	44.44 %	77.78 %	57.69 %	53.4 %
Max possible reward	€ 12.80	€ 8.80	€ 12.80	€ 12.80	€ 13.20	
High reward	€ 0.15	€ 0.10	€ 0.15	€ 0.15	€ 0.10	
Earned bonus: mean (SE)	€ 9.10 (34.05)	€ 7.17 (17.45)	€10.38 (22.09)	€ 10.04 (61.40)	€ 12.05 (12.32)	€ 9.72 (19.50)
Earned bonus: % of max: mean (SE)	71.28 % (2.62)	81.49% (1.98)	81.10 % (1.73)	78.44 %(4.80)	91.29% (0.89)	80.56% (1.18)
Number of trials	160	160	160	160	240	
Type of study	Behavioral control group patient study	fMRI young healthy participants	fMRI control group patient study	fMRI control group patient study	Behavioral control group patient study	
ITI and RC interval	1-2s	2-6s	2-6s	2-6s	1-2s	
CT interval	400 msec.	2-6s	400 msec.	400 msec.	1-2s	

SE = standard error; ITI = inter-trial-interval; RC = reward - task cue; CT = task cue - target.

adulthood, we assessed the effect of reward motivation on cognitive control across the life span, from adolescence (prior to the start of age-related decreases) to senescence.

Methods

Participants and procedure

Pooling the data from five studies that were conducted between 2008 and 2015 enabled us to include 118 healthy participants (63 men, mean age 35.03, range 14-69). Three of these studies (N = 60) were conducted in a functional magnetic resonance environment: one in healthy young participants (Aarts et al., 2010) and the other 2 were patient studies (e.g. Aarts et al., 2015). We only included the healthy control participants who participated in these patient studies. The remaining participants were 26 (Aarts et al., 2012) and 32 healthy control participants who were tested in front of a computer screen (**table 5.1**). All studies were

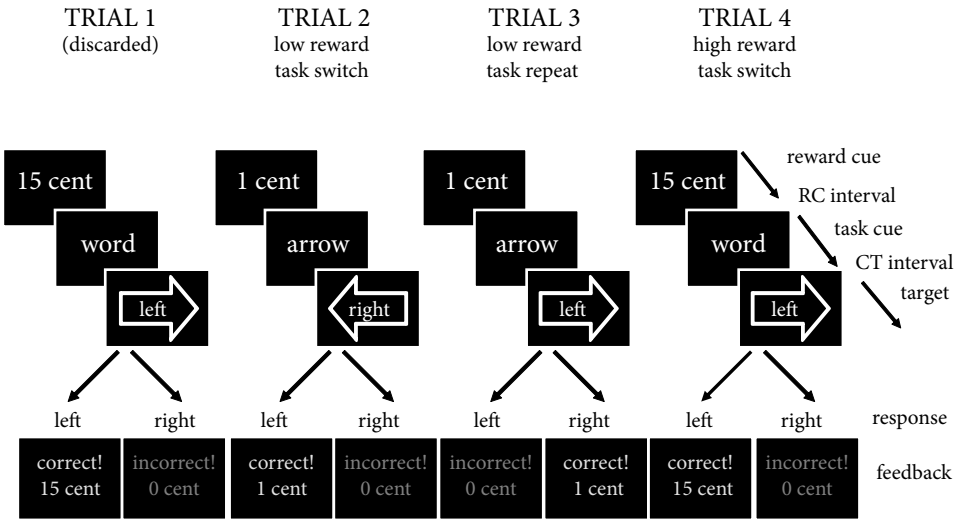


Figure 5.1 Task-switching paradigm with reward manipulation
Participants had to respond to incongruent arrow-word combinations, either by responding to the direction of the arrow (i.e. <- or ->) or to the direction indicated by the word ("left" or "right") with a left or right button press. A task cue preceding the target indicated according to which task (arrow or word) the participant had to respond on the current trial. The task performed on a particular trial either changed unpredictably compared with the preceding trial (i.e. switch trial; arrow - word or word - arrow) or remained the same (i.e. repeat trial; arrow-arrow, word-word). In addition we manipulated the value of each trial on a trial-by-trial basis by means of a reward anticipation cue (i.e. 1 vs. 10 or 15 cents; table 1) (see also (Aarts et al., 2010; Aarts et al., 2015). Reward could be earned with a correct and sufficiently quick response. Immediately following the response, feedback was given (e.g., "correct! 15 cents"). The cues and feedback were shown for 600 msec. RC interval: reward cue - task cue interval; CT interval: task cue - target interval (**table 5.1**).

approved by the local ethics committee (CMO Arnhem-Nijmegen CMO 2001/095; 2007/153; 2008/159; 2009/058; 2010/402) and were in accordance with the Declaration of Helsinki.

Paradigm

All participants performed a task-switching paradigm with a reward manipulation (figure 5.1) (Aarts et al., 2010; van Holstein et al., 2011). The task was programmed and presented using the Presentation® software (Neurobehavioral Systems, Inc.; http://www.neurobs.com).

The test was preceded by 3 practice blocks. The first practice block (24 trials) contained the task cue and target, followed by feedback ("correct", "incorrect"); in the second practice block (24 trials), reward cues were added. Finally, to account for inter-individual differences in response speed and subsequent task difficulty, we used the correct responses during the third practice block (32 trials), without reward or feedback, to determine each individual's response deadline for 4 trials-types (Arrow/Word x Switch/Repeat). Participants were instructed to

respond as quickly and accurately as possible and had to respond correctly within the response deadline to obtain the reward.

The main experiment consisted of 160 (or 240) trials and lasted ~35 minutes with a 30 second break after every 32 (or 48) trials (table 1). In the break, the amount of money the participant earned thus far was displayed on the screen and participants were informed in advance that the total amount would be added to their financial compensation as a bonus.

Analysis

For each participant, we excluded the first trial of each block, trials with a response time (RT) faster than 200ms, and trials on which participants failed to respond. For each trial-type, [Reward (low, high) x Task switching (switch, repeat)], we calculated the proportion of accurate responses. For the RTs, we first excluded the erroneous trials and then calculated the mean RT for each condition.

Older participants usually respond more slowly compared with younger participants and prefer accuracy over speed (Salthouse, 1996). Upon observing such a pattern in the current data, i.e. opposite correlations between age and overall RTs, and between age and accuracy, we assessed our effects in terms of changes in speed-over-accuracy strategy use. To this end, we standardized the accuracy and RT measures into z-scores, inverted these scores for the RTs to obtain a speed measure (i.e. higher z-scores reflect faster responding) and calculated a speed-accuracy-tradeoff (SAT) score ((z-speed - z-accuracy)/2), whereby a higher score indicates faster, but more inaccurate responses.

Data were analyzed using SPSS (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). A Shapiro-Wilk test of normality of the 4 trial-types revealed violation of the normal distribution for one trial type ($p = 0.049$) in terms of the SAT, and all trial-types for the RTs and accuracy were not normally distributed (all $p < 0.001$). We therefore performed non-parametric tests, i.e. the related-samples Wilcoxon signed rank tests to assess the effects of Reward (high vs. low), Task switching (switch vs. repeat) and the interaction between Reward and Task switching. We report the standardized test statistic as *W*.

From the mean scores on the 4 trial types [Reward (high/low) x Task switch (switch/repeat trials)] we calculated (1) the reward effect (high - low reward), (2) switch effect (switch - repeat), and (3) the difference between the reward effect on repeat trials and the reward effect on switch trials, i.e. the degree to which an increase in reward decreases the switch effect. To break down this effect, we also reported the results for the reward effect on switch and repeat trials separately. Because age did not follow a normal distribution (Shapiro-Wilk $p < 0.001$), we used a non-parametric Spearman's ρ correlation – r (ρ) - to assess the relationship between these measures and age.

The sample in this study consists of pooled data from several studies using the same paradigm (**table 5.1**). Although the paradigm and instructions were essentially the same, the amount of reward participants could earn on a high-reward trial (i.e. 10 or 15 cent) or across all trials

(i.e. due to 160 vs. 240 trials) varied between studies (from €8.80 to €13.20). To account for this confound, we validated the age-related effects in a group of participants who received identical low and high reward amounts and the same number of trials (and thus identical total amounts of reward). To this end, we directly compared performance of a subset of 68 participants (from study A, C and D, matched in terms of these factors, **table 5.1**) using an independent samples Mann-Whitney U test (reporting the standardized test statistic, denoted by U), with age (using a median split) as a between subject factor. We consider $p < 0.05$ as significant.

Results

With age, overall accuracy and response times increased (Age, accuracy across trial-types: $r(\rho) = 0.531$, $p < 0.001$; Age, RTs across trial-types: $r(\rho) = 0.607$, $p < 0.001$). In terms of the SAT score, increasing age was associated with a decrease in speed over accuracy, so that older participants traded speed for accuracy across the task as a whole (Age, SAT across trial-types: $r(\rho) = -0.636$, $p < 0.001$).

Effects of reward, task-switching and their interaction

There was a main effect of Reward in terms of SAT: participants increased speed over accuracy on high reward trials, compared with low reward trials (Reward: $W = 6.519$, $p < 0.001$). In addition, there was a main effect of Task switching: Participants also increased speed over accuracy on switch trials compared with repeat trials (Task switching: $W = 2.241$, $p= 0.025$). Moreover, there was an interaction between Reward and Task switching (Reward x Task switching: $W = 6.452$, $p < 0.001$), due to an increase in speed over accuracy on high versus low reward *switch* trials (Reward effect on switch trials: $W = 7.276$, $p < 0.001$; **table S5.1**), but a decrease in speed over accuracy on high versus low reward *repeat* trials (Reward effect on repeat trials: $W = 4.610$, $p < 0.001$).

The effects in terms of SAT were due to a main effect of Reward in the response times, but not accuracy: Participants responded faster on high reward compared with low reward trials (Reward in terms of RTs: $W = 6.519$, $p < 0.001$; Reward in terms of accuracy: $W = 1.656$, $p = 0.098$; **table S5.1**). In addition, there was a main effect of Task switching both in terms of response times and accuracy: Participants responded more slowly on switch trials compared with repeat trials (Task switching: $W = 4.612$, $p < 0.001$) and participants responded less accurately on switch compared with repeat trials (Task switching: $W = 7.205$, $p < 0.001$). There were no interactions between Reward and Task switching in terms of response times (Reward x Task switching: $W = 0.337$, $p = 0.7$) or accuracy (Reward x Task switching: $W = 0.168$, $p = 0.8$).

In sum, we observed faster but equally accurate responding under high versus low reward, which translated into a reward-related increase in the speed-over-accuracy score. In terms of

task switching, we observed slower and less accurate responding on switch than repeat trials. The switch cost in terms of accuracy (i.e. less accurate responding on switch vs. repeat trials) was larger than the switch cost in terms of response times. This resulted in a switch-related increase in the speed-over-accuracy score. Moreover, we observed a reward-related shift in the SAT during task switching: A reward-related increase in speed-over-accuracy on the more demanding switch trials, but a reward-related decrease in speed-over-accuracy on the easier repeat trials.

Effects of age on rewarded task switching

The aim of the current study was to look at age-related changes in the motivational enhancement of cognitive control. Before assessing this primary effect of interest, we first looked at age-related changes in the main effects of Reward and Task switching. In terms of the SAT we observed an age-related decrease in speed over accuracy in terms of the effect of Reward (Reward x Age: $r(\rho) = -0.191$, $p = 0.038$) and of Task switching (Task switching x age: $r(\rho) = -0.225$, $p = 0.014$). This age-related decrease in speed over accuracy as a function of reward was due to a larger age-related increase in response times than accuracy on high compared with low reward trials. In terms of task switching, younger participants exhibit a relatively larger switch cost in terms of accuracy than in terms of speed. With age, this switch cost in terms of speed increased, whereas the switch cost in terms of accuracy decreased. Next, we assessed age-related changes in the main effects of Reward and Task switching in terms of response times and accuracy and observed an age-related decrease in the difference between high versus low reward in terms of accuracy (Age x Reward (high – low): $r(\rho) = -0.238$, $p = 0.009$), and response times (Age x Reward (high – low): $r(\rho) = 0.191$, $p = 0.038$). In addition, there was an age-related increase in slowing and accuracy on switch versus repeat trials (RTs: Age x Task switching (switch – repeat): $r(\rho) = 0.411$, $p < 0.001$; accuracy: Age x Task switching (switch – repeat): $r(\rho) = 0.302$, $p < 0.001$).

Thus aging was accompanied by a reduced reward benefit in terms of accuracy and an increased reward impairment in terms of response times. A larger age-related increase in response times than accuracy on high compared with low reward trials resulted in the age-related decrease in speed over accuracy. In addition, there was an age-related increase in task switching cost in terms of response times and an age-related switch benefit in terms of accuracy, but this switch cost in terms of response times changed more with age, resulting in an age-related decrease in speed over accuracy.

Next, we proceeded to our primary question of interest and assessed the degree to which a promised Reward affected Task switching in terms of SAT and found that this effect changed with age (Age x Reward x Task switching: $r(\rho) = -0.368$, $p < 0.001$; **figure 5.2a**). Breaking down this three-way Age x Reward x Task switching interaction for repeat and switch trials separately revealed a positive correlation between Age and the Reward effect on repeat trials (Age x Reward: $r(\rho) = 0.311$, $p = 0.001$), but a negative correlation between Age and the Reward

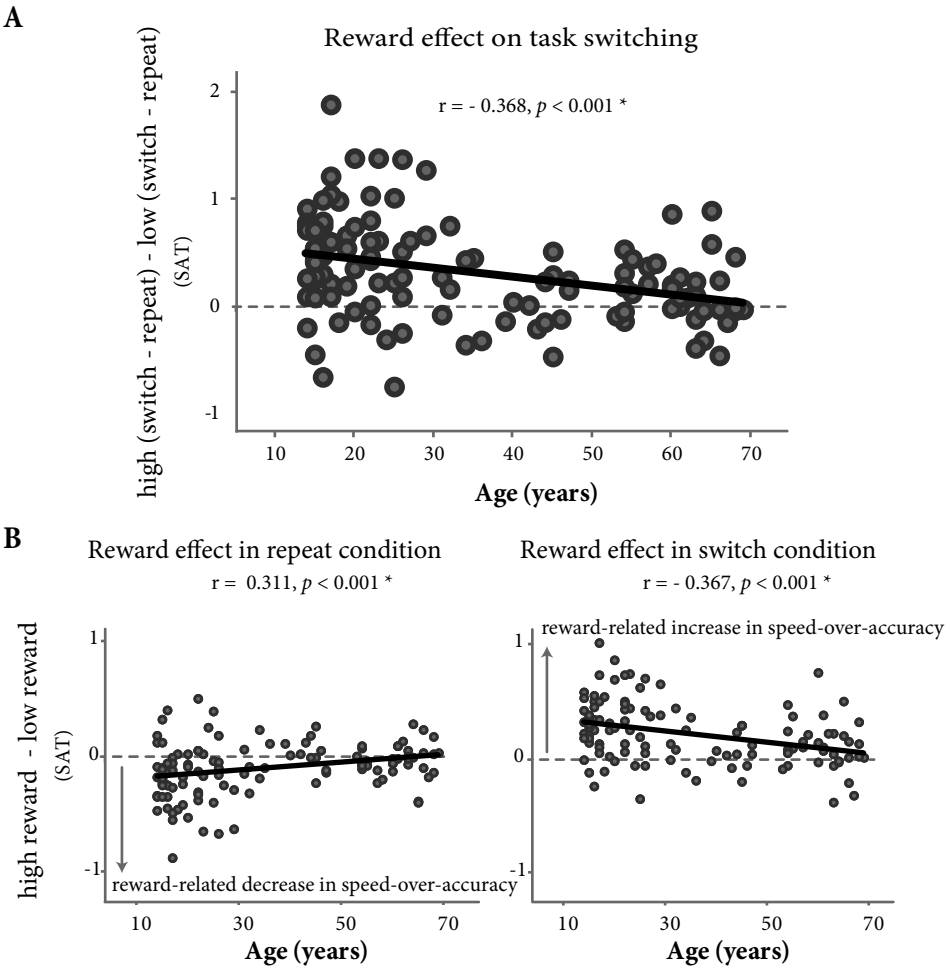


Figure 5.2 Effects of Reward on Task switching as function of Age

A: The effect of a high versus low reward on task switching correlated negatively with age, with reduced reward-related changes in task-switching as participants are older.

B: Breaking down this negative correlation between Age, Reward, and Task switching (in A) for repeat and switch trials revealed opposite age-related changes in the reward effect on repeat and switch trials. Whereas younger participants showed a reward-related decrease in speed-over-accuracy on repeat trials (left) and a reward-related increase in speed-over-accuracy on switch trials (right), this difference was abolished with increasing age.

* Regression lines indicate the Pearson correlation (N = 118), statistics are Spearman correlations.

effect on switch trials (Age x Reward: r (ρ) = - 0.367, p < 0.001; **figure 5.2b**). Inspection of **figure 5.2b** shows that these correlations were driven by Reward effects in young, but not old participants. Young, but not old participants, showed a reward-related increase in speed-over-accuracy on switch trials, and a reward-related decrease in speed-over-accuracy on repeat trials. Thus, the main task effects, observed across the group as a whole and described above, were driven by younger participants and were absent in older participants.

The degree to which a promised reward affected task switching did not change with age in terms of response times (Age x Reward x Task switching: r (ρ) = -0.038, p = 0.714) or accuracy (Age x Reward x Task switching: r (ρ) = -0.178, p = 0.053).

We validated the SAT effects in a subgroup of participants who all received the same reward size (i.e. group A, C and D, **table 5.1**). Age-dependent effects in this subsample, which was not confounded by differential reward size, resembled those observed in the large sample. A negative correlation was observed between Age and the effect of Reward on Task switching (Age x Reward x Task switching: r (ρ) = - 0.360, p = 0.003; **figure 5.3a**). This three-way interaction was again due to a positive correlation between Age and the Reward effect on repeat trials (Age x Reward: r (ρ) = 0.277, p = 0.022) and a negative correlation between Age and the Reward effect on switch trials (Age x Reward: r (ρ) = -0.373, p = 0.002). The result from this continuous analysis with Age as a covariate was confirmed by a between-group independent samples Mann-Whitney U test with Age as a between-subject factor. For this analysis, the subgroup (N = 68, mean age 30.29, range 14 – 67 years) was split into two groups based on the median age (25 years old; youngest group: N = 35, mean 16.23 (SE 0.48) years old; oldest group: N = 33, mean 45.18 (SE 2.29) years old; U = 7.114, p < 0.001). A significant Age x Reward x Task-switching interaction was revealed (U = -2.755, p = 0.006), which was due to a Reward x Task switching interaction in the younger group (W = -3.849, p < 0.001), but not in the older group (W = -1.885, p = 0.059) (**table 5.2, figure 5.3b**).

In sum, aging was accompanied by diminished effects of Reward on Task switching in terms of SAT. This effect was confirmed in a smaller subsample, corrected for reward size.

Age-related changes in response deadlines and earned rewards

We hypothesized that age-related changes in task switching would be grounded in motivational changes. Increasing age was indeed associated with cognitive changes: We observed age-related changes in task switching. In addition, we observed smaller reward effects with age, both across repeat and switch trials and as a function of task switching. In a supplementary analysis, we assessed whether this reward-related deficit in terms of behavior was accompanied by changes in total earnings.

Surprisingly, we observed an age-related *increase* in the total reward earned on the rewarded task-switching paradigm. This effect was observed in the large sample (n=118) (Age x Total reward: r (ρ) = 0.581, p < 0.001), and in the subgroup of 68 participants in which the maximum bonus did not vary across participants (Age x Total reward: r (ρ) = 0.309, p =

Table 5.2 Reward x Task-switching effects for younger and older subgroups*

	Younger (n=35)	**Older** (n=33)	**Difference**
RT	-0.164 (-10.50;10.17)	-0.486 (-9.58;8.61)	-0.055; P > 0.1
Accuracy	0.66 (-3.24;4.56)	-2.21 (-5.70;1.27)	-1.061; P > 0.1
SAT	0.43 (0.25;0.61)	0.15 (0.01;0.29)	-2.755; p = 0.006

SAT = Speed-Accuracy-Tradeoff = (z-speed- z-accuracy) / 2 ; RT = response times
* subgroups (study A, C and D in table 1 and figure 3a) were not confounded by differential reward size

0.010). A between subject analysis in this subgroup revealed that the older group earned more reward than did the younger group (mean €9.01 (SE 0.32) vs. mean €10.50 (SE 0.20); $t(26.448) = 11.343$, $p < 0.001$).

We were puzzled by this effect and reasoned that the age-related increase in total earnings might originate from differences in the response deadline, which was set during a pre-test practice phase (**methods**). When the response deadline was determined, participants were instructed to respond as fast and accurately as possible. We reasoned that participants who put more emphasis on the accuracy instruction would not respond as fast as possible during practice. This would then result in longer, less stringent response deadlines during the actual test. In the current paradigm, inaccurate responses, no matter how fast, are never rewarded. Therefore, adopting such a cautious (slow and accurate) response strategy during practice may result in higher earnings. For example, imagine two participants (A and B) who are theoretically both able to respond within 400ms. If participant *A* responds cautiously during the practice phase, the average response time during practice will be slower (e.g. 900ms) than that of someone who emphasized speed during practice (participant B, e.g. 500ms). As a consequence, participant A will have plenty of time to respond accurately on test, thereby increasing the number of rewarded trials. By contrast, participant B will need to continue to respond relatively fast. Participant B will thus make more errors, and therefore a lower number of trials will be rewarded.

To test the idea that the response strategy during practice differed with age and that this would lead to the observed age-related differences in earnings, we first assessed whether age was associated with the length of the individually determined response deadlines. We observed an overall age-related increase in the response deadline (i.e. across 4 trial-types: Arrow/Word x Switch/Repeat), so that older participants were allowed to respond more slowly on test than did younger participants (Age x Response deadline: $(\rho) = 0.587$, $p < 0.001$). One might argue that the differential Age x Reward effects on repeat and switch trials reported above might

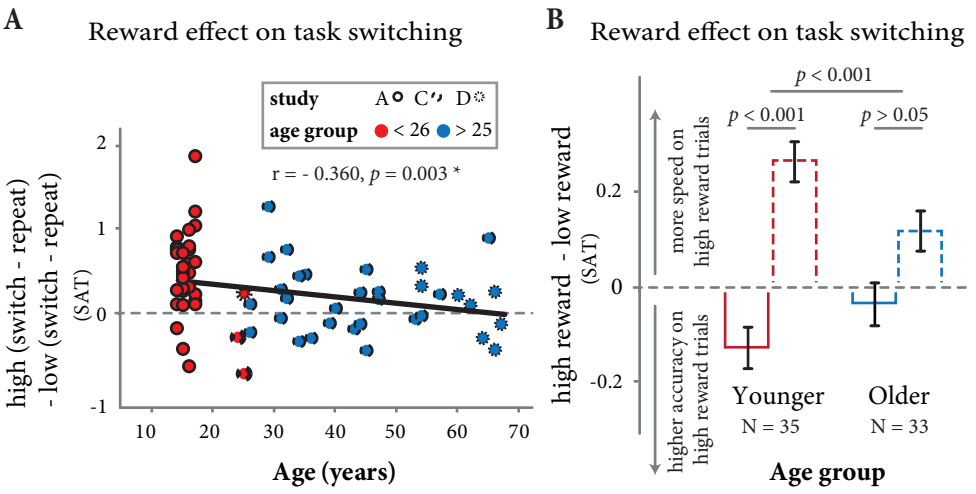


Figure 5.3 The effect of Reward on Task switching diminishes with age in a subgroup matched for maximum available reward

The results in figure 2 were supported by an additional analysis, in which we only included the participants who all received the exact same version of the task (study A, C, D in table 1).

A: This analysis confirmed that the effect of Reward on Task switching is reduced with age. The outline of the data points indicates the study in which each participant participated (table 1).The red and blue data points refer to the younger and older group in a subsequent median split analysis (B), * The black solid line indicates the regression slope (Pearson) for the subgroup (N = 68), the Spearman correlation **is reported.**

B: Analysis with age as a between subject factor (median split) revealed significant effects of Reward on Task switching in the younger group, but not the older group.

also reflect these age-related differences in the maximum time participants had to respond on each trial type. However, this age-related effect in response deadlines was not different for repeat and switch trials (Age x Task switching in terms of response deadline: r (ρ) = 0.050, p = 0.588).

Next, we assessed whether the difference between the average response times during the actual test and the average response times during the practice (i.e. average response deadlines) changed with age. Indeed, this difference increased with age (Age x Response time difference: r (ρ) = 0.467, p < 0.001), suggesting that the average response deadline was less close to their maximum speed for older than younger participants. To test whether this can account for the higher earnings, we assessed whether the response time difference was associated with the total earnings. Indeed, a larger response deadline difference (i.e. increased room for improvement on test compared with practice) was associated with higher earnings (Total earnings x Response time difference: r (ρ) = 0.480, p < 0.001). Crucially however, the difference in response times between practice and test was not associated with the task effects (Rewarded Task switching effects in terms of SAT x Response time difference (r (ρ) = -0.037,

p = 0.693). Together, these results suggest that more cautious responding during practice (i.e. when determining the response deadlines) can explain the higher earnings in the older group during the test, but that it does not explain the differential task-related effects observed during the test.

Discussion

The ability to take into account information about potential rewards is crucial for flexible, adaptive behavior. Increasing age is associated with cognitive decline, yet the psychological mechanisms underlying this decline remain uncharted. In the current study, we investigated whether reward motivational deficits underlie age-related changes in flexible cognitive control across the life span. To this end, we investigated age-related changes in the effect of reward motivation on flexible cognitive control in 118 participants with age ranging from 14 to 69. We observed overall age-related slowing and an age-related increase in accuracy across conditions. With increasing age, participants adopted an overall slower but more accurate strategy. However, whereas younger participants adapted their speed-accuracy strategy to the trial type, aging was accompanied by a more rigid strategy across trial types. Specifically, on the more demanding switch trials, younger participants exhibited a reward-related increase in speed over accuracy, while exhibiting a reward-related decrease in speed over accuracy on the less demanding repeat trials. By contrast, such reward- and task-dependent adaptation of speed-accuracy strategy was absent in older participants.

The between subject analysis (**figure 5.3b**) confirmed that younger participants modulate their behavior differentially in distinct cognitive conditions. By contrast, in the older group, behavior on the switch trials was indistinguishable from behavior on repeat trials. Thus, with increasing age, participants drifted towards a more uniform strategy, where they preferred accuracy over speed across the task as a whole, but failed to adapt their behavior to changing motivational and cognitive task demands. This is generally in line with a diffusion modeling study by Starns and Ratcliff (2010), showing that older - in contrast to younger - adults do not adapt their speed-accuracy strategy to feedback on simple discrimination tasks. Together these results suggest that alterations in reward-based processing underlie cognitive changes in aging.

Previous work has suggested that aging is accompanied by deficits in task switching (Kray et al., 2002). In keeping with this prior work, we observed an age-related increase in the RT switch cost. Also, a number of studies have demonstrated an age-related decrease in reward processing (Schott et al., 2007; Rademacher et al., 2014), although some studies have revealed intact processing of cues predicting an upcoming reward in older individuals (Samanez-Larkin et al., 2007) (Dreher et al., 2008). The present data – showing an age-related decrease in the reward effect as well as in the effects of reward on cognitive control (in terms of SAT) – provide support for the first account. In addition to observing commonly reported age-related changes in task-switching and reward processing, the current results suggest that aging is also

accompanied by reward-based changes in flexible cognitive control, where older participants no longer exhibit an effect of reward motivation on task switching performance.

Reward-induced changes in the speed-accuracy tradeoff have not been widely studied, and never in the context of a cognitive task. However, at least one study suggests that potential rewards can induce more cautious (i.e. more accurate and slow) behavior (Bijleveld et al., 2010). We replicate this effect in the cognitively less demanding repeat trials by showing that young participants exhibit reward-induced cautious behavior in the repeat condition. We extend this finding by showing that reward induced less accurate and faster responding on the more demanding switch trials in younger participants. These results suggest that reward can modulate cautious behavior differentially in distinct cognitive conditions.

Reward motivation, cognitive control and the interaction between reward and cognitive control implicate, among other mechanisms, dopamine in the striatum (Roberts et al., 1994; Ikemoto and Panksepp, 1999; Aarts et al., 2010; Aarts et al., 2011). Furthermore, changes in speed-accuracy tradeoff strategies have been associated with changes in connectivity between the cortex and the striatum (Bogacz et al., 2010). More specifically, stronger corticostriatal connections have been found to promote faster (and premature) responses. The current study does not address the neural mechanisms of age-related effects on rewarded task switching directly. However, several independent studies have revealed age-related changes in dopamine signaling (Volkow et al., 1996b; Bäckman et al., 2000) Erixon-Lindroth et al., 2005), starting in early adulthood (Backman and Farde, 2005). Also, age-related decreases in corticostriatal connectivity, accompanied by slower (and more accurate) responses have been reported (Forstmann et al., 2011). Accordingly, here, we put forward the hypothesis that the observed change in speed-accuracy strategy during the integration of reward and cognitive performance reflects reduced dopamine signaling in the striatum, and a subsequent reduction in the adaptation of corticostriatal responses to the task conditions. The increased effect of reward in younger versus older participants is also in line with a number of previous findings in adolescents. First, neuroimaging work has revealed increases in reward sensitivity and ventral striatal responses in adolescents (Somerville and Casey, 2010). In addition, previous work has reported reward-related improvements in impulse control in adolescents (Kohls et al., 2009; Geier et al., 2010). In older participants, however, if anything a decrease in reward sensitivity is reported (Schott et al., 2007; Rademacher et al., 2014). We extend these findings by showing that young (i.e. < 26 years old) subjects can show reward-related adaptations of flexible cognitive control during task switching, whereas older participants (i.e. > 25 years old) cannot.

One limitation of the current study is the fact that we pooled data from several studies. As a result, there are a number of factors of no interest that differ as a function of age, such as effects of maximum available reward. However, we accounted for this by replicating the effects in a subgroup of participants who received exactly the same amount of reward and number of trials. Nevertheless, it is clear that the reported results require replication in future, preferably longitudinal, work using a single study set-up. Also, it should be noted that a large number of

methods exist which can be used to assess speed accuracy tradeoffs (Salthouse and Hedden, 2002; Forstmann et al., 2011; Heitz, 2014). The method used in this study is an elementary formalization of a speed accuracy tradeoff. Nevertheless, the results clearly show that taking into account both speed and accuracy can reveal differences that would not be revealed when response times and accuracy are assessed separately. However, future work should extend these findings using more sophisticated approaches (e.g. mathematical decision making models) and by experimentally manipulating speed accuracy strategies (Heitz, 2014). Such model-based approaches might be more sensitive, as they take into account trial-by-trial changes in speed and accuracy. The consequence of the simple composite score approach used in the current study is that changes in speed and accuracy are assumed to contribute equally to the decision process. It is therefore hard to interpret the SAT measure used in the current study without taking note of the separate response and accuracy measures. Finally, we cannot rule out completely that older participants show reduced motivational effects because they value money less than young participants. However, we argue that this is unlikely for two reasons. First, age was associated with contrasting effects of reward on switch and repeat trials. Second, older participants actually earned more money than did the younger participants.

In the current study we controlled for general age-related differences in processing speed (Salthouse, 1996) by determining each individual's response deadline, by using a within-subject comparison of conditions, and by taking into account the speed-accuracy tradeoff. In line with previous work (Bijleveld et al., 2010; Forstmann et al., 2011), older participants were more cautious (i.e. slower and more accurate than younger participants). This cautious strategy was already evident during practice and allowed older participants more time to respond accurately during test. It is unlikely that allowing slower (older) participants more time has induced differences in reward-related speed-accuracy strategies, given the equal response deadline for high and low reward (i.e. only arrow/word x switch/repeat trials were adapted). In addition, the response deadline adaptations did not result in an age-related difference in switch and repeat trials, suggesting it is unlikely that this adaptation has changed the accuracy-over-speed strategy during the integration of reward and task switching differently in older and younger participants. The cautiousness of the older participants was further corroborated by the observation that the overall response deadline of the younger participants was closer to their maximum performance in terms of speed (on test). Crucially however, this difference was not related to the age-related adaptation to the task conditions.

Here, we show for the first time that age-related changes in response strategies can be observed when participants need to flexibly adapt to changing task demands. Specifically, we observed an age-related decrease in the degree to which older participants use information about rewards to change their speed-accuracy strategy in changing cognitive control conditions; i.e., older participants no longer used rewards to adapt cognitive control processes. As such the present study goes beyond prior work focusing commonly merely on cognitive deficits (Salthouse, 1996; West, 1996; Kray et al., 2002; Park et al., 2002). An obvious next step would be to unravel the neural mechanisms underlying these changes.

Supplementary material

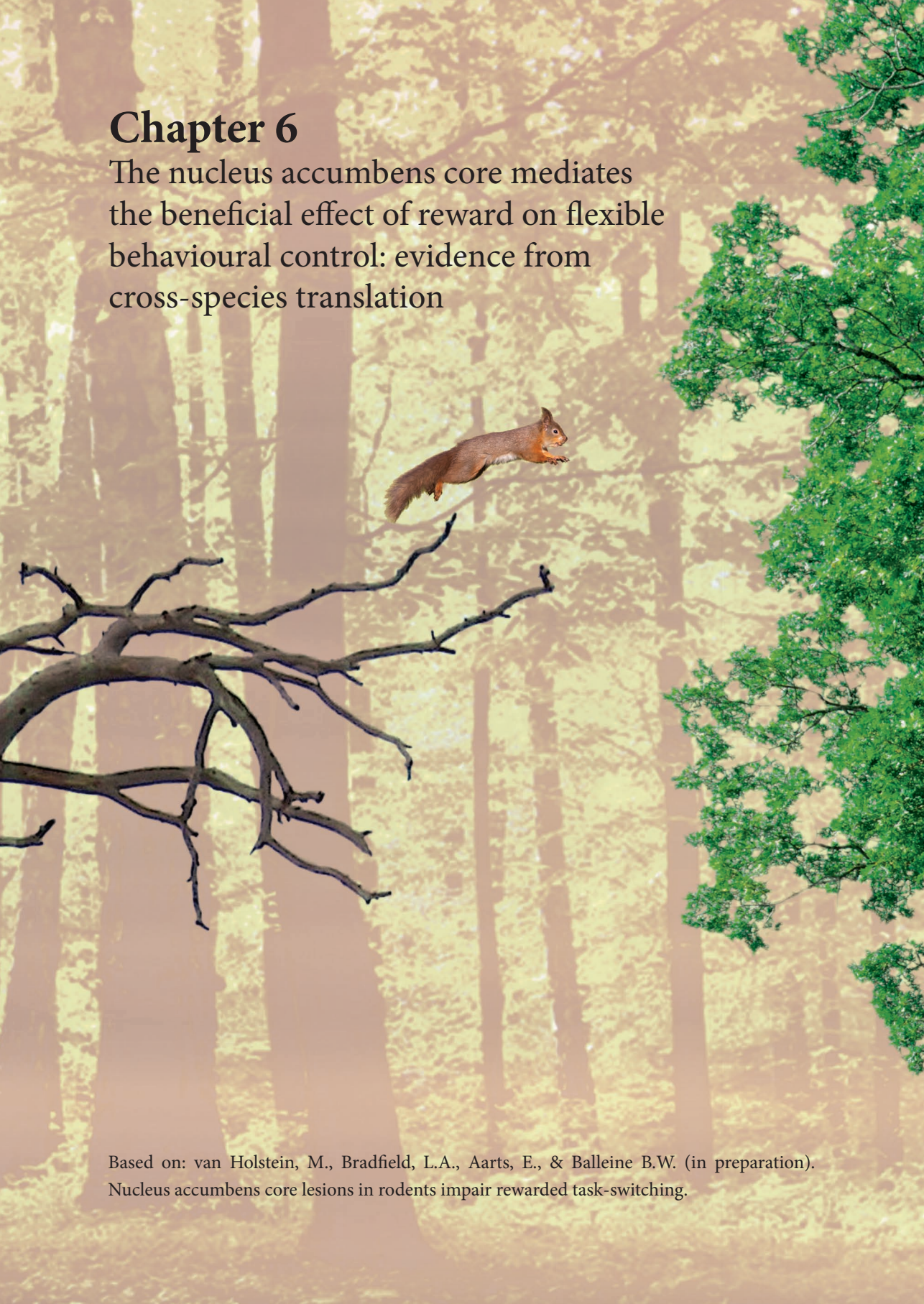
Table S5.1 Means (CI) for all dependent variable on 4-trial types across all participants

		low reward			high reward			main effect control		
		mean	95% CI		mean	95% CI		mean	95% CI	
	RTs [§]	**442.00**	424.66	459.35	**430.07**	412.79	447.36	**436.04**	418.85	453.23
repeat	Accuracy	**90.45**	88.68	92.22	**91.70**	90.09	93.31	**91.07**	89.52	92.63
	SAT[†]	**0.026**	-0.12	0.17	**-0.0785**	-0.22	0.06	**-0.03**	-0.17	0.12
	RTs [§]	**451.49**	431.77	471.20	**440.61**	420.47	460.74	**446.05**	426.25	465.84
switch	Accuracy	**85.46**	83.36	87.55	**86.57**	84.65	88.48	**86.01**	84.14	87.89
	SAT[†]	**-0.082**	-0.24	0.07	**0.134**	-0.03	0.30	**0.026**	-0.13	0.18
	RTs [§]	**446.74**	428.31	465.18	**435.76**	416.76	453.92			
main effect reward	Accuracy	**87.95**	86.17	89.73	**89.13**	87.48	90.78			
	SAT[†]	**-0.028**	-0.18	0.12	**0.028**	-0.12	0.18			

§ RTs = response times in ms; † SAT = speed-accuracy-tradeoff (z-speed + z-accuracy) / 2
95% CI = 95% (lower, upper) confidence interval.

Chapter 6

The nucleus accumbens core mediates the beneficial effect of reward on flexible behavioural control: evidence from cross-species translation



Based on: van Holstein, M., Bradfield, L.A., Aarts, E., & Balleine B.W. (in preparation). Nucleus accumbens core lesions in rodents impair rewarded task-switching.

Abstract

The ability to adapt behavior based on environmental cues (e.g. task switching) is an important aspect of cognitive functioning, one that can be influenced by the prospect of reward. However, experimental evidence elucidating the exact neural mechanism by which changes in reward motivation inform flexible control is lacking. A primary candidate for this function is the nucleus accumbens core (AcbC), which has been proposed as a link between motivation and cognition by several theoretical accounts.

The current study aimed to develop a rewarded task-switching paradigm in rodents, in parallel to a paradigm extensively studied in humans. Using this paradigm, we subsequently aimed to test whether lesions of the AcbC disrupt the integration of reward information and cued flexible control.

First, rats learned to discriminate between two auditory (A1 - A2) and two visual (V1 - V2) stimuli, which were associated with a distinct task cue. Further, training and testing took place in high (3 pellet) and low (1 pellet) reward contexts. On test, animals were presented with response-incongruent compound stimuli (A1V2 / A2V1) and had to rely on the task cue to disambiguate which of the stimuli (i.e. auditory or visual) would yield a rewarded response. Within this test, on a trial-by-trial basis, the task cue could either switch (e.g. auditory -> visual) or remain the same (e.g. auditory -> auditory), allowing the assessment of proactive flexible control by comparing switch and repeat trials. Task-switching performance improved in the high reward condition, but only in animals with an intact AcbC (prior to surgery or after sham surgery). These findings provide direct evidence that the AcbC is involved in using reward information to optimize cognitive control.

Introduction

When an animal is foraging for berries and suddenly comes across a nut tree (a cue) it may want to update its current goal and switch behaviour appropriately (from searching for berries to gathering nuts). Now consider that an animal is foraging in fall- or springtime, the expected reward will be higher in fall, and thus an animal may exert more control (e.g. be more flexible) to find blackberries and nuts in this season. Many everyday actions require flexible adaptation when environmental conditions change, and the use of cues can facilitate such adaptation. Cues can be differentially informative, with certain cues indicating which action will be rewarded, and others signifying the amount of reward to be received.

It is well known that cognitive control processes are under the influence of reward motivation, allowing agents to select the most appropriate and beneficial course of action (Balleine and Dickinson, 1998; Locke and Braver, 2008; Padmala and Pessoa, 2010, 2011; Aarts et al., 2014b), (for reviews see: Pessoa and Engelmann, 2010; Aarts et al., 2011; Braver et al., 2014). Despite a well-established role for motivation in influencing cognitive control, surprisingly little is known about which neural mechanisms are crucial for such integration. Several functional neuroimaging studies in humans report increased neural activity in response to reward in regions typically involved in cognitive control, such as the prefrontal cortex, e.g. the inferior frontal gyrus (Locke and Braver, 2008) and the dorsal striatum (Aarts et al., 2010). Furthermore, several theories suggest a role for the human ventral striatum (VS) or rodent nucleus accumbens core (AcbC) in mediating a link between motivation and cognitive/action control (Mogenson et al., 1980; Pessoa, 2009; Mannella et al., 2013; Floresco, 2015), suggesting that the VS/AcbC modulates the efficient pursuit of rewards or other goals in a constantly changing environment. However, direct evidence for a causal role of the VS/AcbC has thus far not been provided.

Assessing whether there is a direct, causal role of the VS in integrating reward and cognitive control in humans is prevented by ethical and methodological issues. The difficulty in assessing this in rodents, on the other hand, is that existing paradigms for measuring (rewarded) flexible control are conceptually different from the paradigms used in human studies, preventing direct cross-species comparison. Specifically, task-switching paradigms employed in humans typically require a trial-by-trial adaptation to task-sets in response to external cues (Meiran, 1996; Monsell, 2003). In contrast, rodent paradigms assessing flexible cognitive control include reversal learning, set-shifting, and extradimensional shift (EDS) paradigms, none of which involve the use of cues to initiate behavioural changes nor manipulate reward size, but instead assess an animals' capacity to learn that the rule has changed (Birrell and Brown, 2000; Ragozzino et al., 2002; Floresco et al., 2008a; for a review see: Bizon et al., 2012). Although informative about aspects of flexible control, these paradigms ignore the more efficient process of using cues to switch actions (e.g. switching to foraging for nuts is more efficient in the presence of a nut tree than having to encounter several nuts before switching) and ignore the integration of motivational processes (which are generally held constant for such tasks).

A well-established paradigm to assess the effect of reward on flexible behaviour in human subjects is the rewarded task-switching paradigm (Aarts et al., 2010; van Holstein et al., 2011; Aarts et al., 2014a; Aarts et al., 2015; Etzel et al., 2015; Fuentes-Claramonte et al., 2015), which allows the assessment of flexible control in low and high reward conditions separately. A similar rodent paradigm that can tap into these processes, i.e. switching between tasks based on external cues and the effect of reward motivation on this cognitive process, will help the advancement of understanding the neural mechanisms underlying this process in a manner that is unconfounded by learning and working memory. In the current study we developed such a paradigm in rodents, and subsequently assessed whether lesions of the AcbC impair successful motivation-cognition integration.

Methods

Subjects

Twenty-four experimentally naive male hooded Wistar rats were used as subjects. The animals were housed in yellow-tinted plastic boxes located in a temperature and humidity -controlled colony room. They were housed in twos or threes and maintained on a 12 h light/dark cycle. Animals were handled daily for 4 days before training and were kept on a food deprivation schedule during training and testing to maintain them at ~85% of their free feeding weight. All procedures were approved by the Animal Ethics Committee at the University of Sydney.

Apparatus and stimuli

Training and testing took place in 16 MED Associates (East Fairfield, VT) operant chambers (32 x 25 x 25 cm) with a transparent Perspex ceiling, wall and door. Each operant chamber was enclosed in sound- and light-resistant cabinets and equipped with a pellet dispenser that delivered grain pellets (45mg, BioServe Biotechnologies, Beltsville, MD) into a recessed food magazine. The chamber contained two retractable levers at either side of the magazine. Visual stimuli consisted of a panel light (flashing or steady) above each lever. Auditory stimuli (~80dB) were produced by a 28V DC mechanical relay that delivered a 5Hz clicker sound and a sonalert that delivered a 3kHz tone. Task cues were the house light (3W, 24 V) located on the wall opposite the magazine and white noise produced by a white noise generator. Two computers running MED Associates software controlled the experimental events and recorded lever presses. All stimuli were presented against a background sound produced by the ventilation fan (~60 dB).

To signal the reward condition (i.e. high or low reward), the physical appearance of the boxes was manipulated by placing wallpaper behind the Perspex (black and white stripes or black dots on a white background), by placing floorboards on top of the stainless steel floors (smooth black or coarse transparent plastic) and by delivering a distinct scent (vanilla or peppermint) to each chamber before the start of a session. This resulted in two distinct reward contexts; RC-A (striped wallpaper, smooth floors, vanilla scent), and RC-B (dotted wallpapers, coarse

floors and peppermint scent).

Behavioural procedures

We aimed to develop a paradigm similar to the paradigm studied extensively in humans. A detailed description of the paradigm used in humans can be found elsewhere (Aarts et al., 2010; van Holstein et al., 2011; Aarts et al., 2015).

In the rodent version of this paradigm, animals received pre-training-, discrimination training-, and finally test sessions, each of which took place in either reward context (RC-A or RC-B). Each animal always received either one or three food pellets in a certain context, i.e. half the animals always received one pellet per reward delivery in RC-A (low reward condition) and three pellets in RC-B (high reward condition), whereas the other animals received the opposite arrangement. Each animal received two training sessions or tests per day (separated by at least 4 hours); one in a high- and one in a low reward context, the order of which was counterbalanced.

Pre-training and discrimination training procedures, with the exception of the reward context, were similar to previously described by Haddon and Killcross (2006). All sessions took place in either a high or low reward context (counterbalanced).

Training procedure

Pre-training

After 4 days of food deprivation, rats were given two 30 min sessions of magazine training. During each session a reward (1 or 3 pellets, depending on the context) was delivered on average every 60 seconds. On the following four days, rats received two daily 36 min sessions of lever press training. During these sessions levers were extended for 60 s each in random alternation (6 left and 6 right lever presentations) with a variable inter-trial-interval of 45-195 s (mean 120s). Initially lever pressing took place at a continuous reinforcement schedule (resulting in one or three pellets, depending on the context). On the second day this was increased to a RI15 schedule, which remained in place for the remainder of the experiment.

Discrimination training

Animals received two sessions (of ~ 85 minutes each) of discrimination training on each day for 15 days. In one training session, rats were presented with two auditory stimuli (A1 and A2) and on the alternate training session, rats were presented with two visual (V1 and V2) stimuli, during which both left and right levers were available but only one of the levers rewarded. Within each modality, one of the stimuli (A1 during auditory sessions and V1 during visual sessions) indicated that left but not right lever presses would be rewarded, whereas the other stimuli (A2 and V2) indicated the opposite arrangement (e.g. A1-L, A2-R

Table 6.1 Experimental design: discrimination training

Reward context	**Task cue (60s)**	**Discrimination stimulus (60s)**	
		First 10s (no reward)*	Last 50s (RI15)
Low	AÙD	A1 → LL →	1 pellet
		A1 → RL →	no reward
		A2 → RL →	1 pellet
		A2 → LL →	no reward
	VIS	V1 → LL →	1 pellet
		V1 → RL →	no reward
		V2 → RL →	1 pellet
		V2 → LL →	no reward
High	AUD	A1 → LL →	3 pellets
		A1 → RL →	no reward
		A2 → RL →	3 pellets
		A2 → LL →	no reward
	VIS	V1 → LL →	3 pellets
		V1 → RL →	no reward
		V2 → RL →	3 pellets
		V2 → LL →	no reward

Reward contexts were determined by wallpaper, floorboards and odour. AUD and VIS are auditory and visual discrimination cues, respectively (white noise and house light), A1, A2, V1 and V2 refer to auditory stimulus 1 and 2 (i.e. tone and clicker), and visual stimuli 1 and 2 (steady and flashing panel lights). Contexts, task cues and discrimination stimuli are counterbalanced.

* The presentation of the stimulus lasted for the full duration of the trial (60s), but a response was never rewarded during the first 10s of a trial. A trial ended with the retraction of both levers and a variable inter-trial-interval (30s-90s)

and V1-L, V2-R) (**table 6.1**). Each session took place in one of the two reward contexts, which determined the size of the reward earned by each 'correct' lever press (i.e. 1 or 3 pellets). The order of the session (VIS followed by AUD or AUD followed by VIS) and its reward context were counterbalanced. Further, a session consisted of 24 'trials' each of which comprised a 60 s presentation of the task cue (white noise or house light indicating auditory or visual stimuli, counterbalanced) followed by a 60 s presentation of one of the target stimuli. A1 and A2 were each presented pseudorandomly for 12 trials during auditory sessions, and V1 and V2 were each presented pseudorandomly for 12 trials during visual sessions. At this stage the task cues

served to form an association between the task cue (noise and house light) and the relevant task (auditory or visual discrimination), although these associations did not become relevant until test. Trials were separated by inter-trial-intervals of 30s – 90s, during which the levers were retracted. For each 'correct' lever press a reward became available on average every 15 seconds (RI15 schedule), with the restriction that a reward was never delivered during the first 10s of a trial. All reward contexts, stimuli, and task cues were counterbalanced across animals. **Table 6.1** shows the design and conditions for all animals.

Cued task-switching paradigm with reward manipulation

On the day immediately following the last training day, animals were tested. During test (**table 6.2, figure 6.1**), the task cue was presented for 60s, followed by a 60s presentation of a response-incongruent compound stimulus (i.e. A1-V2 or A2-V1, for which one stimulus signals left lever presses will be rewarded, but the other stimulus signals right lever presses will be rewarded). Animals had to disambiguate these compound stimuli (i.e. whether to respond to the auditory or visual modality) by taking into account the task cue. For example, a presentation of A1-V2 preceded by the *auditory* task cue indicated that the animal should attend to the stimulus of the auditory modality, A1, and choose the associated lever press (left lever). The same A1-V2 compound preceded by the *visual* task cue, however, indicated that the animal should attend to the visual modality, and press the right lever. Again, 'correct' lever presses were rewarded according to an RI15 schedule, and never during the first 10s of each compound presentation.

The design of this task afforded a unique opportunity to examine the animals' performance on a trial-by-trial basis. Crucially, the task cue (i.e. AUD or VIS) could either remain the same (i.e. repeat: AUD -> AUD or VIS -> VIS) or change (i.e. switch: AUD -> VIS or VIS -> AUD) unexpectedly from trial to trial, allowing the assessment of task-switch performance (i.e. performance on task-switch versus task-repeat trials) (**figure 6.1**). One test session consisted of 17 trials; one initiation trial (this was discarded, because is it not a repeat nor a switch trial), followed by a random alternation of eight visual (four A1-V2 and four A2-V1) and eight auditory trials (four A1-V2 and four A2-V1), with half the trials being task repetitions and the other half being switch trials.

All 24 animals received the test twice on one day, once in each reward context (in counterbalanced order: AB or BA). After surgery all animals completed an additional two days of testing in an ABBA design.

Surgery

In the next phase of the experiment, half the animals received excitotoxic lesions of the AcbC and half underwent sham surgery. Next animals received an additional five days of discrimination training, followed immediately by two days of testing (again two tests on each day in each reward context), allowing the assessment of the effect of lesions of the AcbC on

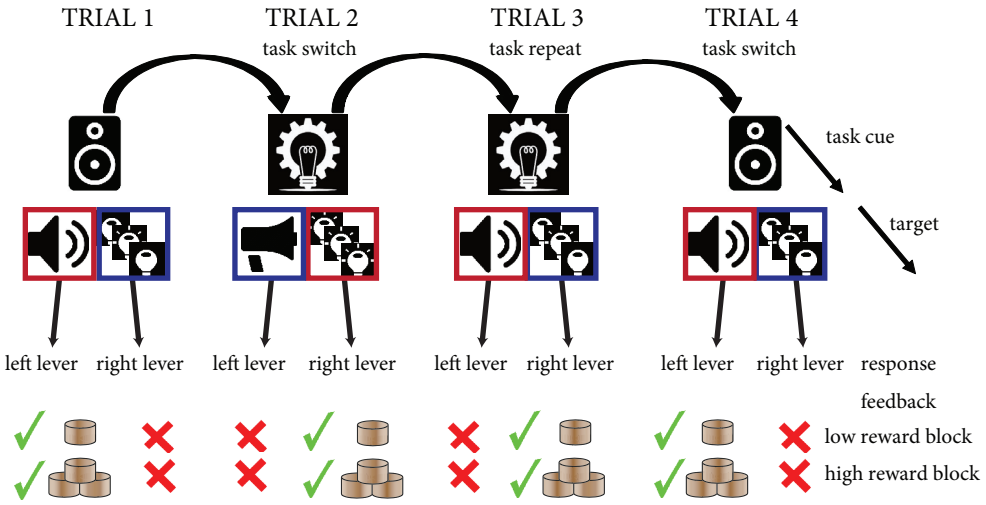


Figure 6.1 Cued task-switching paradigm with reward manipulation

On test, animals were presented with response-incongruent combinations of the auditory and visual stimuli (e.g. tone and house light), inducing a response conflict. Resolving this conflict correctly required the use of the task cue. For example, when a tone and flashing panel lights (associated with a left and right lever press, respectively) were preceded by a task cue signalling the auditory task (e.g. white noise), a left lever press would lead to a reward. However, when the same combination of stimuli was preceded by the presentation of the house light, a discrimination based on the visual stimulus was required (i.e. a right lever press was correct). Crucially, this paradigm allowed the trial-by-trial manipulation of a repetition or switch of the task set, allowing a direct comparison of performance on repeat (i.e. auditory -> auditory and visual -> visual) and switch (auditory -> visual and visual -> auditory) trials. In addition, animals were trained and tested in two distinct reward contexts, allowing the assessment of task-switching under different reward circumstances.

Table 6.2 Experimental design: test

Task cue	Compound stimuli	Correct lever	Reward context	
			Low [RC-A]	High [RC-B]
8 x AUD	4 x A1-V2	Lever 1	1 pellet	3 pellets
	4 x A2-V1	Lever 2	1 pellet	3 pellets
8 x VIS	4 x A1-V2	Lever 2	1 pellet	3 pellets
	4 x A2-V1	Lever 1	1 pellet	3 pellets

Task cues (noise and house light): AUD (auditory) and VIS (visual) signal the relevant modality; compound stimuli are composed of one of two auditory stimuli (A1 or A2; clicker and tone) and one of two visual stimuli (V2 or V1; flashing or steady panel lights), creating a response incongruent compound; In case of AUD → A1-V2 a left lever press is rewarded, whereas in case of VIS → A1-A2 a right lever press is rewarded with 1 or 3 pellets depending on the reward context (RC).

rewarded task-switching performance.

Stereotaxic surgery was performed under isoflurane anaesthesia. Animals were placed on a stereotaxic apparatus (David Kopf Instruments) and received subcutaneously injections with 0.1 ml of bupivicaine at the incision site. An incision was made to expose the skull and the incisor bar was adjusted to align bregma and lambda in the same horizontal plane. Excitotoxic lesions were made by infusing 0.4 µl of N-methyl-D-aspertate (NMDA: 10mg/ml in saline) over 4 minutes into the AcbC [anteroposterior +1.6, mediolateral +/- 2.2, dorsoventral -7.5 mm relative from bregma, according to the rat brain atlas (Paxinos and Watson, 2007)]. The needle was left in place for 2 minutes to allow for diffusion before being retracted. Animals in the sham group underwent the exact same procedure, except that only saline was infused. At the end of surgery, animals received a subcutaneous injection of 0.1 ml Rimadyl and 0.2 ml intraperitoneal injection of procaine penicillin solution (300mg/kg). Rats were given at least 6 (max. 10) days to recover and were subjected to 4 days of food deprivation before the start of 5 days of additional discrimination training and two test days.

Histology

Rats were deeply anaesthetized with sodium pentobarbital and transcardially perfused with 400 ml of 4% paraformaldehyde in 0.1 M sodium phosphate buffer. Brains were postfixed for 1 hour in 4% paraformaldehyde, rinsed in phosphate buffered saline (PBS) for 30 minutes before being placed in 30% sucrose solution in PBS overnight. The brains were frozen and 40 µm sections were collected on a cryostat. Every third section was collected on a slide and stained with cresyl violet. Slides were examined for placement and extent of the lesion by microscopically examining the sections.

Statistical tests

Discrimination training data are presented as the average number of correct and incorrect lever presses per minute (recorded during the first 10s of each trial) on the auditory and visual discrimination sessions separately, and collapsed across the two stimuli.

We present performance on test in terms of accuracy (correct minus incorrect lever presses, again as an average per minute recorded during the first 10s of each trial). We assessed the effect of reward on task-switching performance with a repeated-measures GLM with the factors reward (high vs. low), switching (switch vs. repeat) and accuracy (correct vs. incorrect) and anticipated that reward would improve task-switching performance.

To increase the number of trials on the post-surgery test (where the group sizes are smaller, i.e. 12 instead of 24 during pre-surgery testing), all animals received two tests (post1 and post2) in each reward condition in an ABBA design. We first assessed whether there were any effects of session (post1 vs. post2) on rewarded task-switching performance or overall accuracy. In the absence of an interaction, we collapsed data across post-tests.

Table 6.3 Discrimination training

	AUD			VIS		
Day	**Correct Mean (SEM)**	**Incorrect mean (SEM)**	**F(1,23)**	**Correct Mean(SEM)**	**Incorrect mean (SEM)**	**F(1,23)**
1	18.81 (3.07)	18.85 (2.68)	< 1	17.69 (3.02)	20.19 (3.08)	5.429 *
2	29.13 (3.90)	20.10 (2.29)	15.042 ***	24.19 (3.20)	24.48 (3.43)	<1
3	28.31 (3.45)	17.17 (2.09)	27.455 ***	28.69 (4.41)	26.50 (3.96)	3.372 ^
4	40.96 (5.13)	22.85 (2.45)	31.353 ***	30.33 (3.17)	29.48 (3.21)	<1
5	44.06 (4.21)	21.54 (2.43)	47.350 ***	38.75 (3.37)	34.46 (3.06)	11.607 **
6	45.29 (3.53)	22.44 (2.07)	75.362 ***	42.79 (3.68)	35.77 (3.09)	15.027 ***
7	56.50 (6.27)	25.98 (3.10)	54.420 ***	51.52 (4.59)	44.15 (2.65)	4.347 *
8	58.31 (4.28)	28.90 (3.68)	72.552 ***	52.04 (4.25)	40.79 (3.73)	25.108 ***
9	65.92 (5.75)	22.10 (2.39)	89.538 ***	55.69 (5.78)	40.77 (4.13)	20.971 ***
10	68.56 (7.04)	27.52 (2.91)	51.151 ***	49.27 (4.85)	37.15 (3.42)	23.008 ***
11	66.67 (6.05)	26.60 (2.51)	60.396 ***	57.15 (7.47)	36.54 (3.93)	22.899 ***
12	67.92 (5.99)	24.35 (2.47)	44.035 ***	61.56 (6.01)	40.17 (3.56)	22.500 ***
13	75.90 (6.68)	27.23 (3.13)	82.304 ***	65.92 (6.75)	49.88 (4.67)	16.281 ***
14	82.67 (8.44)	28.81 (3.22)	44.893 ***	62.00 (5.95)	39.90 (3.67)	33.093 ***
15	78.25 (5.61)	29.77 (2.51)	77.400 ***	63.65 (6.01)	39.48 (3.67)	19.949 ***

^ = p < 0.1, * = p < 0.05, ** = p < 0.01, *** p < 0.001,
bold = significant after correction for multiple (i.e. 30) t-tests: p < 0.001

We anticipated that all animals, except for those with lesions of the AcbC would show increased flexibility in the high vs. low reward condition. To assess the role of the AcbC, we first assessed whether surgery affected rewarded task-switching performance in the sham and lesion group separately, by comparing performance on pre- and post-surgery sessions. We anticipated an effect of surgery in the lesion group, but not in the sham group. Next, we assessed group effects on rewarded task-switching performance, by directly comparing the group effect in the pre- and post-surgery sessions separately. We anticipated differences between the sham and lesion group after, but not prior to surgery.

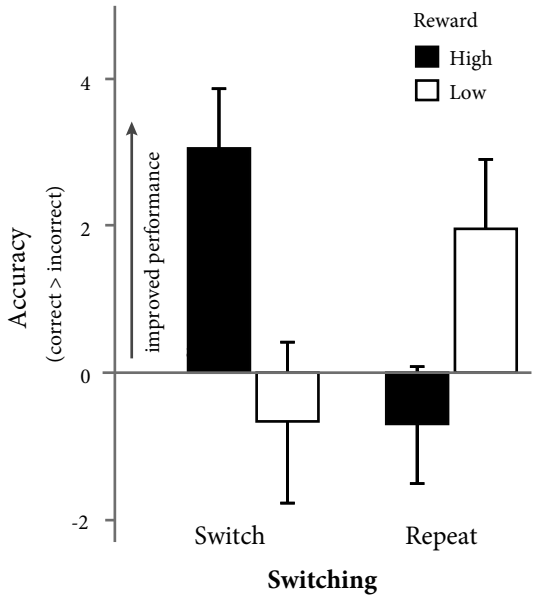


Figure 6.2 Task switching differences in the high versus low reward context
A: For each reward context (high and low), the performance on switch and repeat trials is shown. The y axis represents the number of correct vs. incorrect lever presses (per minute), recorded during the first 10s of each trial. Error bars represent standard errors of the difference between correct and incorrect responses.

Results

Discrimination training

A repeated measures GLM with the factor accuracy (correct vs. incorrect) confirmed that, by the end of training, animals were able to reliably discriminate between the two auditory stimuli ($F(1,23) = 77.400$, $p < 0.001$, $\eta 2 = 0.771$) and between the two visual stimuli ($F(1,23) = 19..949$, $p < 0.001$, $\eta 2 = 0.464$; **Table 6.3**). Reliable discrimination between the correct and incorrect lever was achieved during day 2 of training on the auditory training and from day 8 onwards for the visual discrimination training (**Table 6.3**).

Reward context can alter task-switching performance

Importantly, animals were able to use the task cue to successfully discriminate between the response-incongruent stimuli, which was reflected by a main effect of accuracy (correct vs. incorrect lever presses: ($F(1,23) = 4.667$, $p = 0.041$, $\eta 2 = 0.169$). We did not observe a main effect of reward or of task-switching in terms of accuracy ($F < 1$).

The reward context affected task-switching performance. More specifically, animals were better at switching between the auditory and visual modalities in each compound stimulus

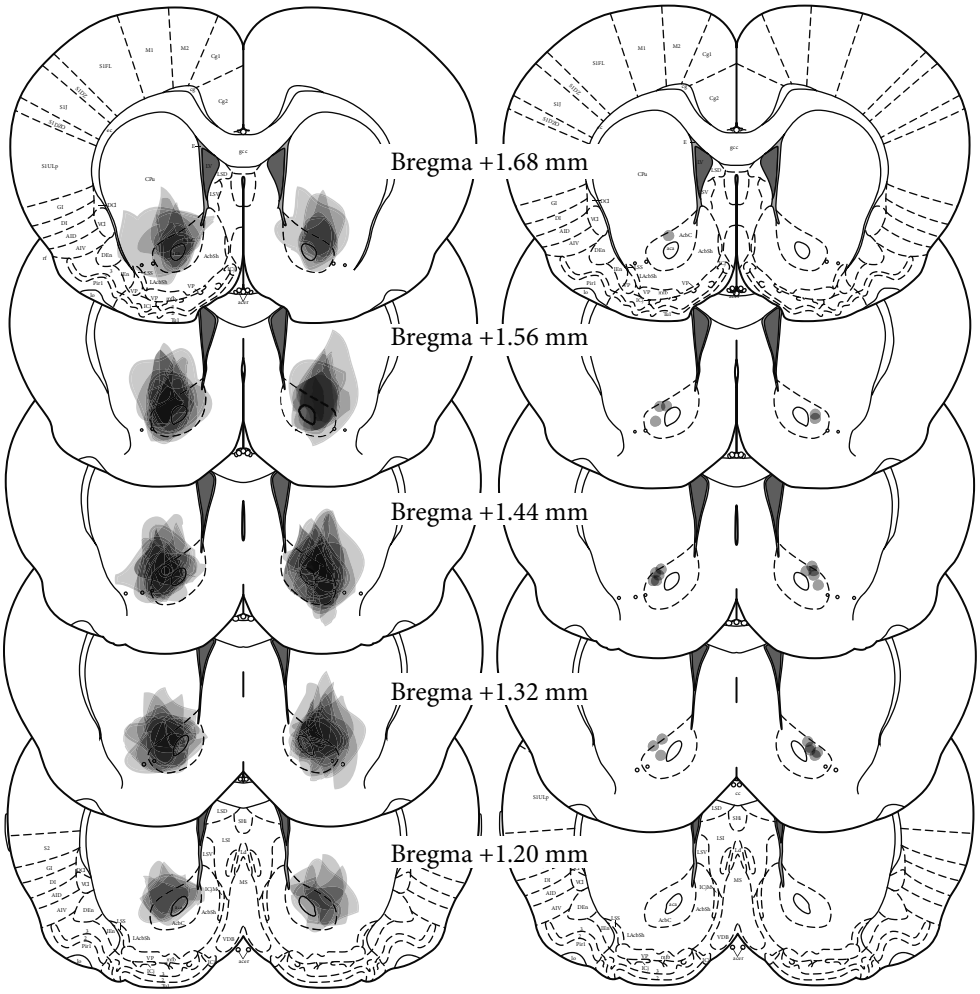


Figure 6.3 Lesion placement showing the extent (left) and peak (right) of the lesion as verified using Nissl staining for the nucleus accumbens core

Shading indicates the extent (left) or peak (right) of the lesion of each subject. The extent is represented as the stacked layers across subjects.

(dependent on the task cue) in the high reward context relative to the low reward context (**figure 6.2**). This was evidenced by a significant reward x task switching interaction ($F(1,23) = 11.395$, $p = 0.003$, $\eta 2 = 0.331$, **figure 6.2**). Breaking down this interaction revealed that the switch cost in the low reward context, i.e. a numerically higher accuracy on repeat than switch trials ($F(1,23) = 3.188$, $p = 0.087$, $\eta 2 = 0.122$, **figure 6.2**), reversed into a switch benefit in the high reward condition ($F(1,23) = 7.411$, $p = 0.012$, $\eta 2 = 0.244$; **figure 6.2**).

Histology and pre-surgery differences between groups

Figure 6.3 shows the extent (left) and peaks (right) of the lesions. Although lesions that extended into the shell were excluded from analyses, a small portion of the striatum dorsal to the core was sometimes affected. Seven animals were excluded after histology due to either the presence of unilateral lesions and/or extension of damage into the NAc shell or peaks located outside of the AcbC, resulting in 12 animals with AcbC lesions and 12 shams.

Prior to surgery, the groups were well matched on discrimination training and test performance. More specifically, on the final day of training, we observed no group-by-accuracy effect on auditory ($F(1,22) = 2.182$, $p > 0.1$) or visual ($F(1,22) = 2.644$, $p > 0.1$) discrimination. In addition, prior to surgery, the lesion group did not differ from the sham group in terms of rewarded task-switching performance ($F(1,22) < 1$; **figure 6.4**), or in terms of overall accuracy on test ($F(1,22) < 1$).

Retraining

The lesions did not affect discrimination training; by the end of five days of retraining, the groups did not differ in terms of either auditory or visual discrimination (group x accuracy: $F(1,22) = 2.594$, $p > 0.1$ and $F(1,22) < 1$, respectively). Also, the surgery did not differentially affect retraining across 5 days (time x group x accuracy: all $F(1,19) < 1$). After correcting for multiple (i.e. 10) tests, animals were able to reliably discriminate between the auditory stimuli on all 5 days (all $F(1,23) > 27.883$, all $p < 0.001$, all $\eta 2 > 0.548$) and between the visual stimuli from day 3 onwards (all $F(1,23) > 10.731$, all $p < 0.004$, all $\eta 2 > 0.318$). Animals were not able to reliably discriminate between the visual stimuli on the first two days (the main effect of accuracy was not significant after multiple comparison correction: $F(1,23) = 8.273$, $p < 0.009$ and $F(1,23) = 9.192$, $p < 0.006$, respectively).

Lesions of the nucleus accumbens core affect rewarded task-switching performance

No test-retest effect on rewarded task-switching performance

All animals performed the post-surgery test twice in each reward context. We first confirmed that the effect of reward on task-switching performance did not vary as function of session ($F(1,22) < 1$). Also, there were no overall differences in terms of accuracy between sessions ($F(1,22) = 2.537$, $p > 0.1$) and we did not observe any group differences in accuracy between the sessions ($F(1,22 = 2.152$, $p > 0.1$). In all subsequent analyses, the data were collapsed across these two sessions.

Lesions of the nucleus accumbens core alter rewarded task-switching performance

Sham surgeries (i.e. pre-surgery test vs. post-surgery tests) had no effect on rewarded task-switching performance. Surgery did not significantly affect performance in the sham group (surgery x reward x switching x accuracy: $F(1,11) = 2.806$, $p > 0.1$), thus across all sessions, task-switching performance in the sham group improved in the high- compared with low

reward condition (reward x task switching x accuracy: $F(1,11) = 7.651$, $p = 0.018$, $\eta 2 = 0.410$; **figure 6.4**). In addition, sham surgeries did not affect overall accuracy (surgery x accuracy: $F(1,11) < 1$; main effect of accuracy: $F(1,11) = 4.997$, $p = 0.047$, $\eta 2 = 0.312$).

Surgeries in the group with lesions of the AcbC on the other hand, did affect rewarded task-switching performance (surgery x reward x task switching x accuracy: $F(1,11) = 6.782$, $p = 0.025$, $\eta 2 = 0.381$; **figure 6.4**), without affecting overall performance (surgery x accuracy: $F(1,11) < 1$; main effect of accuracy: $F(1,11) = 13.189$, $p = 0.004$, $\eta 2 = 0.545$). More specifically, prior to surgery, the task-switching performance improved in the high compared with a low reward context (reward x task switching x accuracy: $F(1,11) = 4.850$, $p = 0.05$, $\eta 2 = 0.306$), while this pattern was reversed after lesions of the core (reward x task switching x accuracy: $F(1,11) = 6.133$, $p = 0.031$, $\eta 2 = 0.358$). The reversal of the effect was characterized by improved task-switching performance on low reward trials after surgery ($F(1,11) = 6.788$, $p = 0.024$, $\eta 2 = 0.382$), in combination with a numerical impairment on task-switching performance during high reward trials ($F(1,11) = 3.229$, $p = 0.1$, $\eta 2 = 0.227$). This effect was confirmed by directly comparing the groups, showing a difference between the sham and lesion group after surgery (group x reward x switch x accuracy: $F(1,22) = 8.099$, $p = 0.009$, $\eta 2 = 0.269$), which was not present before surgery (group x reward x switch x accuracy: $F(1,22) < 1$; group x accuracy ($F(1,22) < 1$). This difference was due to a relative task-switch improvement in the lesion group in the low reward context ($F(1,22) = 7.492$, $p = 0.012$, $\eta 2 = 0.254$), and a numerical impairment in this group in task-switching performance in the high reward context ($F(1,22) = 1.188$, $p > 0.1$), compared with the sham group.

In summary, prior to surgery, task-switching performance was overall better in the high, compared with low reward context. Sham surgeries did not affect this beneficial effect of a high reward context on task-switching performance, whereas lesions of the AcbC did. Importantly, lesions of the AcbC did not affect overall accuracy on test, or performance during discrimination training.

Discussion

The current study assessed whether the core of the nucleus accumbens plays a crucial role in exerting motivational control over behaviour, thereby facilitating an agent to effectively pursue goals. Using a paradigm in rodents that parallels a well-established paradigm in human subjects (Aarts et al., 2010; van Holstein et al., 2011; Aarts et al., 2014a; Aarts et al., 2015), (and see Etzel et al., 2015; Fuentes-Claramonte et al., 2015) we showed that animals were able to use cues to prepare for an upcoming change in cognitive demands and that this task-switching ability was improved in a high reward context. This ability to improve cognitive control in a high-reward situation changed after excitotoxic lesions of the AcbC. More specifically, animals with an intact AcbC exhibited better cognitive control in a high relative to a low reward situation, whereas this effect was reversed after lesions of the AcbC.

The reversal of this effect was characterized in particular by improved task-switching

performance in the low reward condition, in combination with marginally impaired task-switching performance in the high reward context in animals without an intact AcbC. Importantly, lesions of the AcbC did not impair flexible control per se (i.e. lesions did not affect accuracy on the task-switching paradigm). This finding fits remarkably well with previous studies, although none assessed directly whether manipulating the amount of reward earned when executing an appropriate action alters cognitive control. Classical learning paradigms

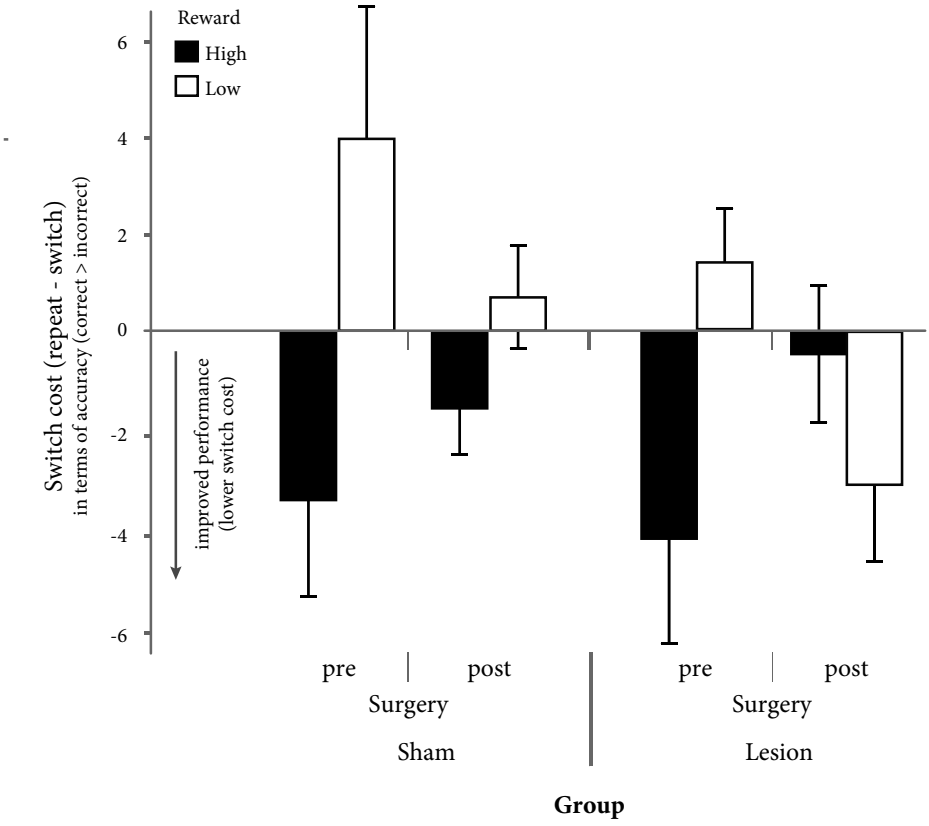


Figure 6.4 | Performance (accuracy) in terms of switch cost (repeat – switch)
We observed no effect of sham surgery on overall or rewarded task-switching performance, while an effect of surgery on rewarded task-switching performance was observed in the group with lesions of the accumbens core, without affecting overall accuracy. Error bars represent standard errors of the difference.

have established a role for the AcbC in helping animals to choose the best action based on prospective rewards. Disrupted functioning of the AcbC in these studies generally reduces the facilitation of appropriate responses, for example assessed with general Pavlovian to instrumental transfer (g-PIT) or cue-induced reinstatement (Floresco et al., 2008b; Corbit and Balleine, 2011). In a PIT procedure, animals receive instrumental- (learning to press a lever to obtain a food reward) and Pavlovian conditioning (learning that a cue predicts the delivery of an outcome), followed by a test on which the Pavlovian stimulus (CS) is delivered with the levers present. The presence of a CS increases lever pressing, i.e. the association between a cue and a reward facilitates instrumental performance, but only in animals with an intact AcbC (Corbit and Balleine, 2011). In addition to this general enhancement of reward-related cues, Pavlovian cues can also selectively increase performance on the basis of the specific outcome predicted by the cue. Animals with lesions of the AcbC are still able to show this specific PIT effect. In the current study, optimal behaviour would entail the facilitation of flexible control in the high reward context over the low reward context. This facilitation of flexible control under high reward was impaired after lesions of the AcbC. Also, lesions of the AcbC are known to reduce the inhibition of inappropriate actions, during outcome devaluation (Shiflett and Balleine, 2010) (Corbit et al., 2001), (but see de Borchgrave et al., 2002). After instrumental training on two levers which deliver two distinct outcomes, the value of one of the outcomes is reduced (e.g. by allowing animals to consume one of the outcomes freely). During a subsequent test, animals with an intact AcbC reduce responding to the lever which previously delivered the devalued outcome. After lesions of the AcbC however, animals no longer show this inhibition. In the current study, the suboptimal strategy would be to maximize cognitive control in the low reward context over the high reward context. In line with a role for the AcbC in the inhibition of inappropriate behaviour, we observed that animals with lesions of the AcbC exhibited more cognitive control in the low reward context than did animals with sham lesions. Combined, these results suggest that the AcbC is necessary to facilitate appropriate responses (e.g. when a CS predicts a reward) and to inhibit irrelevant responses (e.g. when the outcome is undesirable).

Another field of research suggesting a role for the AcbC in facilitating and suppressing goals shows that animals without an intact AcbC are impaired when facing a situation that requires a shift in strategy (Floresco et al., 2006a). However, this deficit was clearly distinct from set-shifting deficits typically observed after lesions of cognitive control areas, such as the dorsomedial striatum (DMS) or the prelimbic cortex (PL). Animals with lesions in the DS and PL generally fail to make the initial shift (i.e. they persevere on the old rule (Ragozzino et al., 2002; Ragozzino, 2007). After lesions of the AcbC on the other hand, animals show no deficit on the initial switch. Instead, their deficit is characterized by an inability to eliminate irrelevant responses after they initially switch, i.e. animals occasionally go back to the previously correct (i.e. now incorrect) response. These studies fit well with a role for the AcbC in orienting behaviour to optimize cognitive control in order to obtain rewards (Floresco et al., 2006a). A failure to optimize cognitive control may result in inefficient facilitation of control in a low

reward context, and the failure to allocate more control in a high than low reward context. We demonstrate, for the first time, that reward plays a crucial role in this process, by showing that manipulating the size of a reward can alter cognitive control in rodents, and that the AcbC is crucial for maintaining the balance between suppressing irrelevant and facilitating relevant goals.

Although not directly tested in the current study, we would like to elaborate on a potential neural circuitry by which information about rewards can modulate cognitive and action goals. Such a mechanism should allow information from the AcbC about which goals to pursuit, to be conveyed to cognitive-control regions involved in flexible control i.e. the DMS (Ragozzino, 2007). Previous work in human subjects has revealed that reward motivation can enhance task-related signalling in the human homologue of the rodent DMS (i.e. the caudate nucleus: (Aarts et al., 2010; Aarts et al., 2015). One mechanism perfectly suited to subserve this interaction is via spiralling striato-nigro-striatal connections (Haber et al., 2000). These dopaminergic midbrain connections allow information in the AcbC to be conveyed to more dorsal regions of the striatum involved in goal-directed control (i.e. DMS) and actions and habits (i.e. the dorsolateral striatum; DLS) (Balleine and O'Doherty, 2010). A functional role for these connections has been shown previously by exploiting the knowledge that the AcbC is involved in the acquisition of drug seeking, but that drug seeking is mediated by the DLS after prolonged training (Belin and Everitt, 2008). Using an elegant design, these authors showed that disconnecting the AcbC from the DLS impairs the transition to habits. Importantly, in one hemisphere the AcbC remained intact (but its connection with the DLS was disrupted), while in the other hemisphere the DLS was intact (but its dopaminergic input from the AcbC was disrupted). Future work will have to reveal whether input from the AcbC to the DMS, or signalling in the AcbC itself, is crucial for optimal motivation-cognition integration.

Using the rewarded task-switching paradigm in humans, we repeatedly observed dopamine-dependent effects on behaviour and striatal responses (e.g. Aarts et al., 2010; Aarts et al., 2015). In addition, we showed that a dopamine D2 receptor agonist did not alter behavioral integration of reward and task-switching, but that it did modulate task-switching performance (irrespective of reward) (van Holstein et al., 2011). It is possible that dopamine D1 receptor stimulation is modulating the effect of reward on task switching, also given the role for dopamine D1 receptor stimulation in reward processing (Ikemoto et al., 1997; Meririnne et al., 2001). Future work in rodents should test this, as D1 specific agents are not available for research in human subjects.

Our previous observation that dopamine D2 receptor stimulation modulates flexible cognitive control is well in line with set-shifting work in rodents (Floresco et al., 2006b). However, when comparing these task- switching and set- shifting studies, it is important to keep in mind that they are conceptually different and that different neural systems may underlie these processes. One important distinction to keep in mind is that the task-switching paradigm requires the alternation between well-established task-sets, in which the striatum is involved (Cools et al.,

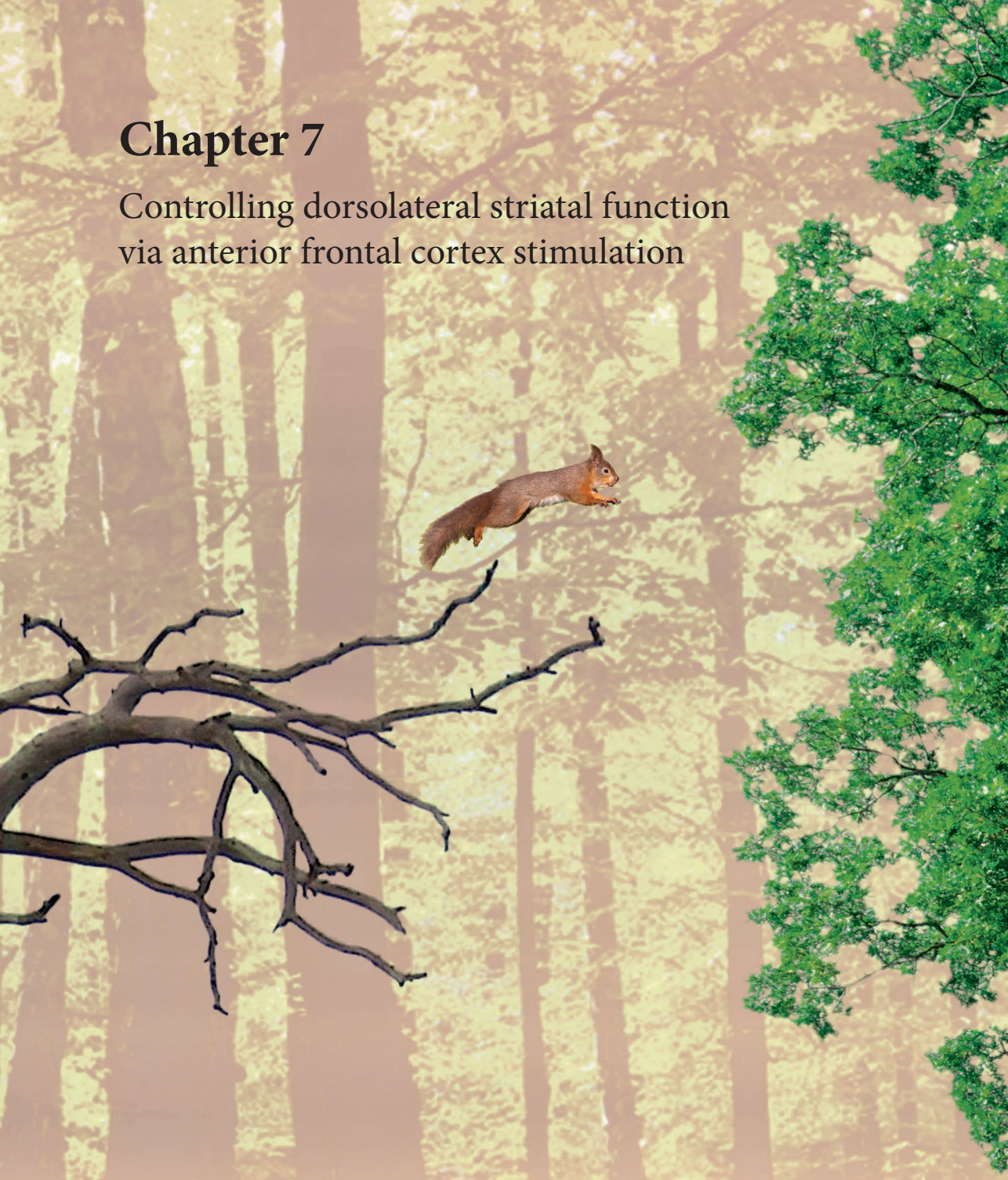
2001a) whereas prefrontal regions and prefrontal dopamine D2 receptor stimulation plays a more prominent role in ED shifting (Floresco et al., 2006b; Robbins, 2007). Future work will need to elucidate the differences between the neural mechanisms underlying these different forms of behavioral flexibility.

This study was not without limitations and future work should aim to address these. Although the current design parallels the paradigm we use in our work with human subjects, a number of differences between the rodent and human version should be noted. First, in human subjects we manipulated the amount of reward on a trial-by-trial basis (Aarts et al., 2010), instead of in blocks, as is done in the rodent version. However, blocked designs have been proven effective in revealing reward-related effects on cognition in studies with human subjects (Kouneiher et al., 2009; Jimura et al., 2010). Second, the paradigm in humans presents a large number of trials in a fast succession. It is well documented that increased preparation times reduce the switch cost (Monsell, 2003). The current experimental design was based on previous work in which conflict adaptation was successfully achieved in rodents (Haddon and Killcross, 2006), and a first step was to expand this to the task-switching domain. The long presentation of task cues in the current paradigm may explain the absence of a main effect of task-switching in the current study. An obvious next step would be to see if the trial duration can be reduced, by increasing the number of trials, reducing the duration of the task cues and/or training animals to perform one action per trial.

Nevertheless, we show for the first time that a complex, cue-driven task-switching task can translate across species from humans to rodents. Also, we provide the first direct, causal evidence that performance on this task relies on the AcbC, as we would expect from previous neuroimaging work in humans (Pessoa, 2009; Aarts et al., 2010). This novel paradigm provides important new opportunities for assessing the neural basis of a range of neuropsychiatric disorders which have been associated with deficits in the functioning of the AcbC and/or corticostriatal circuits (e.g. schizophrenia, attention deficit hyperactivity disorder, addiction and obsessive compulsive disorder (Graybiel and Rauch, 2000; Belin and Everitt, 2008; Shepherd, 2013; Aarts et al., 2015; Morris et al., 2015).

Chapter 7

Controlling dorsolateral striatal function via anterior frontal cortex stimulation



Based on: van Holstein M., Froboese M., O'Shea J., Aarts E., Cools R. (submitted) Controlling dorsolateral striatal function via anterior frontal cortex stimulation.

Abstract

Motivational, cognitive and action goals have been proposed to be processed by distinct corticostriatal circuits that are organized hierarchically. Reward motivation has been proposed to influence cognitive and motor processing via guiding information flow through an anterior/ventromedial to posterior/dorsolateral cascade of topographically specific regions of the striatum and frontal cortex. Here we tested this hypothesis in human volunteers by investigating effects of offline transcranial magnetic stimulation of distinct frontal regions associated with reward, cognition and action processing, on task-related signaling in distinct regions of the striatum. Immediately after stimulation of the anterior prefrontal cortex (aPFC), the dorsolateral prefrontal cortex, or the premotor cortex, participants performed an established paradigm assessing reward anticipation (motivation), task switching (cognition), response switching (action) and their integration, while neural responses were measured with functional magnetic resonance imaging (fMRI). Stimulation of the aPFC, and not of the other cortical regions, decreased reward-related processing in the caudate nucleus, while it decreased processing in the putamen during the interaction of reward, task switching and response switching. Thus stimulation of the aPFC altered processing in distinct regions of the striatum as a function of task demands, providing evidence for a functional cascade of processing across corticostriatal circuits via the striatum.

Introduction

The ability to adapt flexibly to our constantly changing environment requires our actions to be goal-directed, and goals to be hierarchically organized (Koechlin and Summerfield, 2007). Accordingly, when defining goals at different levels, we can distinguish between motivational goals (e.g. a reward), cognitive goals (e.g. a task-set), and action goals (e.g. a stimulus-response mapping). Reward-predictive signals engage cognitive control processes that implement and update abstract cognitive goal representations, which in turn direct action selection. Thus flexible behavior depends on a hierarchy of top-down selection processes, and requires the transformation of information about reward into abstract cognitive decisions, which in turn need to be translated into specific actions. The brain region most commonly implicated in such flexible, goal-directed behavior is the frontal cortex (Miller and Cohen, 2001; Clark et al., 2004; Jimura et al., 2010). However, the cortex does not act in isolation and is connected with subcortical regions, such as the striatum, which is also involved in (reward-guided) cognitive- and motor control (Eslinger and Grattan, 1993; Groenewegen, 2003; Cools, 2011).

Studies combining non-invasive brain stimulation (i.e. transcranial magnetic stimulation; TMS) with brain imaging have shown that stimulation of the frontal cortex can alter signaling in the striatum (Strafella et al., 2001; Strafella et al., 2003; Kanno et al., 2004; Ko et al., 2008; van Schouwenburg et al., 2012). More specifically, stimulating the human motor cortex altered signaling in the motor part of the striatum (i.e. the putamen) (Strafella et al., 2003), whereas stimulating the dorsolateral prefrontal cortex (dlPFC) altered signaling in the cognitive part of the striatum (i.e. the caudate nucleus) (Strafella et al., 2001; Ko et al., 2008). These observations are in line with evidence from anatomical work showing that the cortex and striatum are organized in parallel circuits, linking distinct parts of the cortex with specific regions of the striatum in a topographically and functionally specific way (Alexander et al., 1986).

More recent anatomical work has challenged the idea that the corticostriatal circuits are strictly parallel (Haber et al., 2000; Haber et al., 2006; Draganski et al., 2008; Haber and Knutson, 2010) and several researchers have shown that there is a unidirectional information flow between corticostriatal circuits, i.e. from anterior/ventromedial to posterior/dorsolateral parts of the striatum and/or cortex (Haber et al., 2000; Haber, 2003; Koechlin and Summerfield, 2007; Haber and Knutson, 2010; Badre and Frank, 2012). Such a cascade of information processing might be well suited to subserve integration across the distinct functional domains associated with different frontostriatal circuits. Thus reward motivational processing, associated with a circuit connecting the anterior/ventral prefrontal cortex with the nucleus accumbens and anterior caudate nucleus, might influence cognitive control, by altering processing in a circuit connecting the dlPFC and medial caudate nucleus, to ultimately guide action selection, by altering processing in circuits connecting motor cortices (e.g. the premotor cortex; PMC) and the putamen (**figure 7.1**) (Cromwell and Schultz, 2003; Draganski et al., 2008; Seger, 2008; Haber and Knutson, 2010).

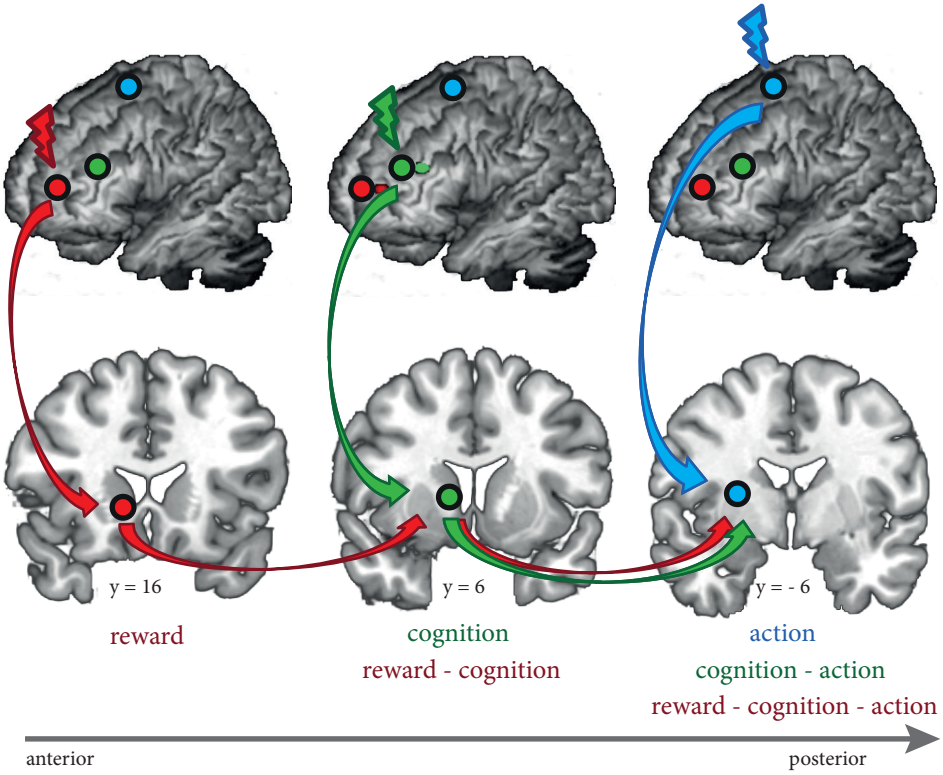


Figure 7.1 Hypothesized interactions between corticostriatal circuits
The red, green and blue vertical arrows between the cortical regions and the subparts of the striatum indicate connections between parts of the frontal cortex involved in reward anticipation (motivation, in red), task switching (cognition, in green) and response switching (action, in blue) and distinct regions in the striatum. The additional arrows in the lower panel indicate directional information flow between circuits, for example, from the reward circuit to the cognitive, and subsequently the action circuit (red arrows). Stimulation with cTBS over the aPFC, dlPFC and PMC is indicated by the red, green and blue thunderbolts, respectively. It is important to note that the arrows between the striatal regions indicate information flow and do not reflect anatomical connections.

We aimed to investigate this functionally cascading architecture in humans by assessing the consequences of manipulating distinct prefrontal regions for reward motivation, cognition and action and associated signaling in distinct striatal subregions. To this end we used offline inhibitory TMS, (continuous theta burst stimulation; cTBS) (Huang et al., 2005), aiming to decrease neural signaling in three corticostriatal circuits (Ko et al., 2008; Volman et al., 2011; Wischnewski and Schutter, 2015), combined with fMRI to measure the impact of stimulation on task evoked activity in the striatum. Task-related processing was assessed using an established paradigm that we have used extensively to investigate reward anticipation, task switching and the effect of reward on task switching (Aarts et al., 2010; van Holstein et al., 2011; Aarts et al., 2014a; Aarts et al., 2015). The cortical stimulation sites were selected

based on the main effect of reward anticipation (motivation), task switching (cognition) and response switching (action) in an independent dataset that used the same paradigm (Aarts et al., 2010 unpublished observations). Hence, a region in the anterior prefrontal cortex (aPFC) was selected as a target for modulating the reward circuit, a region in the dlPFC as the target for the task-switching circuit, and a region in the PMC to target the response switching circuit. These three cortical sites were stimulated on three separate days, using a counterbalanced within-subject crossover design, to directly compare effects on task-related processing between and within circuitries.

Based on *in vivo* evidence about the topography of striatal connectivity from diffusion weighted imaging work (Draganski et al., 2008), we predicted that cTBS over the aPFC would attenuate the main effect of reward on BOLD signals in the anterior/ventral caudate nucleus, i.e. the main striatal target of the aPFC. In addition, we hypothesized that cTBS over the aPFC would influence reward-related task-switching signals in the posterior caudate nucleus, via connections between the motivational and cognitive striatum (**figure 7.1**), and that cTBS over the aPFC would influence the integration of reward, task switching and response switching in the putamen via connections between the motivational, cognitive, and motor striatum (**figure 7.1**). Stimulation over the dlPFC was predicted to attenuate BOLD signal in the posterior caudate nucleus during task switching. This effect should propagate to the putamen, via connections between the cognitive and motor striatum during the integration of task switching and response switching (**figure 7.1**). Finally, cTBS over the PMC was predicted to attenuate BOLD signals in the putamen during response switching. The goal of this experiment was to provide evidence for interactions between the different corticostriatal circuits, as well as for the directionality of these interactions, as has been shown in non-human primates (Haber et al., 2000).

Methods

Participants

Forty-two healthy participants were recruited to take part in the initial 'intake' session (**experimental design and procedures**). Eleven participants were excluded: Six participants did not tolerate the prefrontal stimulation well (**experimental design and procedures**), two did not feel comfortable during the TMS, one brain abnormality was revealed during intake, and for two participants no reliable motor evoked potential (MEP) measure could be obtained. The remaining 31 participants proceeded to the main experiment (**experimental design and procedures**). During the experimental sessions, one participant was excluded due to a contra-indication for MRI, one participants' session was discontinued due to dizziness during MRI, and one participant was excluded due to technical TMS problems and one participant due to technical MRI problems.

This resulted in 27 participants, ranging from 18 – 25 (mean 21.7, SD 1.95) years old (14

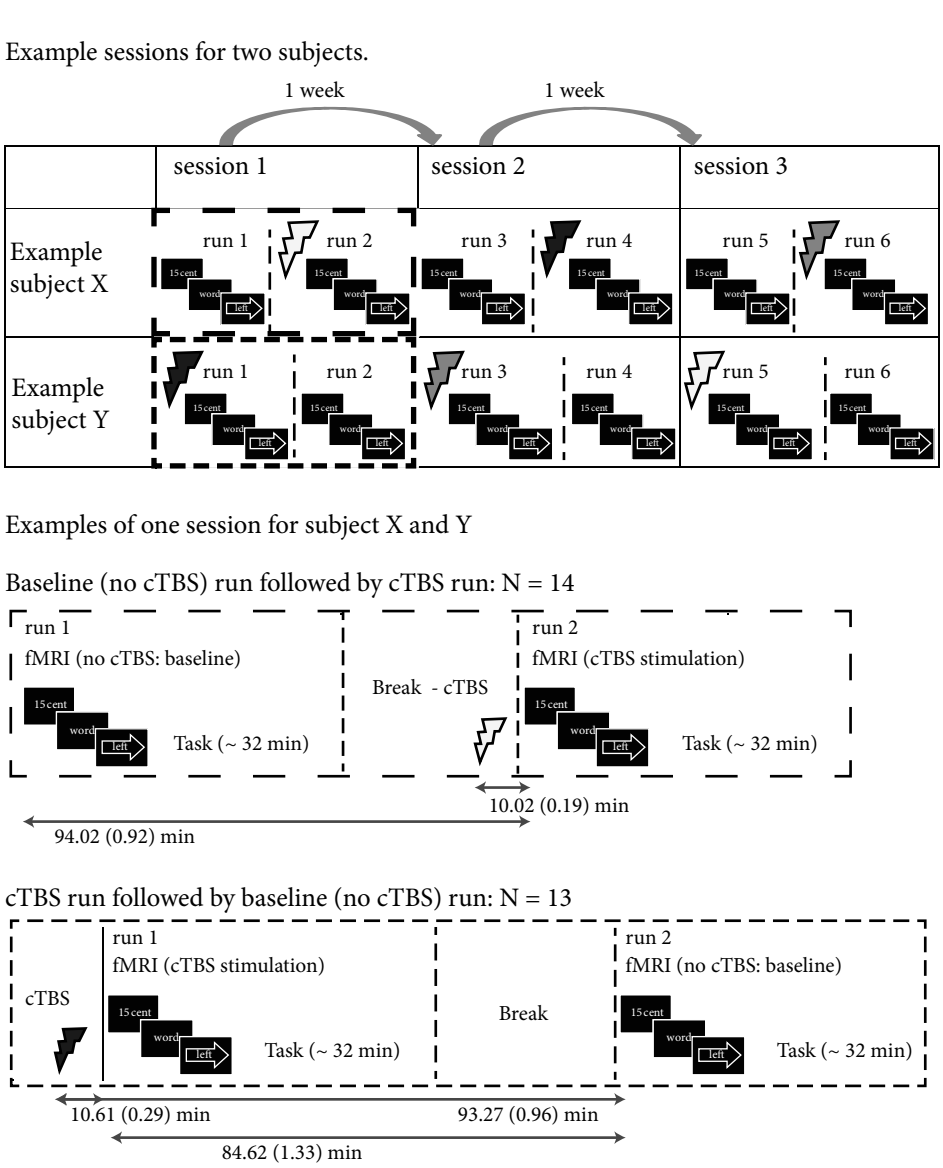


Figure 7.2 Experimental design

A: Across experimental sessions, each participant received stimulation of the anterior prefrontal cortex, dorsolateral PFC, and premotor cortex. The order was counterbalanced between participants (indicated with black, grey and white thunderbolts). Stimulation site order was counterbalanced across participants. Vertical dashed lines indicate a break.

B: The order (stimulation and baseline condition) in which a participant would *always* perform the tasks (**figure 7.3**) was counterbalanced between participants. Values represent mean (SD) time in minutes (min) between the start of two runs and between cTBS administration and the start of the subsequent fMRI session. In addition, in the bottom panel the mean time (across participants and sessions) between cTBS and the start of the baseline session is specified. cTBS: continuous theta burst stimulation; transcranial magnetic stimulation (TMS).

men) who completed all sessions. All participants had normal or corrected-to-normal vision, were right-handed and pre-screened for claustrophobia, psychiatric, neurological, and vascular disorders, drug and medication use, alcohol consumption and smoking behavior, as well as any contraindications for TMS and MRI. Participants gave written informed consent according to the guidelines of the local ethics committee on research involving human participants (CMO Arnhem / Nijmegen: 2011/244). They received course credits or payment for their participation.

Experimental design and procedures

All sessions took place at the Donders Centre for Cognitive Neuroimaging in Nijmegen, The Netherlands. The experiment consisted of four visits to the center: one 'intake' session and three experimental sessions. The intake session consisted of three parts: MRI, questionnaires and TMS. During the MRI part, participants were introduced to the paradigm and completed two practice blocks (**paradigm, figure 7.3, box 2.3**). A third practice block was completed in the scanner during the acquisition of a structural scan (**MRI acquisition**). Finally, we determined the active motor threshold (aMT) and participants were familiarized with the sensation of cTBS in order to ensure tolerability of cTBS over the stimulation sites (TMS procedure). After successful completion of the intake session, three experimental sessions followed. During each experimental session, participants performed the paradigms twice in the fMRI environment (i.e. they completed two runs in each session). These sessions were separated by one week and for each participant the variation in start time between these three sessions was never more than one hour. To account for nonspecific effects related to the day rather than to TMS, the task was administered twice during each session: once after TMS (stimulation), where the mean time between the start of cTBS and the task was 10.31 minutes (SE: 0.18) (**figure 7.2b**) and once without the prior influence of TMS (baseline). Finally, to control for order effects, 14 participants first performed the baseline fMRI run, followed by TMS and another fMRI run (stimulation fMRI; **top panel figure 7.2b**), whereas the remaining 13 participants started with TMS and fMRI, followed by a 30 minute break and another fMRI run (baseline fMRI) to allow for the TMS effects to wear off. Previous work has shown that effects of cTBS over the motor cortex on MEP amplitudes last up to 50 minutes after stimulation, but are no longer present after 60 minutes (Huang et al., 2005; Wischnewski and Schutter, 2015). In the current study, approximately 93 minutes (**bottom panel figure 7.2b**) passed between the administration of cTBS and the start of the baseline task. The time between two runs in a session and between TMS and the start of the task did not vary as a function of stimulation site (all F's < 1.17, all p's > 0.3).

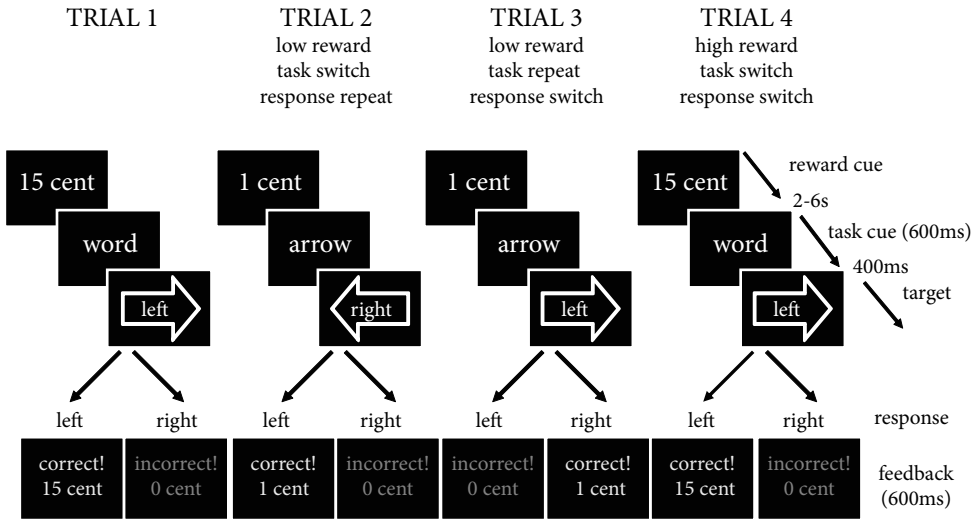


Figure 7.3 Task and response switching paradigm with reward manipulation
Participants had to respond to response-incongruent arrow-word combinations (targets) with a left or right button press, either by responding to the direction indicated by the arrow (i.e. <- or ->) or to the direction indicated by the word (i.e. 'left' or 'right'). A task cue preceding the target (by 400ms) indicated which task (arrow or word) the participant had to respond to on the current trial. Which task was performed on a particular trial could either change unpredictably with respect to the preceding trial (i.e. task switch trial; e.g. arrow – word as in trial 4, or word - arrow as in trial 2) or remain the same (i.e. task repeat trial; arrow-arrow (trial 3), or word-word). In addition to such task switches, the paradigm allowed us to look at response switches, i.e. whether the correct response (left or right button), remained the same compared with the previous trial, or switched. In the current version of the paradigm we made sure that the task switches occurred independently from response switches; half of the task-switch trials and half of the task-repeat trials required a switch of the response button (e.g. trial 4 and 3 respectively, whereas the other half of the trials required a response repetition (e.g. trial 2). In addition we manipulated the amount of anticipated reward (€0.01 vs. €0.15) on a trial-by-trial basis by means of a reward anticipation cue. At the start of each trial this reward cue indicated the amount of reward on that trial, contingent on a correct and sufficiently fast button press. Immediately following the response, feedback was given (e.g., "correct! 15 cents") (see also Aarts et al., 2015). The inter-trial-interval varied (jitter of 2 – 6 seconds).

Paradigm

Participants performed a task-switching paradigm with a reward manipulation that has been extensively described elsewhere (Aarts et al., 2015), with minor changes to include a response-switching component. Details of the task are described in the legend of (**figure 7.3, box 2.3**).

At the start of each session, participants practiced the task (**figure 7.3**). The first practice block (24 trials), which was only administered during the intake session, was merely a switching task. During this block the task (i.e. whether to respond to the arrow or the word) alternated unpredictably from trial to trial (**figure 7.3**) without any reward cues, and the feedback on

each trial was either "correct" or "incorrect". During the intake session and on arrival each experimental day, participants completed a second practice block that was exactly the same as the task used in the actual paradigm, only shorter (i.e. 24 trials). Finally, a block (32 trials) without reward or feedback was administered in the scanner right before the actual task (as well as during the intake session). The average response times on four trial types (arrow/word * task-switch/task-repeat) were used to determine each individual's response window. These response deadlines were used to account for inter-individual and inter-session differences in response speed and subsequent task difficulty.

The paradigm consisted of 160 trials and lasted ~35 minutes with a 30s break every 32 trials. In the breaks and at the end of each run (i.e. after 160 trials) the cumulative amount of money the participant earned was displayed on the screen, (max. €12.80). Participants were informed in advance that we would keep track of the total amount of money on each of the six runs and that their earnings on one run would be added to their financial compensation as a bonus. At the end of the final experimental session, the participant rolled a dice to determine which run's earnings was added as a bonus.

Behavioral analysis

Behavioral analyses were performed on the response times (RTs) and error rates. The first trial of each block, trials with extremely fast responses (<100ms) and trials on which participants failed to respond were excluded from analyses. In addition, trials on which the response was incorrect were excluded from RT analyses. Results were analyzed using a repeated measures ANOVA with the factors TMS condition (stimulation or baseline), Reward (high or low), Task-Switching (switch or repeat) and Response Switching (switch or repeat) for each stimulation site (aPFC, dlPFC, PMC). We transformed the response times (log) and proportions of error (arcsine($\sqrt{x}$)) to improve the distribution of the data (4 out of 48 RT variables: Shapiro-Wilk $p < 0.023$; 14 out of 48 error rate variable: Shapiro-Wilk $p < 0.039$).

TMS procedure

Stimulation sites

The stimulation sites for the motivation, cognition and action network were determined by assessing the peak activations in the frontal cortex in an independent study using the same paradigm (Aarts et al., 2010 unpublished observations). A region in the anterior PFC (aPFC; -30, 60, 8, Brodmann area 10, **figure 7.4a** red circle) was identified as part of the reward network (high reward cue > low reward cue); a region in the dlPFC (-36,36, 20, Brodmann area 46, **Figure 7.4a** green circle) was identified as part of the cognitive network (task switch > task repeat); and a region in the PMC (-28, 10, 66, Brodmann area 6, **7.4a**, blue circle) was identified as part of the action network (response switch > response repeat).

Each participant's structural scan was coregistered to the standard SPM8 T1 template (Montréal Neurological Institute; MNI) and segmented using a unified segmentation

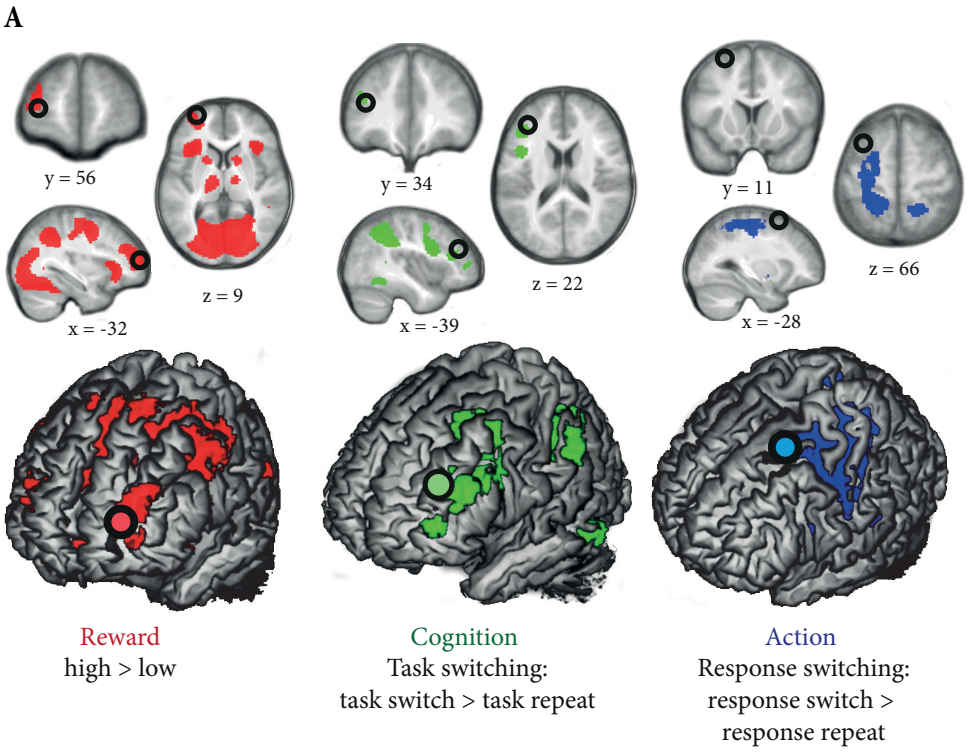

A
y = 56
z = 9
x = -32
y = 34
z = 22
x = -39
y = 11
z = 66
x = -28
Reward
high > low
Cognition
Task switching:
task switch > task repeat
Action
Response switching:
response switch >
response repeat
B
y = 10
y = 5
y = 0
y = -10
z = 15
z = 20
z = 30
z = 35

Figure 7.4 Main effects across sessions

A: Left: The main effect of Reward anticipation (high > low; red); middle: Task switching (switch > repeat; green) and right: Response switching (switch > repeat; blue) at a threshold of t = 3.14 (PUNC < 0.001). Circles with black outline indicate the stimulation sites for the anterior prefrontal cortex (left), dorsolateral prefrontal cortex (middle) and premotor cortex (right). The rendered images show regions with a search depth of 4mm.

B: For illustration purposes and to visualize the relative location of the main effects, the figure depicts the overlay of the main effects of Reward anticipation (red), Task switching (green), and Response switching (blue) at a low threshold ($t > 1.28$, $p < 0.1$) for coronal slices (top row: anterior to posterior) and axial slices (bottom row: ventral to dorsal).

procedure (Ashburner and Friston, 2005). This procedure resulted in a set of inverse parameters allowing the conversion of the stimulation targets in MNI space to subject space.

TMS

During the experimental sessions, a cTBS protocol was employed that was the same as that reported by Huang and colleagues (2005). These authors applied cTBS at 80% of the aMT and reported a depression of MEP amplitudes over a subsequent period up to 60 minutes (see also Volman et al., 2011; Wischnewski and Schutter, 2015).

TMS pulses (biphasic) were administered through a figure-eight coil (75mm diameter), connected to a MagPro X100 stimulator (Mag Venture, Denmark). Mean MNI coordinates for the three cortical stimulation sites were projected onto each individual's structural scan using a frameless stereotactic neuronavigation system (Localite, Sankt Augustin, Germany). We used standard electromyogram (EMG) recordings to visualize MEPs from the first dorsal interosseous (FDI) muscle of the right hand and to determine the resting MT (rMT), using a standard protocol (Schutter and van Honk, 2006; Volman et al., 2011). During the determination of the aMT, participants rested their right hand on a pillow while squeezing a small roll of tape with a pincer grip at 20% of their maximum strength, contracting their FDI muscle continuously. The aMT was defined as the lowest stimulation intensity over the contralateral motor cortex that elicited reproducible MEPs (in at least 5 out of 10 successive stimulations). The aMT was 24%-37% (mean 30.44%, SD 3.61) of the maximum stimulator output.

During the experimental sessions, a cTBS protocol (bursts of three 50 Hz pulses every 200 ms for 40s, i.e. a total of 600 pulses) was administered at 80% of the aMT. The TMS coil was placed as close to the target location (i.e. the aPFC, dlPFC or PMC) as possible using the Localite software. During the intake session, participants received the exact same protocol for 10 instead of 40 seconds over each of the three stimulation sites to acquaint them with the sensation of cTBS.

MRI acquisition

MRI images were acquired on a 3-Tesla MRI system (Magnetom Trio Tim; Siemens Medical Systems, Erlangen, Germany), using a 32-channel head coil. High-resolution T1-weighted MP-RAGE anatomical images were acquired during the intake session (GRAPPA acceleration factor 2; repetition time 2300 ms; echo time 3.03ms; field of view: 256 mm; voxel size 1 mm3). In order to obtain a good signal-to-noise ratio for brain areas susceptible to dropout, functional images were acquired using a T2*-weighted multi-echo gradient-echo planar sequence (repetition time: 2090 ms; echo times for 4 echoes: 9.4, 21.2, 33, 45 ms; flip angle: 90º; 32 ascending slices; 0.5 mm slice gap; voxel size 3.5 x 3.5 x 3 mm) (Poser et al., 2006). In addition, following each task-related fMRI acquisition, we acquired 266 resting state scans (data not reported).

Preprocessing of task-related fMRI data

All data were analyzed using SPM 8 (Statistical Parametric Mapping; Wellcome Department London, UK, http://www.fil.ion.ucl.ac.uk/spm). Prior to standard preprocessing, realignment was performed using the estimated head motion parameters (least-squares approach, 6 parameters) for the images with the shortest echo, which were applied to echo images for each excitation. The images of all sessions were aligned to the shortest echo of each session, and to the first session. After spatial realignment, the four echo images were combined using echo summation. The combined images were slice-time corrected to the middle slice and segmented using a unified segmentation procedure (Ashburner and Friston, 2005). The bias corrected T1 image was coregistered to the mean functional image and the transformation matrix from the segmentation procedure was used for normalization to a standard template (MNI). Normalized images were smoothed using an 8 mm full-width half maximum kernel. A study– specific T1 template was generated from an average of all co-registered and normalized T1 images to display the results, using MRIcron software.

Statistical analysis of fMRI data

The preprocessed fMRI time series were analyzed at the first level using one general linear model (GLM) for each participant, including all sessions. For each session, the following 26 task-related regressors were modeled at the onset of the stimulus (duration = 0) convolved with a canonical hemodynamic response function: Reward cues (high/low), Targets [reward (high/low) x Cue (arrow/word) x Task (switch/repeat) x Response (switch/repeat)], feedback (correct low/correct high/incorrect/too late); we additionally modeled the breaks (duration = 30s), the first trial of each block and response omissions. To account for residual head motion,

Table 7.1 Main effect of Reward anticipation

	Peak MNI coordinate			Statistic		
	x	y	z	t-value	p-value: peak	cluster size
Reward (high > low)						
Frontal lobe						
SFG/ MFG (B10) ^{S}	-32	50	18	6.15	$P_{FWE} < 0.001$	977
SFG: SMA (B6) ^{BI}, dACC (B32) ^{BI}	-8	4	60	8.79	$P_{FWE} < 0.001$	7318
Subcortical						
Striatum ^{BI}: caudate nucleus *	10	10	0	8.11	$P_{FWE} < 0.001$	4543
Thalamus	24	-24	4	4.92	$P_{FWE} = 0.043$	50
Occipital lobe						
Lingual gyrus (B17) ^{BI}	-12	-94	-4	16.18	$P_{FWE} < 0.001$	213500
Parietal lobe						
Posterior cingulate cortex ^{BI} (B23)	-4	-30	26	5.47	$P_{FWE} = 0.005$	538
Reward (low > high)						
Frontal lobe						
IFG (B10)	46	40	2	5.22	$P_{FWE} = 0.013$	555
MFG: OFC (B11)	-40	36	-12	5.2	$P_{FWE} = 0.015$	403
MFG (B9)	32	32	48	5.07	$P_{FWE} = 0.025$	697

The table shows all areas that were significant at peak PFWE < 0.05.
* Cluster includes the caudate nucleus, putamen, nucleus accumbens, midbrain, thalamus, pallidum and extends into the insular cortex and IFG;
SMA = supplementary motor area, dACC = dorsal anterior cingulate cortex; OFC = orbitofrontal cortex; SFG: superior frontal gyrus; MFG: middle frontal gyrus; IFG: inferior frontal gyrus
BI = bilateral cluster; B = Brodmann area; s = cluster falls within the aPFC stimulation site.

Table 7.2 Main effect of Task switching

	Peak MNI coordinate			Statistic		
	x	y	z	t-value	p-value: peak	cluster size
Task switching (switch > repeat)						
Frontal lobe						
IFG (B9) [S]	-40	4	30	6.01	$P_{FWE} < 0.001$	1755
Parietal lobe						
Superior parietal lobule (B7)	-24	-66	20	8.72	$P_{FWE} < 0.001$	3760
Temporal lobe						
Inferior temporal gyrus	-48	-52	-12	6.84	$P_{FWE} < 0.001$	751

The table shows all areas that were significant at peak $P_{FWE} < 0.05$; IFG: Inferior frontal gyrus; PCC = posterior cingulate cortex; MD = medial dorsal nucleus; SMA = supplementary motor area; ACC = anterior cingulate cortex; dlPFC = dorsolateral prefrontal cortex; [BI] = bilateral cluster, B = Brodmann area. s = cluster falls within the dlPFC stimulation site

the six original head motion parameters (3 translation, 3 rotation), their first derivative and the square of the original and first derivative were included in the model, resulting in 24 motion nuisance regressors (Lund et al., 2005). In addition, we used the mean signal from the white matter and CSF to account for movement-related intensity changes (Verhagen et al., 2006). Finally, a high-pass filter (128s) was used to remove low-frequency signals (e.g. scanner drifts) and an AR(1) model was applied to adjust for serial correlations in the data. Microtime onsets were adjusted to account for the earlier mentioned slice time correction.

To assess the three main effects and the interaction effects, we generated, for each participant, a contrast image at the first level for the main effect of Reward (high > low reward cue), and, time-locked to the target, the main effect of Task switching (task switch > task repeat) and Response switching (response switch > response repeat). In addition, we generated contrast images for interactions between these factors (i.e. for the interaction between Reward and Task switching, between Task switching and Response switching and between Reward, Task switching and Response switching).

At the second level, the contrast images of each effect were subjected to a full factorial GLM, taking into account the three TMS sites (aPFC, dlPFC, PMC) and TMS administration (stimulation or baseline). First, we assessed the main effect of each component of the paradigm (i.e. Reward, Task switching and Response switching) across all six sessions. We assessed whether the task elicited a neural response at the stimulation site to assess whether

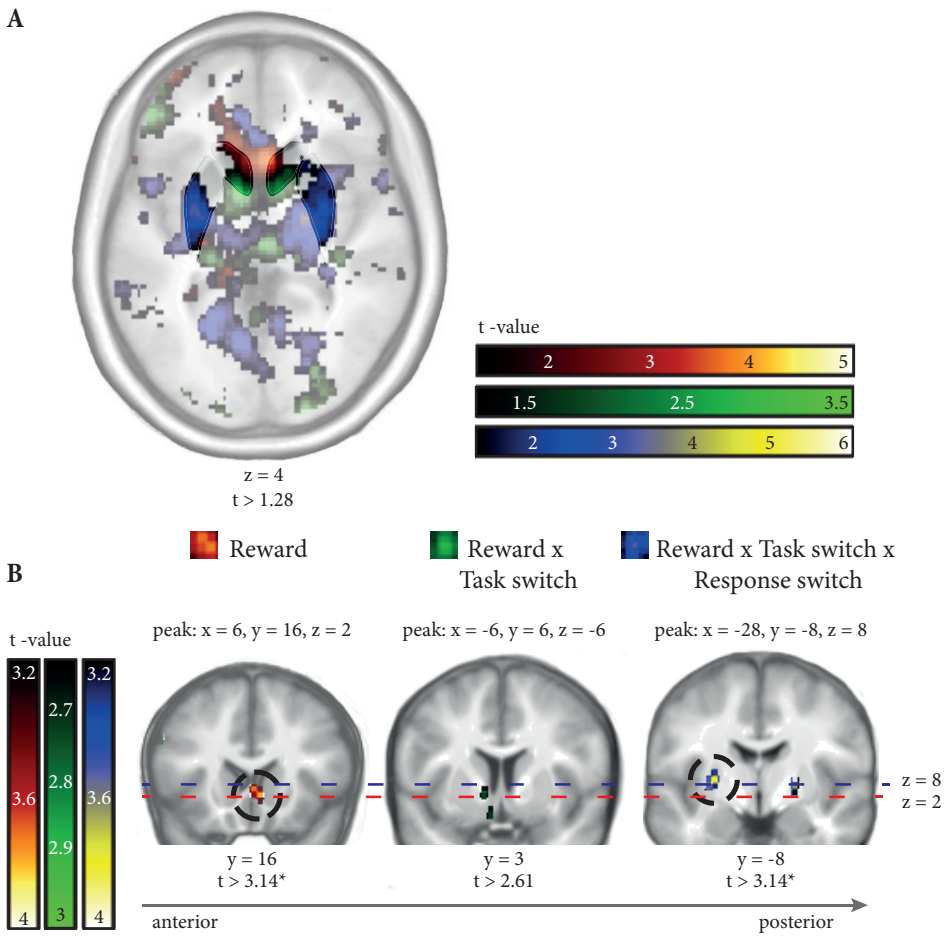


Figure 7.5 Effect of aPFC stimulation (versus baseline) for Reward (red), the interaction between Reward and Task switching (green), and between Reward, Task switching and Response switching (blue)

A: To visualize the gradients in the striatum, the whole-brain maps for these three contrasts are shown in one image at a low threshold ($t = 1.28$, $p < 0.1$). We applied a filter over the image to visualize the anterior-posterior and medial-lateral gradient in the striatum.

B: Whole-brain maps at PUNC < 0.001, $t > 3.14$ (left and right) and at PUNC < 0.005, $t > 2.61$ (middle) for Reward (left), Reward x Task switching (middle) and Reward x Task switching x Response switching (right).

Asterisks (*) and black dashed circles indicate a significant effect of Reward (left) and the Reward x Task switching x Response switching (right) (PFWE < 0.05 within the search volume, i.e. the caudate nucleus or putamen, respectively) and red and blue dashed lines indicate the z-coordinates for the peaks of these respective effects to visualize the ventral to dorsal gradient.

the targeted sites were involved in the task. To this end, we generated a region of interest by drawing a sphere of 8mm around the stimulation coordinate (**figure 7.4a**) and assessed effects of Reward in the aPFC site, effects of Task switching in the dlPFC site and effects of Response switching in the PMC site, using small volume corrections (SVC). In addition, we assessed the effects of Reward on Task switching, the effects of Task switching on Response switching and the three-way interaction between Reward, Task switching and Response switching across all sessions.

Next, we assessed whether stimulation of the aPFC, relative to baseline, (i.e. the contrast aPFCSTIM-BASE), changed Reward-related processing, the effect of Reward on Task switching and the interaction between Reward, Task switching and Response switching. For dlPFC stimulation, we assessed whether stimulation of the dlPFC, relative to baseline (i.e. the contrast dlPFCSTIM-BASE), changed the effect of Task switching and the interaction between Task switching and Response switching. Finally, we assessed whether stimulation of the PMC compared with baseline (i.e. the contrast PMCSTIM-BASE) altered Response switching.

Effects that survive a family wise error (FWE) correction (peak PFWE < 0.05) were considered as significant. We assessed effects at the whole-brain level, but with specific hypotheses regarding the striatum. Therefore we applied small volume corrections in the caudate nucleus or putamen: effects in the caudate nucleus were assessed for the integration of Reward, Task switching and the interaction between Reward and Task switching, but effects in the putamen were assessed for the main effect of Response switching and any interactions with Response switching (i.e. Reward x Task switching x Response switching and Task switching x Response switching). For any significant (PSVC_FWE < 0.05) effect in either of these regions (e.g. the caudate nucleus), we assessed regional specificity by testing for the same effect in the other region of the striatum (e.g. the putamen).

For visualization purposes, statistical maps are overlaid onto a study-specific template (see **preprocessing of task-related fMRI data**) displayed both at a low threshold to allow assessment of physiological plausibility ($t = 1.28$, $p < 0.1$) and at more stringent thresholds to determine statistical significance (e.g. $t = 3.14$, $p < 0.001$; **figure 7.4 and 7.5**).

Results

Neural effects

Main task effects irrespective of site and TMS revealed an anterior/ventrodorsal to posterior/dorsolateral activity gradient in the striatum

Comparing the neural signal during high versus low Reward cues revealed a large bilateral network of regions, including the striatum, lingual gyrus, thalamus, cingulate cortex and the aPFC, overlapping with the stimulation site (SVC aPFC stimulation site: (PSVC_FWE < 0.001) (**table 7.1, figure 7.4**).

During trials on which the task switched, compared with trials on which the task was repeated, a network including the inferior frontal gyrus, cingulate gyrus, superior parietal lobe, and inferior temporal gyrus was activated (**table 7.2**), overlapping with the stimulation site (dlPFC stimulation site: (PSVC_FWE < 0.001) (**table 7.2, figure 7.4a**). Analysis of signal in the striatum did not reveal any significant effects of Task switching (but see below-threshold signal in **figure 7.4b**). One large cluster was more active during response switching compared with response repetition trials. This left lateralized cluster included the primary motor cortex (B4), premotor cortex (B6), primary somatosensory cortex, precentral gyrus (premotor cortex, B6 and primary motor cortex, B4) and the primary somatosensory cortex (B3) and extended posterior into the parietal lobe, i.e. the postcentral gyrus (peak PFWE < 0.001, t = 6.61, z = 6.19, cluster size = 3250, peak x, y, z = -40, -36, 54). However, this cluster did not show any overlap with the stimulation site (**figure 7.4a**). Exploring effects (at $p < 0.005$) in the striatum revealed no FWE corrected effects in the putamen (but see below-threshold effects in **figure 7.4b**).

We did not observe significant neural interaction effects between Reward, Task switching and/or Response switching (across site and TMS).

Functionally specific effects in the striatum after stimulation of the aPFC

During high versus low Reward, neural signaling in the right caudate nucleus was significantly decreased after aPFC stimulation compared with baseline (aPFCSTIM-BASE x Reward, PSVC_FWE = 0.040, k = 17, T = 3.78, z = 3.69, peak x, y, z = 6, 16, 2; **figure 7.5 – red coloring**). There were no reward-related effects of dlPFC or PMC stimulation. The effect of aPFC stimulation was located in the anterior portion of the caudate nucleus (**figure 7.5**) and was regionally specific within the striatum: there was no such effect of aPFC stimulation on reward-related signal in the putamen.

Analysis of the two-way interaction between Reward and Task switching revealed that signaling in a different, more posterior region of the caudate nucleus (**figure 7.5 – green coloring**) was decreased by aPFC stimulation (but not by dlPFC or PMC stimulation), although this effect did not reach significance according to our statistical threshold (aPFCSTIM-BASE x reward x task switch: PSVC_UNC = 0.003, t = 2.78, z = 2.74, peak x, y, z = -6, 6, -6).

Finally, assessment of the three-way interaction between Reward, Task switching and Response switching revealed that aPFC stimulation decreased signaling in the putamen (**figure 7.5 – blue coloring**) (aPFCSTIM-BASE x Reward x Task switch x Response switch: PSVC_ FWE = 0.020, t = 3.96, z = 3.86, peak x, y, z = -28, -8, 8). This putamen effect was greater for aPFC stimulation than for dlPFC or PMC stimulation ([aPFCSTIM-BASE > dlPFC STIM-BASE = PMC STIM-BASE] x Reward x Task switch x Response switch: PSVC_FWE = 0.023, t = 3.92, z = 3.83, peak x, y, z = -26, -8, 12).

There were no Reward-related, Reward x Task switching-related, or Reward x Task switching x Response switching-related *increases* in neural signal after stimulation of the aPFC.

In summary, stimulation of the aPFC modulated processing in the anterior portion of the caudate nucleus as a function of Reward, while it modulated activity in the putamen as a function of the interaction between Reward, Task- and Response switching. Visualization of below-threshold effects (**figure 7.5a**) reveals an anterior to posterior and medial to lateral gradient in the striatum as a function of task demands. In addition, the coronal slices in **figure 7.5b** at a higher threshold illustrate the anterior to posterior (y = 16 vs. y = -8), ventral to dorsal (z = 2 vs. z = 8) and medial to lateral (x = 6 vs. x = -28) gradient.

Assessment of the main effect of task switching did not reveal decreased neural signaling after dlPFC stimulation.

Analysis of the main effect of Task switching (task switch versus task repeat) and of the two-way interaction between Task switching and Response switching did not reveal any regions in which dlPFC stimulation changed neural signaling.

Assessment of the main effect of response switching did not reveal decreased neural signaling after PMC stimulation.

Analysis of the main effect of Response switching (response switch versus response repeat) did not reveal any regions in which PMC stimulation changed neural signaling.

Behavior

Main effects of Reward anticipation, Task switching and Response switching

Across sessions, participants responded faster on high reward trials compared with low reward trials (Reward: $F(1,26) = 39.114$, $p < 0.001$). There was no main effect of reward in terms of error rates (Reward: $F(1,26) < 1$). In terms of task-switching performance, participants made more errors on switch trials compared with repeat trials (Task switching: $F(1,26) = 27.825$, $p < 0.001$), but showed no main effect of task switching in terms of response times (Task switching: $F(1,26) < 1$). Finally, participants responded more slowly and made more errors when the same response had to be repeated compared with trials on which the response switched (Response switching in terms of response times: $F(1,26) = 11.998$, $p = 0.002$), and error rates $F(1,26) = 31.989$, $p < 0.001$).

Integration across goals

Across sessions, participants exhibited a significant effect of reward on task switching in terms of response times (Reward x Task switching: $F(1,26) = 56.089$, $p < 0.001$), but not in terms of error rates (Reward x Task switching: $F(1,26) < 1$). Breaking down this effect in the response times revealed that participants exhibited a switch benefit (i.e. repeat – switch performance) on low reward trials ($F(1,26) = 12.446$, $p = 0.002$) and a switch cost on high reward trials ($F(1,26) = 21.376$, $p < 0.001$). We also observed a Task switch x Response switch interaction in terms of error rates ($F(1,26) = 7.224$, $p = 0.012$), but not in terms of response times ($F(1,26)$ 1.130, $p = 0.298$). Breaking down this effect in the error rates revealed a larger task-switch cost (task switch – task repeat) on response repeat trials ($F(1,26) = 31.019$, $p < 0.001$) compared with response switch trials ($F(1,26) = 4.224$, $p = 0.05$). There was no Reward x Task switch x Response switch interaction ($F(1,26) < 1$ for response times and error rates).

No effects of TMS on behavior

None of the main effects (i.e. of Reward anticipation, Task switching Response switching) were modulated by TMS (i.e. TMS stimulation vs. baseline) for any of the TMS sites (response times and error rates all $F(1,26) < 3.612$, all $p < 0.05$).

We did not observe any significant main effects of stimulation irrespective of task conditions (in response times and error rates: $F(1,26 < 1)$ and no interactions effects of stimulation on the Reward x Task switching, Task switching x Response switching or Reward x Task switching x Response switching effects for any of the stimulation sites (in response times and error rates: all $F(1,26) < 2.316$, all $p > 0.1$).

Discussion

In the current study, we aimed to provide evidence for a functionally cascading architecture of corticostriatal circuits by assessing the consequence of manipulating distinct frontal regions during the processing of reward, cognitive (task switch) and action (response switch) goals while measuring signals in distinct striatal subregions. In support of our hypothesis, we show that task-specific information can be integrated across corticostriatal circuits. More specifically, manipulation of the prefrontal region involved in reward processing decreased reward-related processing in an anterior part of the striatum (in the caudate nucleus: $x = 6$, $y = 16$, $z = 2$), whereas stimulation of this same region decreased processing in a more posterior, dorsal and lateral region of the striatum (in the putamen: $x = -28$, $y = -8$, $z = 8$) when assessing the interaction between reward, task switching and response switching.

The anterior/ventromedial to posterior/dorsolateral task-related gradient we observed during reward processing, task switching and response switching fits well with evidence from anatomical studies, suggesting exactly this gradient in the striatum, forming parallel

loops with functionally similar cortical regions, when moving from the reward circuit to the cognitive and subsequently action circuit (Haber, 2003; Haber et al., 2006; Haber and Knutson, 2010; Choi et al., 2012; Oh et al., 2014). We provide functional evidence that this gradient in the striatum is indeed associated with task-related processing, where signaling in the anterior caudate nucleus was associated with reward processing and increasingly posterior and lateral portions of the striatum were involved in cognitive and motor processes.

Our observation that stimulation of the aPFC can modulate processing in distinct regions of the striatum in a task-specific way provides evidence for the hypothesis that integration of task-related information can occur across circuits, rather than being restricted within parallel loops (Haber et al., 2000). Tracing work in non-human primates has revealed that the dlPFC projects primarily to the dorsal caudate nucleus, but that its projection field extends to other regions in the striatum, primarily the anterior and medial putamen. A similar pattern was observed for cortical regions involved in reward processing: these projections terminated primarily in the ventral striatum, but extent to more dorsal regions of the striatum, including the caudate nucleus (Haber et al., 2006). Although this tracing work did not include the anterior PFC, this work does suggest that these connections could underlie the currently observed interaction between reward, task switching and response switching; a functional, task-related gradient has been shown previously in the frontal cortex (for reviews see: Koechlin and Summerfield, 2007; Botvinick, 2008; Badre and D'Esposito, 2009), where increasingly anterior portions of the frontal cortex are involved in increasingly abstract goals. In addition, using a computational modeling approach, Badre and Frank (2012) recently suggested that a dopaminergic corticostriatal mechanism may underlie the integration across rules when participants need to learn about task structure. We provide, for the first time, functional evidence that integration across corticostriatal circuits takes place when integrating information across functionally dissociable goals by showing that stimulation of the aPFC can have functionally specific effects in distinct regions in the striatum depending on the level of interaction (i.e. evidenced by a reward-related effect of aPFC stimulation in the caudate nucleus, but in the putamen during the integration of reward, task switching and response switching (**figure 7.5**).

However, the mechanisms underlying this integration across circuits are poorly understood. We put forward three ways by which information about rewards can influence cognitive- and action goals. The first involves direct cortico-cortical projections (Fuster, 2001; Wood and Grafman, 2003; Badre and D'Esposito, 2009), while the second and third way assign also a role to the striatum in the integration across corticostriatal circuits: via direct cortico-striatal connections or via spiraling dopaminergic connections between the striatum and the midbrain, i.e. striatal-nigral-striatal (SNS) connections (Haber et al., 2000; Haber, 2003; Haber and Knutson, 2010). Future work should directly test these hypotheses, but here we highlight in particular, based on recent convergent evidence from studies using the same experimental paradigm, a role for the dopaminergic midbrain SNS projections in conveying information about rewards to cognitive and action circuits. Specifically, the SNS account is

congruous with a role for dopamine in mediating the interaction between reward and task switching, which was evidenced by showing that the interaction between reward and task switching depends on inter-individual differences in dopamine signaling (Aarts et al., 2010; Aarts et al., 2011; Aarts et al., 2014a). In line with this, it is well established that TMS over the cortex can alter dopamine release in the striatum (Strafella et al., 2001; Strafella et al., 2003; Ko et al., 2008). TMS in the current design may therefore have inhibited dopamine release in the striatum, eliciting indirectly a decrease in the striatal BOLD response (Knutson and Gibbs, 2007). In addition, the SNS account is congruous with the evidence from tracing work in non-human primates, which has shown that the striatal-midbrain projections that originate in the ventral striatum cover a wide range of dopamine neurons in the midbrain, including neurons of the midbrain that project to the caudate nucleus. Also, cortical regions in the monkey, involved in reward processing (areas 32, 25, 24) and cognitive control (area 46, 9) do not directly innervate the posterior parts of the putamen (Haber 2000). Combined, these results suggest that, at least anatomically, it is unlikely that direct corticostriatal connections mediated the putaminal effects observed after aPFC stimulation, but rather that striatal-nigral-striatal connections, mediated these effects.

A number of limitations require mentioning. First, aPFC stimulation modulated a region in the caudate nucleus more dorsal than the region in the ventral striatum that was activated in anticipation of a reward across all (TMS and baseline) sessions. One may expect that stimulation of the cortical region involved in reward processing would modulate reward-related signaling in the ventral striatum, rather than in the caudate nucleus. In fact, if we had stimulated the orbitofrontal or ventromedial prefrontal cortex (OFC/vmPFC), this is indeed what we would expect. However, given the corticostriatal connectivity pattern (Draganski et al., 2008; Choi et al., 2012), the more dorsal aPFC is likely to modulate a region more dorsal than the ventral striatum. Unfortunately, it is difficult to target the vmPFC/OFC with TMS, especially due to the sensation of prefrontal TMS, which is increasingly uncomfortable when moving to more ventral and anterior parts of the prefrontal cortex. In addition, in our previous (Aarts et al., 2010) and current work, we observed activity in the aPFC when assessing the main effect of reward, which is in line with others suggesting a role for the aPFC and the caudate nucleus in reward-related processes (Kawagoe et al., 1998; Pochon et al., 2002; Locke and Braver, 2008). Second, effects of aPFC stimulation may be experienced as less pleasant than stimulation of e.g. the motor cortex and one may thus argue that the effects observed in the current study may be due to the sensation of aPFC stimulation. However, given the current pattern of results, such an explanation of the current results is highly unlikely. We observed clearly distinct effects of aPFC stimulation as a function of task-related processing. The effects of Reward and those of the interaction between Reward, Task switching and Response switching were assessed in the same aPFC session. Any effects of the sensation of TMS would have resulted in similar neural effects, irrespective of the condition, and such an explanation cannot account for distinct effects of aPFC stimulation. Third, the current study was designed to modulate processing in the striatum. We indeed show that stimulation of

the aPFC modulates neural responses in the striatum, but it did not induce any behavioral changes, which is not uncommon with offline TMS (van Schouwenburg et al., 2012; Tupak et al., 2013). However, the absence of a behavioral effect precludes us from making any claims as to whether stimulation of the aPFC and the subsequent effects on the striatum had beneficial or detrimental effects on functional processes. Finally, contrary to our expectations, there was no modulation of task-related processing after stimulation of the dlPFC or PMC. The dlPFC region we stimulated showed significant overlap with the main effect of task switching. Nevertheless, stimulation of the dlPFC site failed to alter neural processing as a function of task switching or as a function of the interaction between task switching and response switching. One explanation is that the region we stimulated is not crucial for task-related processing in corticostriatal circuits in our paradigm. In fact, a meta-analysis has suggested a role for a more posterior region of the PFC in task switching (i.e. the inferior frontal junction; x, y, z coordinates: -40, 4, 30) (Derrfuss et al., 2005), which overlaps with the peak in the PFC activated by our task-switching contrast, suggesting indeed that the region we stimulated was too dorsal to target the corticostriatal circuitry involved in task switching. The absence of an effect of PMC stimulation likely reflects the finding that the network activated during Response switching did not show any overlap with the stimulation site in the PMC. We may have therefore failed to stimulate the region involved in response switching, and as a result we did not observe task-related modulation of PMC stimulation in the striatum. The SNS account discussed above predicts that the spiraling SNS connections are organized in an ascending way. We set out to test this idea by showing that stimulation of the aPFC, but not of the dlPFC or PMC, would affect processing in the striatum as a function of reward. This is exactly what we observed, although due to the absence of any effects after stimulation of the dlPFC and PMC we cannot be confident that stimulation of the dlPFC and PMC was effective. Thus, the results clearly show that task-related integration can occur across corticostriatal circuits and that is occurs in a unidirectional manner, from anterior/ventral to posterior/dorsal parts of the striatum. However, we cannot rule out that stimulation of the dlPFC or PMC, had it been effective, could also modulate activity in more anterior/ventral parts of the striatum.

The current study is the first to show functional interactions between corticostriatal circuits during the integration of task-related goals, by causally manipulating neuronal excitability. The results of this TMS study show that corticostriatal circuits communicate in order to facilitate the translation of information across goals or functional domains. Understanding exactly how cognitive goals and subsequent actions are informed by reward motivation is important when understanding the etiology of a number of neuropsychiatric disorders with deficits in integrating between these signals and/or deficits in corticostriatal circuits (for a review see Shepherd, 2013), such as attention deficit hyperactivity disorder (Aarts et al., 2015; Hong et al., 2015), schizophrenia (Morris et al., 2015), obsessive compulsive disorder (Graybiel and Rauch, 2000), and addiction (Belin and Everitt, 2008; Tang et al., 2015).

Chapter 8

General discussion

Our environment imposes on us a constant stream of stimuli and potential tasks to engage in. Dealing with this constantly changing environment requires the ability to flexibly adapt our behavioural and cognitive programs to changing task demands. In addition, we adapt our behaviour to changes in potential rewards, which serve both a motivational function, by invigorating and energizing ongoing behaviour and cognition, as well as a directional function, biasing behaviour towards one action or another by influencing choice and learning. In this thesis, I have focused on the motivational function of reward and specifically, on its role in motivating cognitive control. Previous experimental and anatomical work has suggested a role for dopamine, the striatum and connections between the striatum and the prefrontal cortex in motivated cognitive control (**chapters 1 and 2**, (Haber et al., 2000; Haber, 2003; Aarts et al., 2010). Until recently, experimental evidence supporting these hypotheses was either absent, indirect or did not speak to the specific receptor types involved in the underlying process (**chapters 1 and 2**).

In this thesis, I aimed to improve our understanding of the role of dopamine and the corticostriatal network during the integration of reward and flexible cognitive control. More specifically my work aimed to test whether the manipulation of dopamine and specific dopamine receptors (**chapter 3, 4**), and (prefrontal modulation of) signalling in the striatum (**chapter 6 and 7**) can alter motivated cognitive control. In addition, I assessed reward-cognition integration across the life span, from adolescence to senescence (**chapter 5**) and in patients with attention deficit hyperactivity disorder (ADHD) (**chapter 4**).

Summary of findings

In **chapter 1**, we provided an overview of the state of the relevant literature up until the start of my thesis on how motivation can change cognitive control, how the neural signals associated with these processes may be integrated and how signals in the prefrontal cortex may modulate striatal processing. In that same chapter we also put forward a working hypothesis, suggesting an important role for striatal dopamine in motivated cognitive control. However, which specific dopamine receptor subtype is important for motivated cognitive control had not been assessed, and experimental work thus far had not directly manipulated the striatum and the dopamine system. In **chapter 3**, we filled this gap by conducting a pharmacological study to investigate the causal role of dopamine, specifically the dopamine D2 receptor, in task switching and in the integration between reward and task switching. In this study, we replicated the previous observation (Aarts et al., 2010) that inter-individual variation in the dopamine transporter genotype *(DAT1/SLC6A3)* can modulate the effect of reward on task-switching behaviour, suggesting -again- a role for striatal dopamine in this interaction. However, our pharmacological manipulation did not alter motivated cognitive control. The administration of a dopamine D2 receptor agonist did however change task-switching behaviour, irrespective of reward. This observation is in line with previous theorizing and work in humans and rodents implicating the D2 receptor in flexible behaviour (Mehta et

al., 2004; Floresco et al., 2006b; Durstewitz and Seamans, 2008; Stelzel et al., 2010), and was further strengthened by the observation that pre-treatment with a dopamine D2 receptor antagonist blocked these effects. Crucially, these effects depended on individual differences in dopamine signalling, as measured with the *DAT1* genotype: Bromocriptine only improved task-switching behaviour in subjects homozygous for the 10R allele and did not change task-switching behaviour in those carrying the 9R allele. Together with the knowledge that the dopamine transporter is most abundant in the striatum (**chapter 2**), these results suggest that the stimulation of dopamine D2 receptors *in the striatum* is important for flexible cognitive control. In addition, these results highlight the importance of taking into account inter-individual differences in dopamine signalling when assessing drug effects (see **chapter 2** and (Cools and D'Esposito, 2011). However, genetic associations do not imply causality and a causal role for dopamine could thus not be provided. Also, when interpreting these results it is important to keep in mind that expression of the dopamine transporter is not exclusive to the striatum: The dopamine transporter is also abundantly expressed in the pallidum and midbrain (Ciliax et al., 1999; Dahlin et al., 2007). In addition, some dopamine transporter expression is present in the diencephalon, mesencephalon, hippocampus, amygdala and cortex (Ciliax et al., 1999; Dahlin et al., 2007).

In sum, the results in **chapter 3** replicated previous work suggesting a role for striatal dopamine in the integration between reward and cognitive control (Aarts et al., 2010). However, the evidence in **chapter 3** did not support a role for dopamine D2 receptors in motivated cognitive control. Moreover, the evidence for the involvement of *striatal* dopamine (i.e. by means of *DAT1*-dependency of the results) is not indisputable. Combining genetics with neuroimaging (e.g. functional MRI: **box 2.4** and **chapter 4**) can strengthen the evidence for the involvement of striatal dopamine in motivated cognitive control.

Previous work has suggested a role for dopamine D1 receptor stimulation (Meririnne et al., 2001), or both dopamine D1 and D2 receptor stimulation (Ikemoto et al., 1997; Koch et al., 2000) in reward motivation. Methylphenidate (**box 2.2b**) is a drug which blocks the dopamine transporter, thereby increasing dopamine levels. In **chapter 4**, we manipulated the dopamine system by using methylphenidate, which is commonly used to pharmacologically treat ADHD. We assessed patients with ADHD both after intake of their normal dose of Ritalin® (or an equivalent dose for those usually taking Concerta®; **box 2.2b**) and after refraining from methylphenidate intake for at least 24 hours. We compared these patients to a healthy control group to assess cognitive task-related processing as a function of reward-related signalling in the striatum of adults with ADHD. In this study, we observed that patients with ADHD after withdrawal from their medication, compared with adults without ADHD, showed increased neural signalling in the striatum (i.e. in the caudate nucleus) during the integration of reward and cognitive control. As was the case in **chapter 3**, the effects in **chapter 4** also depended on natural variation in the *DAT1* genotype: Only the subset of patients carrying the 9R allele showed this increased striatal activation. Manipulation of the dopamine system, by treatment of these patients with methylphenidate, normalized this increased striatal signal in the group

carrying the 9R allele, but had no effect in those homozygous for the 10R allele.

These results strengthen the evidence for a causal role for dopamine in motivated cognitive control and they reveal differences in striatal dopamine signalling between patients with ADHD and subjects without ADHD during motivated cognitive control.

The effects observed in **chapter 4** seem at odds with those observed in healthy subjects (**chapter 3** and (Aarts et al., 2010)). In healthy young adults who carry the 9R allele, reward previously increased the task-switch related signal in the caudate nucleus (Aarts et al., 2010). In addition, reward anticipation had a *beneficial* effect on task switching performance in young healthy adults (**chapter 3)**. By contrast, in the healthy control group in **chapter 4**, we did not observe any evidence for an effect of reward on task switching, either in terms of neural signalling or behaviour. In patients with ADHD who carry the 9R allele of the *DAT1* genotype, we observed that reward motivation increased the task-switch related signal in the striatum (i.e. the caudate nucleus), as it previously did in young healthy subjects (Aarts et al., 2010). In addition, (if anything) reward had a *detrimental* effect on task switching in these patients. Thus, the neural signal in the ADHD patients was in line with that observed previously in young healthy subjects, but to our surprise, in the healthy control group in **chapter 4**, we did not replicate previous work showing that the integration between reward and cognitive control was associated with a *DAT1* genotype-dependent change in behaviour (**chapter 3**) and striatal signalling (Aarts et al., 2010). One potential explanation for this discrepancy is related to the age of the participants: Whereas the subjects in the healthy control group in the ADHD study were ~38 years old, subjects in the other studies were younger (~22 years old). Striatal dopamine levels decrease dramatically across the lifespan, starting in early adulthood (from ~20 years onwards) (Volkow et al., 1996a; Bäckman et al., 2000; Backman and Farde, 2001). If striatal dopamine is indeed crucial for successful motivation-cognition integration, deficits in motivated cognition should be evident with increasing age. ADHD has been associated with a developmental delay, resulting from dysfunctional nigrostriatal dopamine projections (Sagvolden et al., 2005). Such a developmental delay may explain the observation of an effect of reward on task switching in patients, but not in age-matched healthy controls. The questions remains however why this increased signalling in the 9R ADHD group is not associated with beneficial effects on behaviour, and why they – if anything – are even behaviourally impaired when integrating reward and task-switching signals.

In **chapter 5** we assessed whether any evidence for age-related changes in the motivational enhancement of cognitive control could be revealed. To this end we analyzed data from subjects ranging from 14 to 69 years old who performed the rewarded task-switching paradigm and we observed that increasing age was indeed associated with less flexible adaptation to changing task demands. Specifically, the younger group showed reward-related behaviour that depended on the cognitive condition (i.e. whether a task repetition or a task switch was required), whereas the older group did not show any reward-related change in cognitive control. Based on previous imaging work which revealed decreases in dopamine neurons with increasing age, we speculate that the age-related effects observed in **chapter 5** are due

to the loss of dopamine cells in the midbrain, which project to the striatum. Combined, the *DAT1*-dependent effects in **chapters 3 and 4**, the increased BOLD response in the striatum in **chapter 4** and the age-related deficits in motivated cognitive control (**chapter 5**) suggest a role for striatal dopamine in mediating motivated cognitive control. However, future work should further substantiate this claim (see **future research**).

Based on previous work, we anticipated that the *ventral* part of the striatum would be crucial for motivated cognitive control (**chapter 1 and 2**)(Mogenson et al., 1980; Floresco, 2015). This idea is also in line with previous work, suggesting that the depletion of dopamine neurons in healthy aging is more severe in the midbrain dopamine neurons that project to the ventral part of the striatum compared with those projecting to more dorsal parts of the striatum (Fearnley and Lees, 1991). We tested this hypothesis in **chapter 6** by applying excitotoxic lesions to the rodent ventral striatum, i.e. the nucleus accumbens core. To achieve this, we developed a rewarded task-switching paradigm in rodents and we showed that rodents can increase their flexible cognitive control when a situation is associated with a high reward, compared with a low reward situation, like we previously observed in humans. Importantly, only animals with an intact striatum showed this reward-related improvement in cognitive control: After lesions of the ventral striatum animals no longer showed improved flexible behaviour in the high reward condition, suggesting that the ventral striatum is a crucial player when one needs to facilitate behaviour leading to a desired outcome (a high reward), while inhibiting irrelevant behaviour (yielding merely a low reward) (Floresco, 2015).

Combined, the observed deficits in aging (**chapter 5**), ADHD (**chapter 4**) and rodents with lesions of the striatum (**chapter 6**) suggest a role for the striatum in motivated cognitive control. One of the hypotheses formulated in **chapter 1** suggested that input from the prefrontal cortex can modulate processing in the striatum during motivated cognitive control (**chapter 1 and 2**). We set out to test the hypothesis that manipulation of the prefrontal cortex can alter processing in the striatum during the integration of reward, cognitive control and subsequent action selection (**figure 2.1** and **chapter 1**). To test this hypothesis (in **chapter 7**) we combined fMRI with offline brain stimulation (transcranial magnetic stimulation; TMS) to target the cortical regions involved in reward processing, task switching (cognition) and response switching (action), thereby using knowledge from previous work showing that stimulation of cortical regions can change processing in the regions of the striatum it is connected to (Strafella et al., 2001; Ko et al., 2008). In line with the existence of functionally specific corticostriatal circuits, we showed that stimulation of the cortical region involved in reward processing (the anterior prefrontal cortex) altered neural signalling in the anterior portion of the caudate nucleus, which has been implicated in reward processing in previous work (Cromwell and Schultz, 2003). Crucially however, we also showed that stimulating the same region in the anterior prefrontal cortex modulated signalling in the motor part of the striatum as a function of the integration between reward motivation, cognitive control and action control. Combined, these results show that the prefrontal cortex and the striatum interact during the integration of the functions necessary to execute the task (i.e. when

processing signals about reward, cognition and action).

Combined, the experiments presented in this thesis confirm that striatal dopamine plays a role in (motivated) cognitive control (**chapter 3**), and extend these findings by showing that dopamine and the striatum are causally involved when information about rewards affects cognitive goals (**chapter 4 and 6**). We also show that aberrant integration between reward and cognitive control can surface in populations with deficits in cognitive control and striatal dopamine signalling (**chapter 4 and 5**), suggesting that these cognitive deficits may stem from deficits in translating information about potential rewards into cognitive goals. Dopamine acts by changing the sensitivity of the neurons in the striatum, which is particularly sensitive to input from the prefrontal cortex. We show that the prefrontal cortex modulates processing in the striatum. We also show that signals about rewards in the reward-related corticostriatal circuit are integrated with signals in the motor corticostriatal circuit when information about reward, cognitive control and action control are integrated (**chapter 7**).

Which neural mechanism underlies the integration between reward and cognitive control?

It is clear from the work in this thesis that the striatum and dopamine are crucial for motivated cognitive control. It is also evident that top-down effects from the prefrontal cortex are important for motivated cognitive control and that information from the anterior prefrontal cortex during reward processing can affect processing in the motor part of the striatum (i.e. the putamen). Anatomical evidence from non-human primates has revealed three ways in which information can be transferred between circuits (**chapter 1 and 2**): Via direct cortico-cortical (CC) connections, via cortico-striatal (CS) connections or via striato-nigral-striatal (SNS) connections (**figure 1.1 and 2.1**) (Haber et al., 2000; Wood and Grafman, 2003; Haber and Knutson, 2010). The work in this thesis clearly shows a role for the striatum during integration of information across task-related goals (**chapter 4, 6, 7**), suggesting that information transfer takes place at the level of the striatum. Although the work in this thesis strengthens the case for a role for CS or SNS connections, it is important to realize that this does not rule out entirely that the integration (also) takes place via CC connections. It may still be the case that the striatum receives input from the cortex after signals have been integrated at the cortical level. Given the results of the work presented here I would however speculate that the integration takes place either by means of direct CS connections and/or by means of SNS connections. In the first case (CS connections), the prefrontal input to the striatum is modulated by dopamine (originating from the midbrain). In the case of SNS connections, dopaminergic connections from the midbrain convey information to increasingly posterior/dorsolateral regions of the striatum, which in turn project back to the midbrain (and the prefrontal cortex). The work is **chapter 6** showed that lesions of the ventral striatum clearly affected motivated cognitive control. This argues against a sole role for direct cortico-striatal connections, i.e. connections from reward-related cortical regions to the cognitive striatum, bypassing the ventral striatum.

The SNS account requires a detailed topographically specific organization of the midbrain and its connections to the striatum and thus far it remains unclear whether this organization, which has been shown in non-human primates and rodents (Haber et al., 2000; Bjorklund and Dunnett, 2007; , but see Matsuda et al., 2009), exists in humans. Indeed, rodent work has suggested that the spiralling dopamine connections between ventral- and increasingly dorsal parts of the striatum are organized in a serial manner. This was evidenced recently by the observation that changes in dopamine signalling in the nucleus accumbens shell influenced dopamine levels in the nucleus accumbens core, which in turn affected signalling in the ventrolateral and dorsal striatum in a serial manner (Ikeda et al., 2013).

Several decades ago the idea was proposed that the ventral striatum serves as a limbic-motor interface, mediating the interaction between motivation and action (Mogenson et al., 1980). However, at the time it was unclear how the ventral striatum would do this, apart from the theorizing that midbrain dopamine would be involved. A recent theory has suggested a similar role for the ventral striatum (Mannella et al., 2013) and its input from the prefrontal cortex, amygdala and hippocampus, but it still does not clearly address exactly how reward information can be transferred to motor areas. In **chapter 1** we propose that this information transfer occurs via cognitive control regions, rather than via direct connections between motivation and action regions. Evidence from human (Draganski et al., 2008; Choi et al., 2012), non-human primate (Haber, 2003) and rodent (Oh et al., 2014) work has not revealed any direct connections between cortical reward-processing areas and the motor striatum or between the 'reward midbrain' (VTA) and the 'motor striatum'(the putamen). In fact, Ikeda and colleagues (2013) showed that information is processed serially, and that it is 'forwarded' from more ventromedial regions of the (rodent) striatum to increasingly more dorsolateral regions. Therefore, it is anatomically not plausible that this information transfer occurs via direct CS connections from reward areas to the motor circuit. In **chapter 7** we directly assessed the interaction between reward, cognition and action, showing that integration across these corticostriatal circuits occurs. However, determining whether information bypasses the 'cognitive' striatum requires a replication of the current finding after inactivation or lesion of this region, which is not feasible in human subjects (**future research**). Neuroimaging work (e.g. Aarts et al. 2010 and **chapter 4**) has revealed a role for the caudate nucleus in motivated cognitive control, while a role for the ventral striatum in motivated cognitive control is shown in **chapter 6** (and hypothesized in **chapter 5**). Although these results may seem contradictory at first, they are in fact perfectly in line with our hypothesized underlying neural mechanism. When interpreting the results from **chapter 4**, it is important to realize that the BOLD response is thought to reflect the input from other regions, rather than its output to other regions (Logothetis et al., 2001). The neural signal in the caudate nucleus will thus reflect the input from regions projecting *to* the caudate nucleus. This is perfectly in line with the idea that information in the 'reward striatum (the rodent nucleus accumbens or human ventral striatum / anterior caudate nucleus) is transferred to the 'cognitive striatum' (the rodent dorsomedial striatum or the human (posterior) caudate nucleus). Excessive NMDA receptor activation in the nucleus accumbens (**chapter 6**) will have caused neuronal death

in this region (Sattler and Tymianski, 2001). The loss of neurons in the nucleus accumbens will disrupt both its input from the cortex, as well as its output to the dorsal striatum (e.g. via the midbrain). In summary, these results reflect that information transfer from the nucleus accumbens (disrupted in **chapter 6**) to the dorsal striatum (measured in **chapter 5**) mediates motivated cognitive control. In addition, the results fit well with those from chapter 7: NMDA lesions (**chapter 6**) will also disrupt prefrontal input to the striatum, disrupting prefrontal modulation of striatal processing (**chapter 7**).

It is clear from the literature that dopamine is involved in flexible cognitive control. In **chapter 3** we show a clear and causal role for the dopamine D2 receptor in task switching. Work on the role for dopamine D1 and D2 receptors in reward processing suggests that concurrent activation of dopamine D1 and D2 receptors is crucial for reward-related processes (Ikemoto et al., 1997). Conversely, it was suggested that dopamine D1 –receptor stimulation may be crucial for reward-related processes (Beninger and Miller, 1998; Meririnne et al., 2001). In **chapter 4**, the administration of methylphenidate in adults with ADHD normalized the increased signal in the caudate nucleus which was present when the patients had not taken their medication, possibly by increasing dopamine levels in the striatum (Volkow et al., 2001), but possibly also (noradrenaline) in the prefrontal cortex (Berridge and Arnsten, 2013). Although the work in **chapter 3 and 4** strengthened the evidence for a role for dopamine in motivated cognition, it did not lead to a conclusion about which dopamine receptor is involved. Future work will have to elucidate which dopamine receptor mediates effects of reward motivation on cognitive control (**future research**).

Rewarded task switching vs. motivated cognitive control

The work in this thesis focused on one aspect of cognitive control: switching between well-established task sets. However, as was discussed in **chapter 1**, there are numerous ways to manipulate and measure motivation and cognitive control and differences between these paradigms result in the recruitment of different brain regions and potentially opposing effects of dopamine.

Studies that measure attention, working memory, or forms of flexible control that require new learning commonly report effects in the prefrontal cortex (Pochon et al., 2002; Locke and Braver, 2008; Engelmann et al., 2009; Pessoa and Engelmann, 2010), while our form of flexible 'habit-like' cognitive control appears to rely more heavily on the striatum than it does on the cortex (Aarts et al., 2010) (**chapter 1**). However, our work and that of others has shown that effects of reward motivation on cognitive control are not restricted to the prefrontal cortex and often both cortical and striatal regions are activated during motivated cognitive control, also when 'prefrontal' paradigms are used. For example, signals in the striatum and inferior frontal gyrus have been associated with reward effects on response inhibition and attention tasks (Padmala and Pessoa, 2010; Krebs et al., 2012) and reward reduced conflict-related signalling in the medial PFC during a Stroop-like task and increased coupling between the ventral

striatum and a cortical region involved in attention processing, i.e. the intraparietal sulcus (Padmala and Pessoa, 2011). This is illustrated further (and causally) in **chapter 7**, where we show that manipulating the prefrontal cortex with TMS has effects on the integration across task-related goals in the striatum without directly altering processing in the cortex. In fact, activity in **chapter 4** was not restricted to the striatum, but was also revealed in the posterior cingulate cortex, an area that is connected to the dorsal striatum (Di Martino et al., 2008; Beckmann et al., 2009), suggesting indeed that processing in the corticostriatal network was altered during motivated cognitive control in these patients.

The absence of significant effects in the striatum in studies that report prefrontal effects does not necessarily imply that the striatum is not playing a role in the underlying process. Instead, the measurement technique in studies that report effects in the prefrontal cortex may simply not be sufficiently sensitive to detect changes in striatal BOLD response. The BOLD signal in the ventral part of the brain, including the striatum is more susceptible to signal drop out. Functional MRI may therefore generally be more sensitive to changes in signal in 'cognitive' dorsal cortical regions. Taking into account the *DAT1* genotype to account for inter-individual differences in dopamine signalling in our work (e.g. **chapter 4** and (Aarts et al., 2010)) can increase the sensitivity to detect changes in the striatum.

These studies are generally in line with the idea that reward changes processing in the cognitive control region involved in the task at hand. And they suggest that the prefrontal cortex and striatum can act in concert to mediate the interaction between different task aspects. However, in **chapter 1** we argued and illustrated that reward motivation can have opposite effects on cognitive flexibility and stability and we argued that this effect may be due to opposing effect of dopamine on cognitive flexibility and stability (Durstewitz and Seamans, 2008). The idea that dopamine can be detrimental for cognitive focussing was demonstrated recently in a study using a Stroop task (Aarts et al., 2014b), for which good task performance requires a stable task representation (i.e. not be distracted by the irrelevant dimension in the incongruent condition). Importantly, rewarded Stroop performance was associated with dopamine levels (i.e. dopamine synthesis capacity). More specifically, increased dopamine levels in this study were associated with a detrimental effect of reward on cognitive performance. The work in this thesis focused on cognitive flexibility, and did not formally manipulate stability. However, whereas one may think of switch trials as a form of cognitive flexibility, performance on repeat trials will likely benefit from stable task representations. The results in **chapter 5** revealed opposing age-related effect of reward motivation on switch and repeat trials, suggesting that (reward and age-induced changes in) dopamine can have opposite effects on cognitive flexibility and cognitive focussing (**limitations**). The number of studies that assessed the role of striatal dopamine in mediating the integration between reward and cognitive control (whether it is flexible control or maintaining stable task representations) is scarce. Therefore it remains unclear which factors determine whether the effects of dopamine are beneficial or detrimental for cognitive control. Reward-induced changes in dopamine may modulate how susceptible the cognitive (dorsal) striatum is for input from the reward (ventral) striatum or

from the prefrontal cortex. Reward motivation may serve to bias the gating mechanism of the striatum to a more flexible state, which is beneficial in some cases (e.g. in the case of task switching), but not others (e.g. on a Stroop task or on repeat trials) (**future research**).

To date not many studies have directly manipulated the dopamine system during motivated cognitive control. The work in this thesis fills this gap and combines experiments using pharmacology, excitotoxic lesions, and non-invasive brain stimulation to show that (prefrontal input to) the striatum is involved in motivated cognitive control and that integration across corticostriatal circuits occurs when integration across goals is required. These results may even extend beyond motivation-cognition integration to other goals. For example, a role for a prefrontal-striatal gating mechanism and integration across corticostriatal circuits has been suggested when subjects need to integrate information across hierarchical rules (Badre and Frank, 2012).

What can we learn from cross-species evidence?

The ability to use information about upcoming rewards to adapt their cognitive control strategy changed with increasing age in healthy human subjects and in rats with lesions of the ventral striatum (**chapter 5 and 6**). When their striatum was intact, the animals in **chapter 6** showed a reward-related improvement of flexible cognitive control, as we previously showed in a subset of healthy young human subjects (e.g. the 9R carriers in **chapter 3**). When comparing the results obtained in work with human subjects with those from the rodent work in **chapter 6**, a number of things are worth considering. First, it is important to keep in mind to what extent findings from the rodent literature generally translate to human work. Secondly, it is important to take note of the parallels and differences between the human and rodent rewarded task-switching paradigm.

Cross-species translation: Evidence from task switching in humans and rodents

Flexible behaviour and its underlying neural substrates have been extensively studied in both human and rodent subjects. One paradigm that is commonly used to assess flexible cognitive control in rodents is the strategy set-shifting paradigm (Ragozzino et al., 1999). In a T-maze (Ragozzino et al., 1999) or operant (Floresco et al., 2008a) version of this task, animals learn to obtain a food reward by making a left (turn or lever press) response, thereby ignoring the illumination of a light (over either the left or right arm or lever). After the successful acquisition of this response strategy, the previously correct strategy (e.g. a going left) is no longer rewarded, and the animal has to learn that the rule has changed. Crucially, the previously irrelevant stimulus (the light) now becomes relevant and the previously relevant rule ('go left') needs to be suppressed. The number of trials the animals needs to reach a pre-defined criterion (e.g. 8 consecutive correct responses) is taken as a measure for cognitive flexibility. A major advantage of this paradigm is its ability to distinguish between several

aspects of flexible control by analysis of the types of errors: Animals may fail to shift (i.e. they persevere on the old rule) or they may exhibit deficits in rule maintenance (i.e. they initially shift, but then fail to maintain this new strategy). One draw-back, when trying to compare the results obtained with this paradigm to those observed with the human cued task-switching paradigm is that switches are not signalled by a cue, but need to be learned. In addition, set-shifting paradigms only allow one switch per test, rather than testing the fast trial-by-trial adaptation generally measured in humans.

Extensive studies on strategy set-shifting have revealed a prominent role for the rodent medial PFC, in particular the prelimbic cortex (Ragozzino et al., 1999; Floresco et al., 2006b; Floresco et al., 2008a). In addition, dopamine signalling plays an important role in successful shifting behaviour (Floresco et al., 2006b; Haluk and Floresco, 2009), as does the dorsal striatum (Ragozzino et al., 2002). Human cued task switching work generally reports neural responses in the dorsal striatum and dorsal prefrontal cortex (inferior frontal gyrus) and a role for dopamine (Crone et al., 2006; Stelzel et al., 2010; Aarts et al., 2012; Aarts et al., 2014a), (see Derrfuss et al., 2005) for a meta-analysis.

An interesting open question relates to if and how strategy set-shifting differs from cued task switching. A particularly important distinction resides in the learning component. Whereas the strategy set-shifting paradigm assesses how well animals *learn* to change their behaviour; cued switching requires the ability to quickly change task-sets. Given the role for the nucleus accumbens in learning (Schultz et al., 1997), it is perhaps not surprising that the rodent nucleus accumbens is crucial for certain aspects of successful strategy shifting (Floresco et al., 2006a). Interestingly, this nucleus is not involved in the initial shift, a role reserved for the dorsal striatum, but it is crucial to maintain a recently introduced novel rule. The first study that tested cued task switching in rodents (Baker and Ragozzino, 2014b, a) revealed that flexible behaviour was disrupted by lesions of the medial PFC and the basal ganglia, including the dorsal striatum. However, one major confound in this paradigm is caused by the occurrence of ~4 times more repeat than switch trials. As a consequence, switching between task-sets is no longer the only difference between switch and repeat trials. Instead, potential confounds are introduced (e.g. increased novelty or saliency of switch trials, and the overall expectation that a task will repeat). This confound is not present in the novel paradigm presented in **chapter 6** where trials switch and repeat equally often.

Together, the work in human subjects and in rodents both show an important role for dopamine, the dorsal striatum and corticostriatal circuit in task-switching, in particular the inferior frontal gyrus in humans and the prelimbic cortex in rodents (Robbins, 2007; Klanker et al., 2013), suggesting that these processes translate quite well across species. So far it is unclear how the role of the nucleus accumbens in strategy set-shifting (Floresco et al., 2006a) can be reconciled with its role in motivated cognitive control (**chapter 6**). One possibility may be related to the role of this region in the approach of reward-related stimuli and its role in facilitating appropriate actions. The nucleus accumbens may play a role in how much updating takes place in prefrontal cortex, thereby mediating a balance between flexible

updating of task-sets in the high reward condition (**chapter 6**) or in maintaining the new strategy after new learning has taken place (after a successful set-shift and the receipts of a reward).

Rewarded task-switching

In the rewarded task-switching paradigm presented in **chapter 6**, two discrimination tasks alternate unpredictably on a trial by trial basis and the use of cues is required to determine the relevant stimulus dimension. This paradigm is the first rodent paradigm that manipulates and compares reward conditions (i.e. high vs. low reward) and cognitive conditions (i.e. switch vs. repeat trials). The paradigm parallels the human paradigm (**chapters 3, 4, 5, and 7**; but see **limitations**) and the pattern of results in **chapter 6** is generally congruous with our previous work: Reward can improve cognitive flexibility both in (a genetically determined subset of) humans and in rodents. The results from the rodent work (**chapter 6**) also fit remarkably well with the pattern of results in the aging work (**chapter 5**): A reduction in the reward benefit on task switching was observed both in older adults and in animals with lesions of the ventral striatum, strengthening the hypothesis that the age-related effects observed in **chapter 5** were related to age-related changes in striatal dopamine.

Implications for neuropsychiatry

In **chapter 4 and 5** we tested the hypothesis that cognitive deficits in ADHD and aging may be grounded in a deficit to use information about potential gains to adequately allocate cognitive processes. A similar deficit could underlie cognitive deficits observed in other neuropsychiatric disorders such as schizophrenia, addiction, Parkinson's disease and obsessive compulsive disorder (OCD).

For example, both schizophrenia and OCD have been associated with cognitive deficits (**chapter 2**) and changes in the corticostriatal circuitry (Shepherd, 2013). Cognitive deficits in schizophrenia are thought to be related to hypoactivity in the mesocortical dopamine system, whereas positive symptoms (e.g. hallucinations and delusions) are thought to be related to hyperactivity in the dopaminergic nigro-striatal connections and increased dopamine D2 receptor signalling (Simpson et al., 2010). In line with the work in this thesis, excessive dopamine D2 receptor stimulation may induce a flexible state, at the expense of the ability to maintain stable representations (Barch and Ceaser, 2012) decreasing the ability of patients with schizophrenia to filter out irrelevant input. The repetitive behaviours typically observed in OCD on the other hand are thought to originate from increased activity in the corticostriatal circuitry, in particular hyperactivity in the cortex and hypoactivity in the striatum. Combined with the potential involvement of (at least) dopamine D1 receptor in OCD (Nordstrom and Burton, 2002), this underlying pathology may yield excessive maintenance of prefrontal representations, causing the inflexible, repetitive behaviours observed in OCD. In addition,

previous work has revealed that dopamine-dependent connections between the ventral and dorsal striatum are crucial for the development of cocaine-seeking habitual behaviour (**chapter 1** and (Belin and Everitt, 2008).

Overall, the work in this thesis contributes to a better understanding of the role of dopamine in the cortico-striatal-nigral circuitry, thereby contributing to our understanding of the underlying neuropathology in at least aging, ADHD, schizophrenia, addiction and OCD.

The work in this thesis contributes to our general understanding of how reward motivation can alter cognitive control. The results suggest that reward motivation can have dissociable effects in subjects with different genetic predispositions, both in healthy subjects (**chapter 3**) and in patients with ADHD (**chapter 4**). These findings once more emphasize the importance of taking into account differences in the baseline state of the (dopamine) system when assessing the effect of dopaminergic drug. In addition, the results in patients with ADHD highlight the heterogeneity of the disorder: The effects of reward motivation on cognitive signalling in the striatum were only revealed in a subset of patients. If the inter-individual variation in the *DAT1* genotype was not taken into account, the aberrant striatal processing would not have been revealed. Additional work is needed to assess whether taking into account inter-individual differences in dopamine signalling can predict individual responses to methylphenidate treatment in ADHD.

Knowing exactly which neural mechanisms -including which receptor subtype- underlie changes in motivated cognitive control may be an important step forward in treating patients with ADHD and potentially also schizophrenia and OCD.

Limitations

Although the work in this thesis generally contributed to our understanding of the role of the striatum and dopamine in motivated cognitive control, the experiments in this thesis were not without limitations and these should be mentioned.

In **chapter 4** we assessed the effects of methylphenidate on motivated cognitive control in patients with ADHD. A number of limitations with respect to the effects of methylphenidate are worth mentioning. First, the effects in **chapter 4** were especially evident when comparing the ADHD group to the healthy control group, but they were less conclusive when directly comparing the effects of methylphenidate within the ADHD patients (medicated vs. withdrawn from methylphenidate). Second, we cannot exclude entirely the possibility that the effects of methylphenidate in **chapter 4** were due to noradrenaline, rather than dopamine (**chapter 2**). This explanation is quite unlikely, given the observation of *DAT1*–dependent effects in the striatum in **chapter 4**, but firm conclusions can only be drawn after the observation that the effects of methylphenidate can be blocked with co-administration of a (non-selective) dopamine receptor antagonist (**see chapter 3 and box 2.2**) (**future research**). Third, it is important to keep in mind that the effects of methylphenidate were assessed in patients with

ADHD who take methylphenidate on a daily basis and who refrained from taking their normal medication prior to the experimental session. When comparing this to drug administration studies in non-medicated subjects, the long term effect of methylphenidate should be taken into account. For example, it has been suggested that long-term use of methylphenidate may – among other things – decrease excessive reward-related signalling in the striatum (Seeman and Madras, 1998; Robbins, 2002). It remains unclear from **chapter 4** to what extent the effects in the ADHD patients after medication withdrawal reflect deficits related to ADHD, or to long term effect of methylphenidate use. Another limitation of the work in **chapter 4** is that it failed to reveal clear behavioural effects, i.e. it remains unclear how the change in striatal signalling would affect behaviour.

The results in **chapter 5** speak to opposite effects of dopamine on cognitive focusing (task repetition) and cognitive flexibility (task switching). However, cognitive flexibility and stability were not formally manipulated in this study. Moreover given the age-related degeneration of dopamine neurons, and the opposite effects of reward on task switching and repeat trials, it is reasonable to speculate that dopamine mediated these opposite reward-related effects on cognitive control. However, future work should test this hypothesis (**future research**).

In **chapter 6** I present a novel rodent paradigm allowing the independent manipulation of reward motivation and cognitive control, enabling the assessment of the interaction between reward and task switching. Although this paradigm parallels the paradigm used in human subjects (**box 2.3**), at least two differences should be considered when comparing the results between species. First, whereas the size of the reward varied on a trial-by-trial basis in the human version, the rodents performed the task-switching paradigm in separate high and low reward blocks. However, similar block-designs have been used in humans to reveal motivation–cognition interactions (Locke and Braver, 2008; Kouneiher et al., 2009), although not with the rewarded task-switching paradigm. It is therefore unlikely that these differences in trial-by-trial fluctuations in reward expectancy will have dissociable effects on task-switching behaviour. Second, the trial duration in the rodent paradigm is much larger than that in the human paradigm: The animals were presented with the task cue for one minute and were then given another minute to press the levers during the presentation of the target, whereas these events lasted merely a second in the human paradigm. As a consequence, the time between the task cue and the target was much shorter in the human version of the paradigm than it was in the rodent paradigm (i.e. 400ms instead of 1 minute). Longer cue-target intervals in humans are known to decrease the switch cost (Meiran et al., 2000). Moreover, situations in real-life often require instantaneous decisions and the need for lengthy preparation times can be detrimental for survival. In the future it is thus advisable to reduce the the cue-target interval. The large cue-target interval in chapter 6 may potentially account for a switch benefit in the high reward condition, and a non-significant switch cost in the low reward condition: If increasing the cue-target interval will increase the difficulty of switching, animals may well show the same pattern of results as that observed in the 9R subjects in the healthy population. One additional question that is raised when comparing the results in rodents to those in

humans (**chapter 3 and 4**) is related to the baseline-dependency of these effects. Whereas the effect of reward on task switching in humans were only revealed when taking into account a baseline measure of dopamine signalling, in rodents the effects were revealed without accounting for individual differences. This discrepancy is possibly explained by the absence of genetic variation in rodents, caused by the inbred nature of laboratory animals.

In **chapter 7** we assessed the role of prefrontal modulation of striatal processing during motivated cognitive control and subsequent action selection. However, the effects of prefrontal stimulation on the processing of information about motivated cognitive control (without taking into account response switching) did not reach significance. One potential explanation for the effect may be related to the nature of the spiralling dopamine connections between the striatum and the midbrain (Ikeda et al., 2013). The striatum sends inhibitory (GABA-ergic) projections to the midbrain. These GABA-ergic connections inhibit the dopamine neurons that project back to the ('next' region) in the striatum (**figure 2.1**). If we assume that distinct SNS projections originate from the ventral striatum, the anterior caudate nucleus, posterior caudate nucleus and putamen (**figure 2.1**), then I would speculate that the inhibition caused by stimulation of the anterior prefrontal cortex (reflected by the decrease in reward-related BOLD response after prefrontal stimulation observed in **chapter 7**), decreased the inhibition of the projection from the anterior caudate nucleus to the section of the midbrain it projects to. This part of the midbrain (which in turn projects to the posterior caudate nucleus) will cause an increase in dopamine signalling in the posterior caudate nucleus (i.e. attenuating the inhibitory effect of TMS, masking any direct prefrontal modulation of the prefrontal stimulation). Crucially then, this increased signalling in the posterior caudate will increase the inhibition on the midbrain and will subsequently decrease dopamine release from the midbrain to the putamen (reflected by a decrease in BOLD response in the putamen during the integration of motivation, cognition and action in **chapter 7**). However, this idea is highly speculative and evidence to substantiate the projections assumed above is currently absent (**future research**).

Future research

Based on the combined evidence presented in **chapter 3, 4, and 5** we propose a role for striatal dopamine in mediating motivated cognitive control. This claim can be assessed in a number of ways. First, direct measurements of dopamine signalling in the striatum, for example using voltammetry or microdialysis in rodents, should reveal increases in striatal dopamine signalling during motivated cognitive control. Second, age-related dopamine cell loss in the striatum, measured using molecular imaging (e.g. single photon emission computed tomography; SPECT) should be related to age-related changes in motivated cognitive control. This latter approach would parallel the way in which the relationship between motivated cognitive control and dopamine was previously established in Parkinson's disease (**chapter 1: figure 1.2f** (Aarts et al., 2012). Third, in addition to the results of NMDA lesions in **chapter**

6, the demonstration that infusion of a dopamine antagonist in the striatum will impair performance on the rewarded task-switching paradigm will further substantiate a role for striatal dopamine in motivated cognitive control.

In **chapter 3 and 5**, we aimed to elucidate the role of specific dopamine receptors in motivated cognitive control. Two hypotheses should be assessed in future work. First, given previous work showing that reward-related effects of methylphenidate are blocked by a dopamine D1 antagonist, but not by dopamine D2 receptor antagonism (Meririnne et al., 2001), dopamine D1 receptor stimulation is a likely candidate for a role in motivated cognitive control. Second, a role for concurrent dopamine D1 and D2 receptor stimulation in reward motivation (Ikemoto et al., 1997) has been suggested. This suggests that concurrent D1 and D2 receptor stimulation may also be crucial for motivated cognitive control. These hypotheses can be tested by administration of a compound which increases dopamine levels (e.g. methylphenidate), in combination with the pre-treatment approach we used in **chapter 3**. More specifically, in addition to a placebo session, the administration of methylphenidate should be combined with the pre-treatment of (1) placebo, (2) a dopamine D1 receptor antagonist, (3) a dopamine D2 receptor antagonist and (4) a combination of both a D1 and D2 receptor antagonist. The administration of methylphenidate after pre-treatment with a placebo is hypothesized to improve motivated cognitive control compared with the placebo session. Pre-treatment with a dopamine D2 receptor antagonist will not have any effect on motivated cognitive control (**chapter 3**). However, if dopamine D1 receptor stimulation mediates the effect of methylphenidate on motivated cognitive control, the effects of methylphenidate will be blocked after pre-treatment with a dopamine D1 receptor antagonist. Crucially, if motivated cognitive control is mediated by a combination of dopamine D1 and D2 receptor stimulation, only pre-treatment of both a dopamine D1 and D2 receptor antagonist will fully block the effects of methylphenidate. One problem however is the lack of an available dopamine D1 agonist or antagonist for use in research with healthy human subjects. Until a suitable pharmacological agent becomes available, the rodent paradigm presented in **chapter 6** can be used to assess whether a dopamine D1 agonist (which *is* available for use in rodents) affects successful motivated cognitive control. In addition, methylphenidate acts not only on dopamine transporters, but it also blocks noradrenaline transporters. To confirm that dopamine mediated the effects of methylphenidate, an additional session should be included to show that the effects of methylphenidate can be blocked with co-administration of a (non-selective) dopamine receptor antagonist.

In **chapter 1**, we proposed that motivation can have opposite effects on cognitive stability and flexibility. Although the results in **chapter 5** are generally congruous with this idea, this should be addressed formally in future experimental work. For example by using the reward Stroop paradigm presented in **chapter 1** (**figure 1.3**) to contrast the effects of cognitive widening and focusing on Stroop performance in one paradigm. Cognitive widening will be beneficial for performance on congruent Stroop targets, whereas cognitive focussing will benefit performance on incongruent trials. Future experimental work is necessary to reveal whether

reward motivation can indeed have opposite effects on cognitive stability and focussing.

In **chapter 7** we provided evidence for prefrontal modulation of processing in the striatum during reward processing and the integration of reward, cognition and action. This design did now allow the testing of the exact nature of these projections. First, we cannot exclude that information is transferred directly from the anterior prefrontal cortex to the putamen (or the anterior caudate nucleus to the putamen), thereby bypassing the 'cognitive' striatum. The new rodent paradigm developed in **chapter 6**, with the addition of an action component (i.e. response switching as in **chapter 7**), allows further testing of this hypothesis. Using a disconnection approach, lesions of the ventral striatum and of the dorsal contralateral striatum (which leave intact one ventral striatum and one dorsal striatum in each hemisphere) (Belin and Everitt, 2008), can be used to assess whether connections between the ventral striatum and dorsal striatum are crucial for the integration between motivation, cognition and action. Also, lesions (or stimulation) of the midbrain neurons that project to the dorsal striatum should affect motivated cognition if the SNS account is valid. Finally, the idea that serial connections from the ventromedial to increasingly dorsal regions of the striatum, via dopaminergic midbrain connections (Ikeda et al., 2013), mediate motivated cognitive control should be substantiated. This can be achieved by showing that the effects of inhibition of the 'reward cortex' and 'reward striatum' on processing in the 'motor striatum' (**chapter 7**) can be blocked after dopamine receptor antagonism in the 'cognitive striatum' (**limitations**).

Conclusion

Imagine again that you are a squirrel. You are still in the forest, alternating between collecting nuts and berries. You have just collected a nut, but now you see a larger berry (i.e. another task) coming up. What happens in your squirrel brain? Well, I would speculate (based on the existent literature and the work in this thesis) that the appearance of the large berry (i.e. a large reward) will elicit a dopamine response in your midbrain. The projections of these dopamine neurons to your ventral striatum will increase the sensitivity of your ventral striatum to input from your prefrontal cortex. These reward-related signals in the ventral striatum will enhance processing in the regions involved in flexible updating. This may occur via a number of routes. First, these reward-related signals will alter signalling in the dorsal parts of the striatum via the spiralling dopamine connections in the midbrain (thereby increasing the stimulation of dopamine D2 receptors in the caudate nucleus, causing a D2-dominated state thereby enabling you to quickly update the new task set). Alternatively (or concurrently) these signals in the striatum act by changing the gating mechanism from the striatum to the 'cognitive' prefrontal cortex and subsequently the other regions in the cognitive corticostriatal circuit. If the berry you are about to collect is smaller, then the updating signals in your cognitive control network will also be smaller, leading to less flexible updating of your task sets.

In conclusion, **the research in this thesis aimed to elucidate the causal role for striatal dopamine and the corticostriatal network during the integration of reward and flexible cognitive control.** We showed that dopaminergic manipulation with methylphenidate indeed changed motivation-cognition signalling in the striatum. In addition, a causal role for the ventral striatum in motivated cognitive control was established, followed by evidence for frontal modulation of striatal processing during the integration of signals related to motivation, cognition, and action across subparts of the striatum. Together, these results are in line with a role for striatal dopamine in motivated cognitive control, and they show that integration across corticostriatal circuits is involved in this process.

Appendix

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Nederlandse samenvatting

Om goed te kunnen functioneren is het belangrijk dat we ons gedrag snel en gecontroleerd kunnen aanpassen aan de omgeving. Er zijn dagelijks veel situaties waarin we snel verschillende bezigheden moeten afwisselen. Bijvoorbeeld als je een artikel schrijft en tussendoor besprekingen hebt. Om efficiënt en snel te kunnen wisselen tussen taken is een goede coördinatie van verschillende functies (gedragscontrole) nodig; je moet je aandacht richten op wat je aan het doen bent, maar vlug kunnen schakelen wanneer dat nodig is. Deze vorm van gedragscontrole wordt in het Engels 'task switching' genoemd. Hier zal ik het multi-tasken noemen.

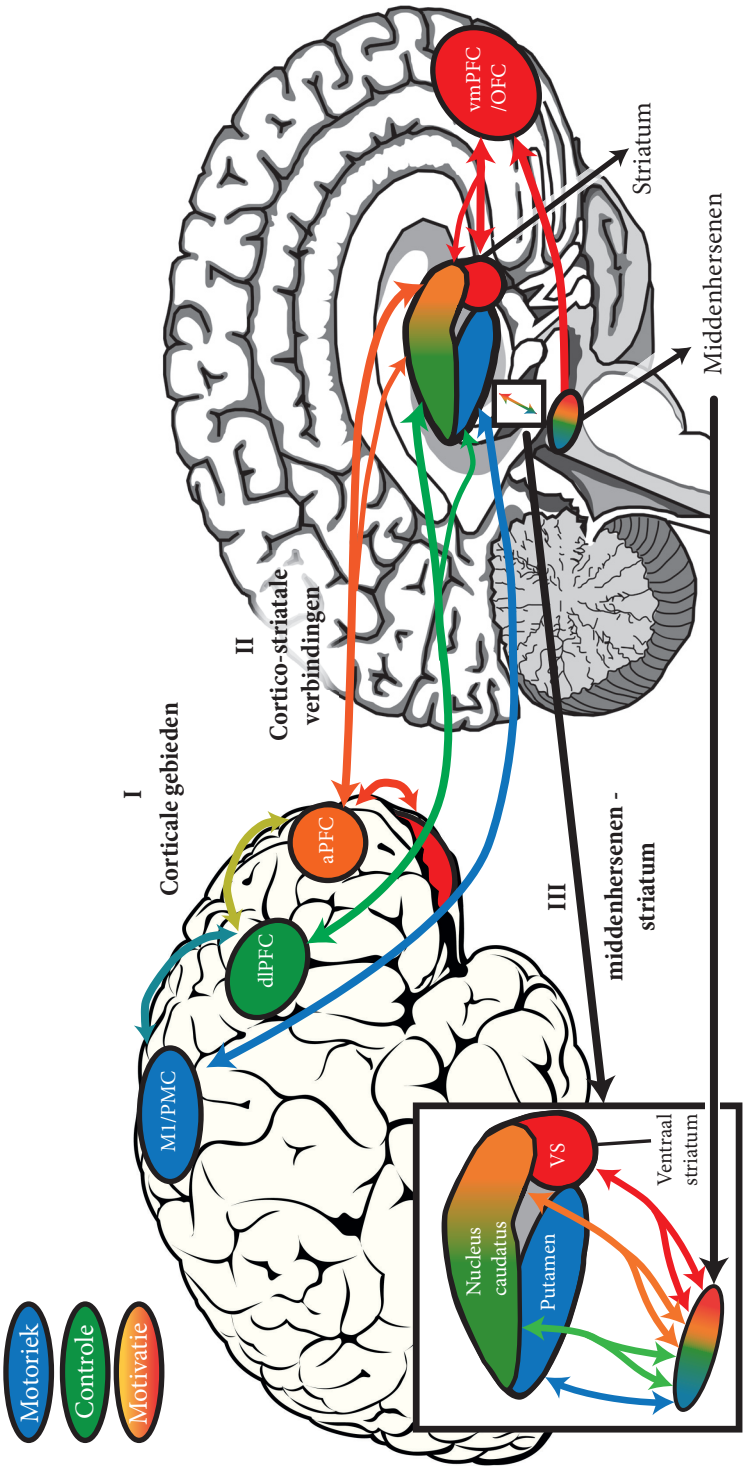
Als je een stuk moet schrijven en een aantal besprekingen hebt zul je waarschijnlijk vrij productief zijn als je één dagdeel aan schrijven besteedt en een ander dagdeel aan vergaderen. Het wordt lastiger als je om het uur een korte vergadering hebt en vaak moet afwisselen tussen schrijven en vergaderen. Als je kans op een promotie toeneemt als je op beide taken goed werk levert, wordt het waarschijnlijk makkelijker om tussen verschillende werkzaamheden af te wisselen. Met andere woorden, multi-tasken gaat beter als je gemotiveerder bent. Informatie over potentiële beloningen moet ons vermogen om te kunnen multi-tasken dus beïnvloeden. Alleen dan weten we wanneer het de moeite waard is om extra goed tussen verschillende werkzaamheden te schakelen. Problemen met gedragscontrole kunnen daarom veroorzaakt worden door problemen in motivatie. Dit kan betekenen dat hersengebieden die belangrijk zijn voor gedragscontrole (bijvoorbeeld multi-tasken) niet goed van de beloningsgebieden te horen krijgen of het de moeite waard is om gedragscontrole uit te oefenen.

Psychiatrische stoornissen gaan vaak gepaard met problemen in gedragscontrole en het verwerken van beloningen. Dit is bijvoorbeeld het geval bij mensen met schizofrenie, verslavingsproblemen en aandachtstekort-hyperactiviteitstoornis (ADHD). Het is daarom belangrijk goed te weten welke hersenprocessen ervoor zorgen dat multi-tasken beter gaat als je gemotiveerder bent. **In mijn promotieonderzoek heb ik de hersenprocessen onderzocht die ervoor zorgen dat multi-tasken beter gaat als je gemotiveerd bent.**

De wisselwerking tussen motivatie en multi-tasken in het brein

Dit proefschrift begint met een overzicht van wat er al bekend was over de rol van het striatum en de hersenstof dopamine bij motivatie, multi-tasken en de wisselwerking tussen deze processen (motivatie heeft invloed op multi-tasken). In **hoofdstuk 1** bespreek ik hoe het samenspel van verschillende hersengebieden het mogelijk maakt dat beloningsinformatie de hersengebieden voor multi-tasken kan bereiken. **Figuur 1** laat de hersengebieden zien die in mijn proefschrift de hoofdrol spelen.

Voor ik aan mijn promotieonderzoek begon was al aangetoond dat dopamine en het striatum betrokken zijn bij de wisselwerking tussen beloning en multi-tasken. Hiervoor werd een computertaak gebruikt waarbij deelnemers geld konden verdienen als ze goed konden multi-


Motoriek
Controle
Motivatie
M1/PMC
dlPFC
aPFC
I
Corticale gebieden
II
Cortico-striatale verbindingen
III
middenhersenen - striatum
vmPFC /OFC
Striatum
Middenhersenen
Nucleus caudatus
Putamen
VS
Ventraal striatum

Figuur 1 De verbindingen tussen het striatum en de prefrontale cortex
Het striatum is grofweg in te delen in drie deelgebieden: de onder/voorkant (rood/oranje), het midden (groen) en de buitenkant (blauw). Het onderste en voorste deel (rood/oranje) spelen een belangrijke rol bij beloning (in het vervolg het "beloningsstriatum" genoemd). Het middelste deel, de nucleus caudatus (groen), is belangrijk voor gedragscontrole zoals multi-tasken. Het putamen (blauw), helpt bij de regulatie van bewegingen, of motoriek. Bij al deze processen speelt dopamine signalen uit de middenhersenen een belangrijke rol. De cortex, het buitenste deel van de hersenen, speelt ook een belangrijke rol bij motivatie, gedragscontrole en motoriek. Er zijn gebieden in het voorste deel van de cortex, de voorhoofdskwab, die betrokken zijn bij beloning (rood/oranje), gedragscontrole (groen) en motoriek (blauw). De beloningsgebieden in de voorhoofdskwab en het striatum werken nauw samen en zijn sterk met elkaar verbonden (rode en oranje pijl tussen deze gebieden). Hetzelfde geldt voor de gedragscontrole gebieden (groene pijl) en de motoriek gebieden (blauwe pijl). Maar beloning zou nooit invloed op ons gedrag kunnen hebben wanneer informatie over beloningen beperkt zou blijven tot de rood/oranje gebieden. Er zijn verbindingen in het brein die ervoor zorgen dat informatie over beloningen uit de rood/oranje gebieden in de groene gedragscontrole en blauwe motoriek gebieden terecht komt. I) door middel van directe verbindingen tussen de delen van de cortex, II) door directe verbindingen tussen de delen van het striatum, III) via de middenhersenen. Dopamine en het striatum spelen een belangrijke rol bij de integratie van beloningsinformatie en multi-task informatie. Scenario II en III zijn daarom het meest waarschijnlijk. Bij veel psychiatrische stoornissen is sprake van een verstoring in dopamine signalen en van een verstoring in de overdracht van signalen tussen de cortex en het striatum.

tasken (het multi-task spel). Dit onderzoek toonde echter geen oorzakelijk verband aan tussen dopamine en prestaties op het multi-task spel. In het brein zijn bovendien 5 soorten dopamine receptoren (type 1 tot 5) aanwezig. Een receptor is als een antenne die signalen oppikt en aan de zenuwcel doorgeeft. Medicatie werkt vaak op meerdere soorten receptoren. Het is daarom belangrijk om te weten welke dopamine receptoren een rol spelen bij multi-tasken.

Dopamine D2 receptoren in het striatum zijn betrokken bij multi-tasken

In het werk in **hoofdstuk 3** heb ik onderzocht of dopamine D2 receptoren in het striatum een rol spelen tijdens multi-tasken. Om dopamine D2 receptoren te stimuleren werd het medicijn bromocriptine gebruikt. Bovendien keek ik of er een oorzakelijk verband tussen dopamine en prestaties op het multi-task spel was.

In eerste instantie liet ik de beloning die verdiend kon worden buiten beschouwing en keek ik puur naar het vermogen om te multi-tasken. Ik zag dat deelnemers beter konden multi-tasken nadat ze bromocriptine hadden ingenomen. Eén probleem was echter dat dopamine D1 receptoren ook op bromocriptine kunnen reageren. Om te bevestigen dat het verbeterde multi-tasken *echt* door dopamine D2 receptoren kwam, werd een truc toegepast die in dieronderzoek veel gebruikt wordt. Vlak voor de inname van bromocriptine werd een ander medicijn ingenomen dat dopamine D2 receptoren blokkeert. Als bromocriptine een positief effect op multi-tasken had door de stimulatie van D2 receptoren, dan zou bromocriptine nu geen effect op multi-tasken meer moeten hebben. Dit was precies wat ik vond: wanneer dopamine D2 receptoren geblokkeerd waren, zag ik geen verbetering van bromocriptine meer.

Medicatie werkt echter niet bij iedereen hetzelfde; sommige mensen ervaren een positief effect, terwijl bij anderen geen verschil merkbaar is. Deze variabiliteit in de effectiviteit van medicatie kan deels verklaard worden door individuele genetische verschillen. Daarmee wordt bedoeld dat mensen met een bepaalde variant van een gen anders op medicatie reageren dan mensen met een andere variant van hetzelfde gen. Dit was nu ook het geval: Alleen mensen met een bepaald type dopamine gen lieten een verbetering van bromocriptine zien. Dit gen reguleert de aanmaak van dopamine transporters. Deze bevinden zich op de rand van de zenuwcel. Hier zorgt de dopamine transporter ervoor dat vrijgekomen dopamine weer opgeruimd wordt. Gebeurt dat niet, dan veroorzaakt dopamine ruis in de informatieoverdracht van de ene naar de andere cel. Het is bekend dat de effecten van dit dopamine gen vooral in het striatum zichtbaar zijn. De conclusie van het werk in hoofdstuk 3 was dat dopamine D2 receptoren in het striatum cruciaal zijn voor multi-tasken en dat het belangrijk is naar individuele verschillen te kijken wanneer we medicatie bestuderen.

Deelnemers konden tijdens het multi-tasken geld verdienen. Zo kon ik onderzoeken wat de invloed van beloning op multi-task prestaties was. De belofte van een hoge beloning zorgde ervoor dat mensen beter konden multi-tasken. Ik zag echter geen effect van bromocriptine en kon dus geen oorzakelijk verband tussen dopamine en de integratie van beloning en multi-tasken aantonen.

Metylfenidaat beïnvloedt de manier waarop beloningssignalen en multi-task signalen in het striatum geïntegreerd worden

In hoofdstuk 3 kon ik geen bewijs vinden voor een effect van bromocriptine op de integratie van beloning en multi-tasken. In **hoofdstuk 4** wilde ik op een andere manier een verband tussen dopamine en de integratie tussen beloningssignalen en multi-task signalen onderzoeken. Hiervoor gebruikte ik een medicijn dat veel gebruikt wordt bij de behandeling van ADHD: metylfenidaat (bijvoorbeeld Ritalin®). Metylfenidaat heeft invloed op dopamine niveaus in het brein en heeft geen specifiek effect op een bepaalde dopamine receptor. In hoofdstuk 4 keek ik eerst of de hersenen van mensen met ADHD, vergeleken met mensen zonder ADHD, op een andere manier signalen over beloning en multi-tasken integreren. Daarna onderzocht ik de invloed van metylfenidaat, en daarmee dopamine.

We weten dat patiënten met ADHD een verstoring laten zien in hersengebieden die betrokken zijn bij gedragscontrole en dat patiënten met ADHD vaak minder activiteit hebben in beloningsgebieden. Het is mogelijk dat beloningssignalen in patiënten met ADHD moeite hebben gedragscontrole gebieden bereiken. Als dit zo is, dan zouden problemen met gedragscontrole in ADHD (zoals impulsief reageren, of niet gecontroleerd tussen taken kunnen wisselen) veroorzaakt worden door een verstoring in motivationele en beloningsprocessen. Dit zou bijvoorbeeld kunnen verklaren waarom kinderen met ADHD die zich op school niet kunnen concentreren, maar wel uren achtereen met volle aandacht een computerspel kunnen spelen.

In **hoofdstuk 4** vergeleek ik deelnemers met en zonder ADHD terwijl ze het multi-task spel

speelden. De resultaten lieten een verhoogde hersenactiviteit in deelnemers met ADHD zien tijdens de integratie van belonings- en multi-task signalen. Deze verhoogde hersenactiviteit werd gemeten in de nucleus caudatus (**figuur 1**). Dit verschil was alleen aanwezig wanneer de patiënten met ADHD *geen* medicatie hadden ingenomen.

Dit was echter niet het hele verhaal. Van mensen met een bepaald type dopamine transporter gen (het "ADHD gerelateerd gen") is het waarschijnlijker dat ze ADHD hebben. Ik zag alleen een verhoogde hersenactiviteit in de deelnemers met ADHD die het ADHD gerelateerd gen bij zich droegen. Metylfenidaat had ook alleen in deze deelnemers een effect. Deze resultaten tonen aan dat de hersenen van mensen met ADHD, vergeleken met die van mensen zonder ADHD, op een andere manier signalen over beloningen overbrengen naar gebieden die bij gedragscontrole betrokken zijn. Het werk toont ook aan dat het belangrijk is verschillen tussen mensen te bekijken wanneer we de werking van medicatie bestuderen. Dat metylfenidaat het verschil in hersenactiviteit kon verhelpen toont een direct verband aan tussen dopamine en de integratie van belonings- en multi-task signalen in het striatum.

Ouderen gebruiken een andere strategie tijdens het multi-task spel

Een opmerkelijk resultaat in hoofdstuk 4 was dat alleen in de groep deelnemers met ADHD een effect van beloning op multi-tasken te zien was. In **hoofdstuk 3** liet ik zien dat beloning het multi-tasken beïnvloedde in gezonde deelnemers, maar dit zag ik in de groep zonder ADHD in hoofdstuk 4 niet. Eén mogelijke verklaring hiervoor is de leeftijd van de deelnemers. De deelnemers in hoofdstuk 3 waren jonger (gemiddeld 21 jaar oud) dan de gezonde deelnemers uit hoofdstuk 4 (gemiddeld 38 jaar oud). In **hoofdstuk 5** liet ik zien dat jongeren tijdens het multi-tasken extra snel zijn als ze een beloning kunnen verdienen, terwijl het gedrag van ouderen niet door de beloningen beïnvloed werd.

Om beloningsinformatie te gebruiken voor het optimaliseren van multi-tasken is het ventrale striatum cruciaal

Eén verklaring voor de effecten in ADHD (**hoofdstuk 4**) is dat de communicatie tussen het beloningsstriatum en controle gebieden verstoord is. Als dit zo is, dan zou het uitschakelen van het beloningsstriatum ervoor moeten zorgen dat een beloning het multi-tasken niet langer verbetert. In mensen is het echter ethisch gezien niet mogelijk een hersengebied uit te schakelen. In proefdieren kan dit wel. In **hoofdstuk 6** heb ik daarom een versie van het multi-task spel gemaakt die door ratten gespeeld kan worden. Nadat de ratten het spel hadden geleerd zag ik dat ze beter konden wisselen tussen taken wanneer ze meer eten konden verdienen. Vervolgens injecteerde ik in het beloningsstriatum van de helft van de ratten een stofje dat ervoor zorgt dat de zenuwcellen rondom de plaats van de injectie niet meer functioneren. In de dieren met een uitgeschakeld beloningsstriatum zorgde beloning er niet langer voor dat ze beter werden. Dit werk levert direct bewijs voor het idee dat het ventrale striatum cruciaal is om beloningsinformatie te gebruiken voor het optimaliseren van multi-tasken.

Signalen uit hersennetwerken kunnen geïntegreerd worden

Zoals gezegd kunnen we bij mensen geen hersengebieden uitschakelen. Voor onderzoek met mensen is wel een stimulatie techniek beschikbaar waardoor gebieden die direct onder de schedel liggen tijdelijk minder signalen aan andere gebieden kunnen doorgeven. Gebieden in de voorhoofdskwab vormen een netwerk met de gebieden in het striatum die een vergelijkbare functie hebben (**figuur 1**). Als beloningen een effect op ons gedrag (gedragscontrole en reacties) hebben moet informatie uit de beloningsgebieden in controle- en motoriek gebieden terechtkomen. De verbindingen zijn aanwezig. In mensen was echter niet eerder onderzocht of beloningssignalen geïntegreerd kunnen worden met signalen in de andere gebieden in het striatum terwijl mensen een taak uitvoeren waarvoor deze informatieoverdracht nodig is. In **hoofdstuk 7** heb ik dat onderzocht.

Ik heb het gebied in de voorhoofdskwab dat betrokken is bij het verwerken van beloningen (de aPFC) gestimuleerd (**figuur 1)**. Vervolgens keek ik wat het effect daarvan was op de hersenactiviteit in het striatum. Ik heb eerst gekeken of ik door het stimuleren van de aPFC de hersenactiviteit in het beloningsstriatum kon veranderen. Dit was inderdaad het geval: na het minder gevoelig maken van de aPFC zag ik dat het beloningsstriatum minder sterk op beloningsinformatie reageerde. Hierna heb ik gekeken of ik bewijs kon vinden voor de integratie van signalen tussen de netwerken. Wanneer informatie beperkt blijft tot het beloningsnetwerk, dan zou het stimuleren van de aPFC alleen een effect moeten hebben in het beloningsstriatum. Het stimuleren van de aPFC zou dan geen verandering in hersenactiviteit in de andere netwerken teweeg moeten brengen. Na stimulatie van de aPFC zag ik een afname van de hersenactiviteit in het putamen (motorisch striatum) terwijl mensen verschillende informatiebronnen tijdens het multi-task spel integreerden. Het werk in **hoofdstuk 7** laat zien dat signalen uit afzonderlijke netwerken in het striatum geïntegreerd kunnen worden.

Conclusie

Om goed te kunnen functioneren is het belangrijk dat we ons gedrag snel en gecontroleerd kunnen aanpassen aan de omgeving. Het is belangrijk om te weten wanneer het de moeite waard is om tussen werkzaamheden te schakelen.

In **hoofdstuk 3 en 4** liet ik zien dat dopamine belangrijk is voor de effecten van beloningsmotivatie op multi-tasken. In **hoofdstuk 4** toonde ik aan dat het effect van beloningsmotivatie op multi-tasken verstoord is bij mensen met ADHD. In **hoofdstuk 5** zag ik dat ouderen anders omgingen met beloningen tijdens het multi-tasken dan jongere deelnemers. Het onderzoek in **hoofdstuk 4 en 5** levert bewijs voor het idee dat stoornissen met gedragscontrole door een verandering van de invloed van beloning kunnen komen. In **hoofdstuk 3 en 4** liet ik zien dat het belangrijk is naar individuele verschillen te kijken als we effecten van medicatie bestuderen. In **hoofdstuk 6 en 7** heb ik informatieoverdracht tussen de netwerken onderzocht wanneer beloningen invloed op ons gedrag hebben. In **hoofdstuk 6** liet ik zien dat het beloningsstriatum cruciaal is voor de overdracht van beloningsinformatie tijdens multi-tasken. Met het werk in **hoofdstuk 7** toonde ik voor de eerste keer in mensen aan dat informatie tussen verschillende netwerken geïntegreerd kan worden.

Het werk in dit proefschrift laat zien dat het belangrijk is om bij de behandeling van gedragsproblemen ook naar beloningsfactoren te kijken. Deze bevindingen bieden perspectief en onderbouwing voor de ontwikkeling van het gebruik van tactieken van ouders of therapeuten. Denk daarbij aan het verhogen van beloningen als een kind zich weet in te houden of te concentreren. Mijn werk laat zien dat de verbindingen tussen de netwerken een belangrijk doelwit kunnen zijn voor de ontwikkeling van nieuwe medicatie om problemen met gedragscontrole te behandelen.

Dankwoord | Acknowledgements

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Biography

Mieke was born in Valkenswaard (The Netherlands). After attending high school there ("HAVO" at Were-Di college), she obtained a college certificate in applied psychology at Fontys in Eindhoven in 2003. After her undergraduate degree in psychology at the Radboud University in Nijmegen and a backpacking trip in Asia, Mieke went on to start a Master's in psychology (specializing in psychonomics), at the University of Amsterdam. During this period, she did an internship at the Amsterdam institute for addiction research (part of the Academic Medical Center). Under the supervision of Dr. Anneke Goudriaan and Ruth van Holst she investigated the neural mechanisms underlying a number of cognitive control processes in patients with alcohol dependence and pathological gamblers. A month after obtaining her master's degree Mieke started working as a research assistant with dr. Esther Aarts, in the Motivation and Cognitive Control lab of dr. Roshan Cools. With Esther, she worked primarily on a project studying adults with attention deficit hyperactivity disorder (ADHD). She studied the effects of ADHD medication on brain activity during cognitive control processes. In January 2011 Mieke was granted a full PhD scholarship (the DCCN TOPtalent scholarship) and she started her PhD in September of that year. During her PhD she used a number of techniques, including genetics, brain imaging (fMRI), brain stimulation (TMS), pharmacology to study how rewards can alter ones mental flexibility. During this period she also gained an interest in animal work. To test this curiosity, Mieke arranged a 1-year lab visit in the lab of dr. Bernard Balleine, at the university of Sydney, Australia.

Mieke is currently a postdoctoral researcher in the neural circuits and cognition laboratory of dr. Stan Floresco at the university of British Columbia in Vancouver in Canada, where she studies how dissociable regions of the prefrontal cortex are involved during cue-guided behaviour in the context of risky decision making and when switching between well-established tasks.

List of publications

Published work

1. Ma I, **van Holstein M**, Mies G, Mennes M, Buitelaar J, Cools R, Cillessen AHN , Krebs RM, Scheres A (2016) Ventral striatal hyperconnectivity during rewarded interference control in adolescents with ADHD. Cortex
2. Bradfield LA, Dezfouli A, **van Holstein M**, Chieng B, Balleine BW (2015) Medial Orbitofrontal Cortex Mediates Outcome Retrieval in Partially Observable Task Situations. Neuron 88:1268-1280.
3. Aarts E*, **van Holstein M***, Hoogman M, Onnink M, Kan C, Franke B, Buitelaar J, Cools R (2015) Reward modulation of cognitive function in adult attention-deficit/hyperactivity disorder: a pilot study on the role of striatal dopamine. Behav Pharmacol 26:227-240.
4. Cools R, Geurts DEM, **van Holstein M** (2013) Onderzoek naar gedragscontrole op het Donders Instituut. In: Wetenschappelijke doorbraken in de klas! DNA, Gedrag en Infecties onder de loep (Peeters MF, Meijer W, Verhoeff R, eds). Nijmegen.
5. van Holst RJ, **van Holstein M**, van den Brink W, Veltman DJ, Goudriaan AE (2012) Response inhibition during cue reactivity in problem gamblers: an fMRI study. PLoS One 7:e30909.
6. Aarts E, **van Holstein M**, Cools R (2011) Striatal Dopamine and the Interface between Motivation and Cognition. Front Psychol 2:163.
7. **van Holstein M***, Aarts E*, van der Schaaf ME, Geurts DE, Verkes RJ, Franke B, van Schouwenburg MR, Cools R (2011) Human cognitive flexibility depends on dopamine D2 receptor signaling. Psychopharmacology (Berl) 218:567-578.

* = shared first author

Papers in preparation

8. **van Holstein M**, Bradfield LA, Aarts E, Balleine BW
   Nucleus accumbens core lesions in rodents impair rewarded task-switching.

9. **van Holstein M**, Froboese M, O'Shea J, Aarts E, Cools R
   Controlling dorsolateral striatal function via anterior frontal cortex stimulation.

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