Resisting temptation

The role of the anterior cingulate cortex in adjusting cognitive control

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Resisting temptation:
The role of the anterior cingulate cortex in adjusting cognitive control

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“I can resist everything except temptation.”

Oscar Wilde

Inhoudsopgave

1.

Introduction

1.1 Cognitive Control

In order to flexibly adapt to our constantly changing environment, we need regulative processes that allow us to act in a goal-directed manner in the face of distractors or temptations. The research presented in this thesis is concerned with these regulative processes of resisting temptations, which I will refer to as *cognitive control*.

A region in medial frontal cortex, the anterior cingulate cortex (ACC), is often implicated in cognitive control. One of the dominant theories in the field, the conflict monitoring theory, states that the ACC monitors for response conflict and subsequently transmits signals to other regions that implement control adjustments. A role for the ACC in conflict monitoring has been particularly supported by brain imaging studies that have measured adjustments of behavior as a function of the previous trial (i.e., trial-to-trial adjustments). However, other findings indicate that the ACC regulates control itself, even in situations not involving response conflict. Moreover, it has been suggested that the ACC also uses motivational information to adjust control, which can be independent of response conflict.

The studies presented in this thesis aimed to elucidate the role of the ACC in cognitive control by using functional magnetic resonance imaging (fMRI; **Box 1**). Specifically, in chapters 2 and 3, I have investigated whether activity in the ACC is driven only by response conflict or also by other signals that indicate the need for cognitive adjustment. In chapter 4, I have investigated whether the ACC is involved in control adjustments at the task-set level in addition to the response level. In chapter 5, I have included motivational manipulations to investigate the role of motivation in control adjustments in the ACC and other connected regions. The results demonstrate that the ACC is involved in adjusting control itself, independent of response conflict. Moreover, I have shown that the ACC is involved not only in the cognitive adjustment of behavior, at both the response and task-set level, but also in the motivational adjustment of behavior. The neurotransmitter dopamine appears to play a critical role in this interface between motivation and cognition in the ACC. Below, I give a brief description of what control processes and motivational processes entail and which brain circuits they recruit.

1.1.1 Cognitive Control Paradigms

We often need to resist temptation to perform a less common (weak) response rather than a more common, more automatic (strong) response. This ability requires the inhibition of prepotent responses and the ignoring of distracting irrelevant information. For example, when a policeman takes over the control of the traffic, it might be hard to ignore the traffic light. Yet, one should focus on the policeman who tells you to stop, withholding the response to drive when the light turns green. A laboratory task that mimics such conflict situations is the Stroop task (Stroop, 1935). In the original color-word version of this task, participants name the ink color of written color words or read the words aloud (MacLeod, 1991). Stimuli can be congruent (e.g., the word RED in red ink), incongruent (e.g., the word BLUE in red ink), or neutral (e.g., a row of Xs in red ink for color naming or the word RED in black ink for word reading). In a blocked task design, only the color-naming task elicits conflict effects, that is, participants are slower when naming the color of an incongruent Stroop target compared with neutral or congruent targets, whereas there are no effects in the 'stronger' word reading task (for a computational account, see Roelofs, 2003). In every experiment discussed in this thesis, I have used an arrow-word variant of the Stroop task (**Figure 1.1**). In this Stroop-like task, participants respond either to the direction of the arrow (arrow task) or to the direction indicated by the word (word task). The arrow-word Stroop task is ideally suited to use with fMRI, because it allows manual (instead of vocal) responding with non-arbitrary mapping of responses onto buttons (i.e., *left* response with a left button press and *right* response with a right button press). Manual responding in the scanner is preferred because vocal responding elicits (movement) artifacts, and response times of vocal responses cannot be easily measured due to scanner noise. In a blocked task situation with manual responses to arrow-word stimuli, the word task is the 'weaker' task evoking conflict effects (Baldo et al., 1998; Turken and Swick, 1999; Roelofs et al., 2006). Like in classic color-word Stroop, the response time (RT) difference in responding to incongruent as compared to congruent targets reflects *response conflict*. The measure of response conflict was used in chapters 2-4.

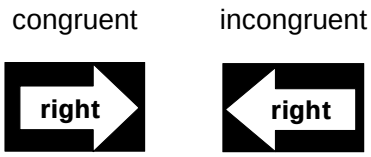

Figure 1.1 Examples of arrow-word Stroop stimuli. In the congruent condition, the arrow and meaning of the word denote the same direction. In the incongruent condition, the arrow and meaning of the word denote the opposite direction. Participants responded either to the arrow (arrow task) or the word (word task) by pressing a left or right button.

The Stroop task can be used to study *trial-to-trial adjustments* in control. Conflict effects in task performance are smaller following an incongruent trial than following a congruent one (for a review, see Egner, 2007). These sequential effects have been explained in terms of different cognitive control mechanisms. One of the dominant theories in the literature states that response conflict drives these adjustments in cognitive control (Botvinick et al., 2001). According to these theories, the level of control is low during trials that follow a congruent trial, because congruent trials are not associated with response conflict. Consequently, conflict effects are greater following these 'low control' congruent trials than following 'high control' incongruent trials. However, control adjustments can also be made if environmental *cues* provide information about which type of target is coming and, as a consequence, about which control setting is most appropriate for processing the upcoming target (Logan and Zbrodoff, 1982; Logan, 1985; Gratton et al., 1992). These cues manipulate subjects' expectancies about the upcoming target, even though they do not necessarily have to predict response conflict. In chapters 2 and 3, I have explored these cue-based adjustments in cognitive control to investigate whether abstract cues can elicit control adjustments independent of response conflict.

Another way to study goal-directed behavior is by using *task switching*. In task-switching designs, participants have to switch repeatedly between two or more tasks (Monsell, 2003), resisting the temptation to keep on repeating the same task. A task-switching design can also be employed with Stroop stimuli. When participants switch between responding to the two dimensions of the stimuli, Stroop conflict effects arise in both the weaker and stronger task (Allport and Wylie, 2000; Gilbert and Shallice, 2002; Yeung and Monsell, 2003). Because switching between tasks creates not only conflict at

the level of individual responses but also at the level of the whole task set (e.g., Rogers and Monsell, 1995; Allport and Wylie, 2000; Monsell, 2003), task switching can be used to study control adjustments at the task level. Specifically, in task-switching Stroop tasks, it has been observed that participants respond more slowly to congruent stimuli - affording both tasks in an experiment (i.e., they are bivalent) - than to neutral stimuli - affording only one task (i.e., they are univalent) (Rogers and Monsell, 1995; Aron et al., 2004; Monsell, 2005) (note, this is in contrast to the facilitation effect (RT congruent < RT neutral) usually observed in a blocked task situation (MacLeod, 1991)). This competition at the task-set level is termed *task conflict*, and I used this index in chapter 4. Another measure used in task switching, is simply the comparison of trials in which participants have to switch to the other task with trials in which participants can repeat the same task. Participants are typically slower when switching to another task than when repeating a task. Preceding cues can be helpful in preparing for an upcoming switch trial. Cues usually indicate the task to be performed on the following target. Thus, depending on the previous trial, these cues signal whether to repeat the previous task or switch task. Cued task switching was used as an experimental paradigm in chapters 4 and 5. Importantly, the switch cost is observed even when participants get ample time to prepare for a switch. The remaining switch cost (after >600 ms of preparation) is called the *residual switch cost* (Monsell, 2003). I used this residual switch cost as a cognitive measure in chapter 5.

1.1.2 Frontal Cortex

Numerous studies have implicated the frontal cortex of the human brain in cognitive control (for reviews, see Duncan and Owen, 2000; Miller, 2000; Kane and Engle, 2002). The frontal cortex consists of both lateral and medial areas, but I have focused primarily on the region in medial frontal cortex (MFC) that wraps around the anterior part of the corpus callosum: the anterior cingulate cortex[1] (ACC, Brodmann area [BA] 32 and 24), depicted in **Figure 1.2** (*top*). Neuroimaging studies have shown that the (dorsal) ACC plays a significant role in cognitive control (for reviews, see Picard and Strick, 1996; Bush et al., 2000; Paus, 2001; Ridderinkhof et al., 2004a). Particularly, early positron

emission tomography (PET) studies have found increased activity in the ACC for incongruent compared with congruent or neutral Stroop stimuli (Pardo et al., 1990; Bench et al., 1993; Carter et al., 1995); a finding that has been replicated repeatedly.

In early PET studies investigating focal awareness of a target, it was shown that ACC activity increased with number of targets in a set, and decreased with practice on a set (Posner, 1994). Similarly, Raichle and colleagues (1994) found practice-related decreases in the ACC in a word generation task, and ACC activity for response conflict was likewise observed to diminish with practice in a Stroop task (Bush et al., 1998). These findings gave rise to the theory stating that the ACC is important for executive functions of awareness and control (Posner, 1994).

Studies investigating trial-to-trial adjustments during the Stroop task further refined and revised the views on the role of the ACC in cognitive control. It was found that activity in the ACC shows a pattern which parallels behavioral performance, i.e., conflict effects in the ACC are greater following congruent trials than following incongruent trials (Botvinick et al., 1999; Kerns et al., 2004). Specifically, greater ACC activity on the previous trial predicted better behavioral adjustments on the present trial. Moreover, these adjustments were associated with increased activity on the present trial in the dorsolateral prefrontal cortex (DLPFC; middle frontal gyrus, BA 9/46, see **Figure 1.2**, *bottom*) (Kerns et al., 2004), a region that is richly connected to the ACC (Bates and Goldman-Rakic, 1993; Van Hoesen et al., 1993). These findings supported the *response conflict monitoring theory*, according to which the ACC monitors for conflict, and subsequently signals to the DLPFC to implement top-down control processes (e.g., MacDonald et al., 2000; Botvinick et al., 2004). Thus, according to this theory, the ACC drives adjustments in control by monitoring for response conflict.

However, other views exist in the literature about the role of the ACC. Recently, using the arrow-word Stroop paradigm, Roelofs and colleagues (2006) have observed not only differential ACC activity when comparing incongruent with congruent stimuli, but also when comparing neutral with congruent stimuli. In both neutral and congruent stimuli, there is no response conflict involved, thus, the ACC was differentially active in the absence of response conflict. The authors suggested that the ACC might have a regulatory role, instead of merely detecting response conflict. Moreover, single cell

recordings in monkey ACC suggested that activity in the area varies with the amount of control exerted rather than with conflict per se (for a review, see Schall and Boucher, 2007). Also, monkey studies suggest that the ACC exerts control over vocal responding (for reviews, see Jürgens, 2002; Roelofs, 2008a). These results are in agreement with the interpretation that the ACC implements cognitive control rather than monitoring conflict (Posner and DiGirolamo, 1998; Turken and Swick, 1999). According to this view, the ACC is implicated in 'selection-for-action' (e.g., Paus et al., 1993; Posner and Raichle, 1994; Posner and DiGirolamo, 1998; Roelofs and Hagoort, 2002; Matsumoto et al., 2003) (see **Table 1.1**).

In addition to being activated by control demands at the response level, the ACC has been shown to be engaged by task switching (e.g., Luks et al., 2002; Yeung et al., 2006; Leber et al., 2008), which involves competition between task sets. Importantly, the ACC was also found to be active during preparation for a task switch (e.g., Luks et al., 2002; Johnston et al., 2007), which is in accordance with other studies finding anticipatory ACC activity before a response has to be executed (Murtha et al., 1996; Weissman et al., 2005; Dosenbach et al., 2006; Parris et al., 2007). This cue-related ACC activity cannot easily be explained by a response conflict monitoring account of ACC functioning as the cues in these studies did not convey any response conflict themselves. In chapter 5, a study is reported in which participants could use task cues to prepare for a task switch and reward cues to anticipate reward. The study revealed that the ACC is involved in task switching, and, importantly, that switch-related activity in the ACC was influenced by the anticipation of reward and striatal dopamine levels. This reward-related ACC activity is not likely to be explained by the response conflict monitoring theory. Below, I give a description of motivational processes and the role of dopamine.

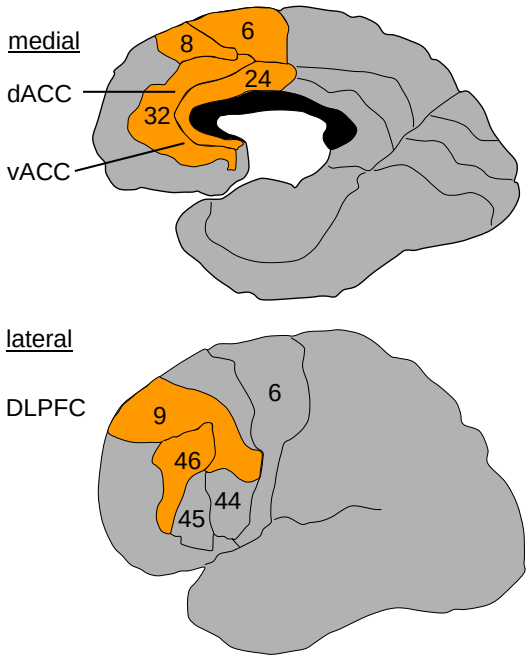

Figure 1.2 Medial (*top*) and lateral (*bottom*) views of the frontal cortex depicting the Brodmann areas (BA). Anterior cingulate cortex (ACC) consists of BA 24 and 32, with dorsal ACC (dACC) activity often spreading to BA 8 and 6. Dorsolateral prefrontal cortex (DLPFC) consists of BA 9 and 46.

1.2 Motivational Control

Because our goals are often directed to obtaining rewards or avoiding punishments, incentive *motivational control* is intrinsically linked to cognitive control processes.

Incentive motivation refers to the state triggered by external stimuli that have appetitive (rewarding) or aversive (punishing) properties. There is ample evidence that such incentive motivational processes interact with cognitive control processes (e.g., task switching) to facilitate behavioral adjustment (Nieuwenhuis and Monsell, 2002; Pochon et al., 2002; Gilbert and Fiez, 2004; Taylor et al., 2004; Small et al., 2005; Krawczyk et al., 2007; Locke and Braver, 2008; Mohanty et al., 2008; Pleger et al., 2008). Given recent emphasis on a role for the ACC not only in the cognitive adjustment of behavior,

but also in the influence of reward on behavior (see below), I have adapted my arrow-word paradigm to be able to assess its role in motivational control as well. In chapter 5, I have added a second type of anticipatory cue to my arrow-word paradigm. Specifically, in this experiment the task-switching cues were preceded by cues signaling high reward or low reward.

In animals, incentive motivation is commonly assessed using conditioned reinforcement or pavlovian-to-instrumental transfer paradigms (Robbins et al., 1989). In short, these paradigms assess the effects of (pavlovian) cues associated with reward on subsequent (instrumental) responding for reward on one of more levers. This work has elucidated important neurobiological mechanisms underlying incentive motivation.

1.2.1 Fronto-Striatal Loops and Dopamine

A subcortical region that is typically associated with reward and motivation, is the nucleus accumbens in the ventral striatum (for reviews, see Robbins and Everitt, 1992; Ikemoto and Panksepp, 1999; Cardinal et al., 2002; Robbins and Everitt, 2003). In the 1950s, Olds and Milner (1954) discovered that rats will keep pressing a lever that results in (reinforcing) electrical self-stimulation in certain regions in their brains, especially along the medial forebrain bundle, a major pathway interconnecting the midbrain and forebrain. The medial forebrain bundle represents a part of the mesolimbic pathway, which carries information between the ventral tegmental area (VTA) in the midbrain and the nucleus accumbens (**Figure 1.3**). Midbrain areas VTA and the substantia nigra, with their high density of dopaminergic neurons, also innervate the PFC and dorsal striatum via so-called mesocortical and nigrostriatal pathways (**Figure 1.3**). These pathways innervate functionally segregated circuits: a ("limbic") ventral fronto-striatal circuit, including the ventral striatum and ventral/medial PFC areas involved in motivational processes, and a ("associative-sensorimotor") dorsal fronto-striatal circuit, including the dorsal striatum (caudate nucleus and putamen) and dorsal/lateral PFC areas involved in cognitive-motor processes (Alexander et al., 1986). Accordingly, this anatomical arrangement of dopaminergic pathways is perfectly suited to influence motivational as

well as cognitive control. An important role for dopamine in incentive motivation is supported by empirical evidence from behavioral studies.

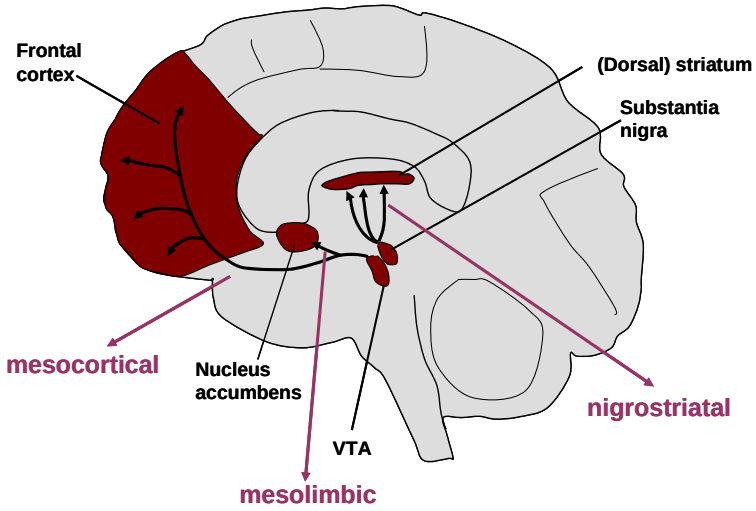

Figure 1.3 Medial view of the brain showing mesocortical, mesolimbic, and nigrostriatal dopamine pathways from midbrain areas VTA and substantia nigra to dorsal striatum ("striatum"), ventral striatum ("nucleus accumbens"), and frontal cortex.

Dopamine-blocking drugs have been found to decrease operant responding for electrical self-stimulation (see above), leading to the idea that dopamine plays an important role in reward processing (Liebman and Butcher, 1973; Lippa et al., 1973; Fouriezos and Wise, 1976). Originally, it was stated, in the hedonia hypothesis, that dopamine mediates the subjective feeling of satisfaction (or 'liking') during reward receipt (Wise et al., 1978). However, accumulating evidence from psychopharmacological work with experimental animals, in which paradigms of conditioned reinforcement and pavlovian-to-instrumental transfer were employed, indicates that dopamine is much more key for preparatory processes in anticipation of reward than for consummatory processes during reward receipt (Taylor and Robbins, 1984; Wyvell and Berridge, 2000; Baldo and Kelley, 2007). Subsequent electrophysiological work of Schultz and colleagues (for reviews, see Schultz et al., 1997; Schultz, 2002, 2006) has substantiated the general notion that dopamine is important for reward by showing that reward elicits a phasic response in dopamine

neurons. However, when learning occurred, presentation of the reward no longer elicited a phasic dopamine response, but instead the conditioned stimulus (that predicted reward) did. Moreover, when an expected reward was not given, dopamine neurons decreased their firing rate at the time of reward omission. Interestingly, these dopamine neurons appeared to behave according to a *reinforcement learning* algorithm, originally developed in computer science (for a review, see Sutton and Barto, 1998), encoding a *temporal difference* or *prediction error* (Montague et al., 1996). According to this model, positive prediction errors are accompanied by phasic dopamine bursts, indicating that ongoing events are better than expected (i.e., more reward), while negative prediction errors are accompanied by phasic dopamine dips, indicating that ongoing events are worse than expected. This observation has led to the hypothesis that dopamine neurons subserve learning and become active, over the course of learning, in anticipation of a reward rather than during the receipt of the reward, arguing against the hedonia hypothesis in which dopamine is associated with the subjective pleasures of reward consumption only (see also Berridge and Robinson, 1998; Baldo and Kelley, 2007). Similar to dopamine in the ventral fronto-striatal circuit, dopamine in the dorsolateral fronto-striatal circuit seems to be important for anticipatory or preparatory processes. Specifically, dopamine in the dorsal striatum - which is strongly connected to the dorsolateral PFC and implicated in motor and cognitive control (White, 1997; Toni and Passingham, 1999; Packard and Knowlton, 2002) - has been suggested to contribute to preparatory processes in establishing a cognitive or motor set (Robbins and Everitt, 1992).

Neuroimaging studies investigating reward processes in humans have consistently found differential activity in regions in the ventral fronto-striatal circuit, like the ventral striatum, the medial frontal cortex (including the ACC), and the orbitofrontal cortex (OFC) (for reviews, see O'Doherty, 2004; Knutson and Cooper, 2005). In particular, the anticipation or prediction of reward has been demonstrated to activate the ventral striatum (e.g., Knutson et al., 2001; O'Doherty et al., 2004). Moreover, model-based fMRI studies investigating reinforcement learning have implicated the ventral striatum and the OFC in the encoding of the reward prediction error (for a review, see O'Doherty et al., 2007). Specifically, Pessiglione and colleagues (2006) have recently reported that striatal

activity associated with the reward prediction error during reinforcement learning in humans was modulated by dopaminergic drugs, in line with the findings of Schultz and colleagues (see above).

Various theories have linked control adjustments in the ACC to motivational processes (see **Table 1.1**). The ACC receives dense projections from cortical and subcortical limbic areas, like the amygdala and the ventral striatum. Moreover, the error-related negativity (ERN), a negative deflection in the ongoing electroencephalogram (EEG) seen when human participants commit errors, appears to be generated in the ACC (Dehaene et al., 1994). On the basis of these findings and the role of the ACC in learning (see also above mentioned studies in paragraph 1.1.2 of practice-related decreases in ACC activity), Holroyd and Coles (2002) have implicated the ACC in outcome evaluation during reinforcement learning, using negative dopaminergic reinforcement learning signals. Other theories of ACC functioning that incorporate motivational processes state that the ACC learns to predict error likelihood or avoid negative outcomes (Ridderinkhof et al., 2004b; Brown and Braver, 2005; Magno et al., 2006), or regulates arousal states on the basis of affective or physiological signals (Critchley et al., 2003). In keeping with these motivational theories of ACC function, it has been suggested that the ACC - which receives dense projections from limbic areas, projecting to a diversity of motor areas - is ideally suited to provide a critical pathway for emotional and motivational factors to influence motor activity (Pandya et al., 1981; Vogt et al., 1993; Morecraft and Van Hoesen, 1998). Rushworth, Walton, and colleagues elaborated this theory by stating that the ACC engages in a cost-benefit analysis; encoding gains, costs, and effort of an action to guide decision making (Rushworth et al., 2007; Walton et al., 2007; Rushworth and Behrens, 2008).

The above mentioned studies have highlighted that the ACC is not merely involved in cognitive control processes, but also uses motivational input to adjust control. Such a motivation-cognition interface is likely to be modulated by the dopamine system. The ventral striatum, a region heavily connected to the ACC and an important node in the dopaminergic pathway, is also well-documented as an interface between motivation and cognition/action (Mogenson et al., 1980; Cardinal et al., 2002). Furthermore, Haber and colleagues (2000; 2003) have established striato-nigro-striatal spiraling loops that would

be perfectly suited to subserve a mechanism by which dopamine can direct information flow between ventral and dorsal striatum, thus providing an anatomical basis for the motivation-cognition interface via the ventral midbrain. Evidence of such a dopamine-modulated interaction between motivation and cognition will be provided in chapter 5 of this thesis.

1.3 Outline of the Thesis

The main issue addressed in this thesis is the role of the ACC, and strongly connected structures, in adjusting cognitive control. I chose to measure these control adjustments by using different types of cues that participants could use to prepare for the upcoming arrow-word Stroop target (see **Figure 1.1**). In chapters 2 and 3, I informed participants about the upcoming Stroop condition (e.g., incongruent or congruent) while they performed the word task in the arrow-word Stroop paradigm. Specifically, in chapter 2, by using 100% valid cues, I found that control adjustments in the ACC can be elicited in anticipation of a target stimulus and independent of response conflict and error likelihood. In chapter 3, the cues were no longer 100% valid but correctly predicted an incongruent or congruent target on only 75% of trials (probabilistic cues). In 25% of cases the cue was followed by an unpredicted target. This uncertain task situation is comparable to trial-to-trial adjustment studies in which the following target can also not exactly be predicted. The results showed that, in a probabilistic task, the ACC was even more active for congruency-predicting cues than for incongruency-predicting cues. Accordingly, these data strengthen the results from chapter 2, and also suggest that different strategies for control adjustment are adopted in deterministic (chapter 2) and probabilistic tasks (chapter 3).

In chapters 4 and 5, participants had to perform both the word and the arrow task with the arrow-word Stroop stimuli. Participants had to switch between both tasks as indicated by preceding task cues. Task switching was used in chapter 4 to elicit task conflict, besides the response conflict elicited by incongruent Stroop targets. This enabled me to find possible dissociations within and between medial and lateral frontal regions

regarding response and task conflict. It turns out that the ACC and more dorsal regions in MFC were engaged for both response conflict and task conflict, similar to ventrolateral PFC, whereas dorsolateral PFC was mainly engaged by task conflict. In chapter 5, random task switches were used to study switch effects as a measure of cognitive control that could be influenced by the anticipation of reward. The reward-cued task-switching paradigm in chapter 5 provided the opportunity to investigate whether ACC activity also reflects cognitive adjustment signalled by motivational cues. By looking at brain activity as a function of inter-individual variation in the dopamine transporter genotype ("genetic imaging", see **Box 1**) I could show that such effects are indeed present, but only in certain individuals with genetically determined high levels of dopamine. These latter data elucidate the role of striatal dopamine in reward and its influence on cognitive control and ACC activity.

Table 1.1 Theories of the role of the ACC in adjusting cognitive control

theory of ACC functioning	**control adjustments on the basis of**	**evaluating need for control**	**implementing control**
conflict monitoring[1]	response conflict	ACC	dlPFC
selection-for-action[2]	attentional demands	PFC	ACC, PFC
reinforcement learning[3]	negative outcomes*	striatum	ACC
error prediction / risk avoidance[4]	error likelihood*	ACC	(dl)PFC
arousal regulation[5]	autonomic / cognitive signals of effort; pain	cognitive: PFC	ACC
cost-benefit analysis[6]	positive and negative outcome / prediction values	ACC	ACC

[1] MacDonald et al., 2000; Botvinick et al., 2004

[2] Paus et al., 1993; Posner and DiGirolamo, 1998; Turken and Swick, 1999; Matsumoto et al., 2003; Roelofs et al., 2006

[3] Holroyd and Coles, 2002

[4] Ridderinkhof et al., 2004b; Brown and Braver, 2005; Magno et al., 2006

[5] Critchley et al., 2003

[6] Walton et al., 2007; Rushworth and Behrens, 2008

* with the help of dopaminergic teaching signals

ACC: anterior cingulate cortex; dlPFC: dorsolateral prefrontal cortex

[1]Throughout this thesis, when activity in the ACC spreads to more posterior and dorsal regions (BA 8 and 6, including pre-supplementary motor area [pre-SMA]), we refer to the dorsal ACC (dACC), comparable to the rostral cingulate zone (RCZ, Picard and Strick, 1996). When we refer to the ventral ACC (vACC) we mean the region of the ACC anterior to the corpus callosum or subcallosal (see also Bush et al., 2000; Koski and Paus, 2000).

BOX 1: Functional magnetic resonance imaging

The magnetic resonance (MR) scanner, with a static magnetic field typically ranging between 1.5 and 4.0 Tesla, uses a series of changing magnetic gradients and oscillating electromagnetic fields to create images of biological tissue, like brain structures. However, to be able to investigate the active function of the brain, *functional* neuroimaging studies are necessary. Functional neuroimaging attempts to localize different mental processes to different parts of the brain, in effect creating a map of which areas are responsible for which processes. Functional magnetic resonance imaging (fMRI) is the technique used in the research described in this thesis. Functional MRI has only been available since the early 1990s. Although it is not a perfect technology (i.e., it is sensitive to participant head motion, participants with certain types of metal in their bodies or claustrophobia cannot be scanned, and changing currents in the gradient coils induce loud noise), fMRI presents a number of advantages over other functional imaging techniques like SPECT (single photon emission computed tomography) and PET (positron emission tomography). Namely, fMRI is noninvasive (no injections or inhalations needed) and does not require participants to be exposed to ionizing radiation. Like most researchers, I used fMRI to measure changes in blood oxygenation over time, which is intrinsic to normal brain physiology. Because blood oxygenation levels change rapidly following activity of neurons in a brain region, fMRI offers millimeter spatial resolution and temporal resolution on the order of seconds. It is important to note that this blood-oxygenation-level dependent (BOLD) contrast is a *correlate* of neuronal activity, reflecting sensitivity to the amount of paramagnetic deoxyhemoglobin present, which changes according to the metabolic demands of active neurons (Huettel et al., 2004).

Following image reconstruction from the scanner, computational procedures are applied to the fMRI data. So-called preprocessing steps are necessary to reduce variability in the data that is not associated with the experimental task and to prepare the data for statistical testing. In the experiments presented in this thesis, I have used event-related designs. This means that short-duration events (i.e., trials consisting of for example cues and target stimuli) were presented in a randomized order with variable timing rather than clustered together in a block. During statistical testing (following preprocessing), we compared brain activity for the different type of events (i.e., conditions) in the context of the general linear model (GLM) on a group level. Typically, I show subtracted activity elicited in two conditions, for example brain regions showing more activity during the incongruent than the congruent Stroop condition.

Additionally, one can look at brain activity as a function of inter-individual genetic variation, called *genetic imaging* (for reviews, see Goldberg and Weinberger, 2004; Green et al., 2008). The role of a neuromodulator like dopamine can be investigated non-invasively in humans by looking at brain activity as a function of genetic variation in dopaminergic genes (see chapter 5). For example, a group of participants with a variant of a gene associated with more dopamine availability in certain brain regions might have different task-related brain activity as compared to a group of participants with another variant of that gene. This intermediate phenotype, i.e., variation in brain activity, is more sensitive than behavioral measures alone in elucidating the role of genetic variation in cognitive functioning.

2.

Anticipatory Activity in Anterior Cingulate Cortex can be Independent of Conflict and Error Likelihood

Esther Aarts, Ardi Roelofs, and Miranda van Turennout

Adapted from:

Aarts, E, Roelofs, A, & Van Turennout, M (2008). Anticipatory activity in anterior cingulate cortex can be independent of conflict and error likelihood. *Journal of Neuroscience* 28(18): 4671– 4678.

2.1 Abstract

Previous studies have found no agreement on whether anticipatory activity in anterior cingulate cortex (ACC) reflects upcoming conflict, error likelihood, or actual control adjustments. Using event-related fMRI, we investigated the nature of preparatory activity in the ACC. Informative cues told the participants whether an upcoming target would or would not involve conflict in a Stroop-like task. Uninformative cues provided no such information. Behavioral responses were faster after informative than after uninformative cues, indicating cue-based adjustments in control. ACC activity was larger following informative than uninformative cues, as would be expected if the ACC is involved in anticipatory control. Importantly, this activation in the ACC was observed for informative cues even when the information conveyed by the cue was that the upcoming target evokes no response conflict and has low error likelihood. This finding demonstrates that ACC is involved in anticipatory control processes independent of upcoming response conflict or error likelihood. Moreover, the response of the ACC to the target stimuli was critically dependent upon whether the cue was informative or not. ACC activity differed among target conditions after uninformative cues only, indicating ACC involvement in actual control adjustments. Taken together, these findings argue strongly for a role of the ACC in anticipatory control independent of anticipated conflict and error likelihood, and also show that such control can eliminate conflict-related ACC activity during target processing. Models of frontal cortex conflict-detection and conflict-resolution mechanisms require modification to include consideration of these anticipatory control properties of the ACC.

2.2 Introduction

Cognitive control refers to regulatory processes that ensure that our actions are in accordance with our goals. Neuroimaging experiments have shown that the anterior cingulate cortex (ACC) plays a role in cognitive control, together with other areas in frontal and parietal cortex (for reviews, see Picard and Strick, 1996; Bush et al., 2000; Miller, 2000; Paus, 2001). However, the exact function of the ACC in cognitive control is still a matter of debate. Some researchers have claimed that ACC activity reflects top-

down regulation processes (Posner and Raichle, 1994; Roelofs and Hagoort, 2002; Swick and Turken, 2002; Roelofs, 2003; Dosenbach et al., 2006; Roelofs et al., 2006; Posner and Rothbart, 2007), while others have argued that ACC activity reflects the detection of competing response alternatives (Carter et al., 1999; MacDonald et al., 2000; Botvinick et al., 2001; Kerns et al., 2004). According to this latter conflict monitoring hypothesis, the occurrence of response conflict is signalled by the ACC and leads to the recruitment of more cognitive control for subsequent performance executed by the lateral prefrontal cortex (LPFC).

Recently, Sohn et al. (2007) extended the role of the ACC as a response conflict monitor to include anticipatory conflict monitoring. Brown and Braver (2005) argued that the ACC predicts error likelihood, independent of response conflict. More generally, control adjustments can be made if environmental cues provide information about which type of target is coming and, as a consequence, about which control setting is most appropriate for processing the upcoming target (Logan and Zbrodoff, 1982; Logan, 1985; Gratton et al., 1992). However, these cues do not necessarily have to predict response conflict or error likelihood (Gratton et al., 1992). This raises the question whether anticipatory activity in the ACC may be obtained independent of upcoming conflict or error likelihood. We report an fMRI experiment that examined this issue.

Participants were informed about Stroop-like target conditions by means of symbolic cues, which were presented well before the imperative target on each trial (**Figure 2.1**). The symbolic cue indicated whether the upcoming Stroop target was congruent, incongruent, or neutral, or the cue provided no information about the upcoming condition. Earlier behavioral studies indicated that participants are able to process the cue and extract the information about the target condition it conveys and adjust their control accordingly (Logan and Zbrodoff, 1982; Gratton et al., 1992).

If the ACC plays a role in anticipatory adjustments in control, ACC activity should be higher in response to informative cues than to uninformative cues. If the adjustments are independent of response conflict or error likelihood, enhanced ACC activity should be obtained for cues preceding congruent targets. Adjustments are expected in premotor cortex, where response rules are implemented (Wallis and Miller, 2003). Moreover, if the advance adjustments are successful, ACC activity should exhibit

smaller differences among target conditions in response to targets after informative cues (when control was adjusted in advance) than following uninformative cues (when control was not adjusted in advance).

2.3 Materials and Methods

2.3.1 Subjects

Twelve neurologically healthy Dutch undergraduates (10 female and 2 male, mean age 21.2 years, range 18-24) participated in the experiment. All participants were right-handed and native speakers of Dutch. They were compensated for participation and gave written informed consent in a manner approved by the Dutch Central Committee on Research Involving Human Subjects (CCMO).

2.3.2 Stimuli and Paradigm

The participants were scanned while performing a manual arrow-word version of the Stroop task. As with color-word Stroop stimuli, responding in this task is usually slower on incongruent than on neutral trials and it is fastest on congruent trials (Baldo et al., 1998; Turken and Swick, 1999; Roelofs et al., 2006). The targets consisted of written words in arrows (**Figure 2.1**). The lines and letters of the targets were white on a black background. The arrows pointed to the left or to the right. The word in the arrow was the Dutch word for *right* (*rechts*) or for *left* (*links*). Participants responded manually to the words of the Stroop-like targets by pressing a left or right button on a scanner-compatible button box. Participants were told to respond as quickly and accurately as possible with the left middle finger (for *left* response) and the left index finger (for *right* response). In the congruent target condition, the arrow and the word denoted the same direction (e.g. the word *right* in an arrow pointing to the right). In the incongruent target condition, the arrow and the word denoted a different direction (e.g., the word *left* in an arrow pointing to the right). In the neutral target condition, the targets consisted of words (*left* or *right*) in rectangles without arrow points.

Every target was preceded by a cue (see **Figure 2.1**). The cue was a coloured square giving either information about the upcoming target condition (informative cue) or giving no information (uninformative cue). The informative cues were 100% valid with green squares preceding congruent targets, red squares preceding incongruent targets, and yellow squares preceding neutral targets. The uninformative cues were grey squares, which could be followed by either one of the target types. Participants were told to pay explicit attention to the cues in order to let them be of help in processing the target. It was brought to the participants' attention that during congruent trials one could be helped by the non-relevant dimension of the target (i.e., the arrow) and that one should not be distracted by the arrow in case of an incongruent trial (Logan and Zbrodoff, 1982). The experiment included 240 trials, consisting of 120 informative and 120 uninformative cues, and each type of trial containing 40 incongruent, 40 congruent and 40 neutral targets. Informative and uninformative cues, as well as congruent, incongruent, and neutral targets were randomly intermixed.

The target followed the cue after a variable delay of 2 - 7 s. Similarly, a variable delay of 2-7 s was used between a target and the next cue. The jitter was calculated with a simulation of the BOLD response in SPM99 (Wellcome Dept. of Cognitive Neurology, London). The variable delays enabled us to characterize the haemodynamic responses at a finer temporal resolution than the actual TR (Josephs et al., 1997) and thus allowed us to reliably distinguish the BOLD response to the cue from the BOLD response to the target (see for a similar procedure: Toni et al., 1999; Mars et al., 2005). This calculation was repeated to generate a random sequence with optimal delays for every participant separately. Because the delay between cue and target could not be predicted, the participant needed to be ready to respond at any time. Cues and targets remained on the screen for 600 ms.

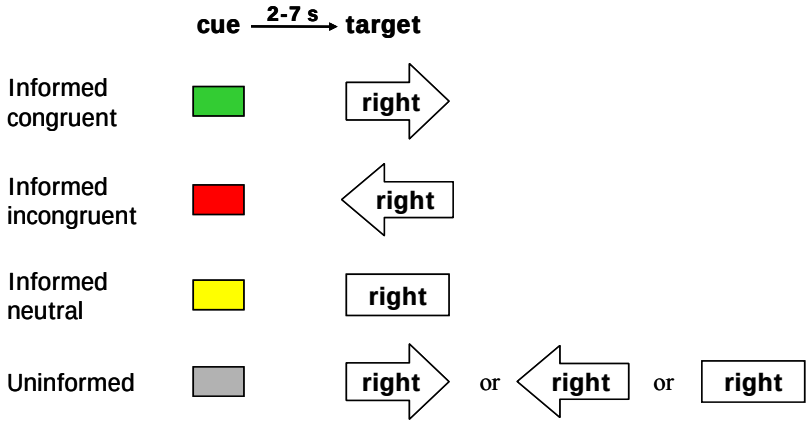

Figure 2.1 Experimental paradigm. Depicted are the informative and uninformative cues and examples of congruent, incongruent, and neutral targets with the word 'right'. Green cues were always followed by congruent targets, red cues were always followed by incongruent targets, and yellow cues were always followed by neutral targets. Gray cues could be followed by either one of the three target conditions, and hence were uninformative. The task was to indicate the direction denoted by the word by pressing a left or right button.

2.3.3 Functional Imaging

Whole-brain imaging was performed on a 3 Tesla MR scanner (Magnetom Trio, Siemens Medical Systems, Erlangen, Germany). Functional data were acquired using a gradient-echo echo-planar scanning sequence (repetition time = 2100 ms, echo time = 30 ms, 33 axial slices, voxel size = 3.5 mm x 3.5 mm x 3.5 mm, field of view = 224 mm, flip angle = 70º). All functional images were acquired in a single run lasting 40 minutes. Visual stimuli were projected on a screen and were viewed through a mirror attached to the head coil. After the acquisition of functional images, a high-resolution anatomical scan (T1-weighted MP-RAGE, 192 slices) was obtained.

2.3.4 Behavioral Data Analysis

The mean latencies of the correct manual responses and the error rates were analyzed using repeated-measures analyses of variance (ANOVA) with the factors target condition

(congruent, incongruent, neutral) and cue condition (informed, uninformed). All variables were tested within participants. Specific effects were tested with paired *t*-tests. An effect was called significant when $p < .05$.

2.3.5 FMRI Data Analysis

fMRI data were analysed with BrainVoyager QX (Brain Innovation, Maastricht, the Netherlands). Functional images were corrected for slice time acquisition (using sinc interpolation) and 3D motion correction was performed to detect and correct for small head movements. Estimated translation and rotation parameters were inspected and never exceeded 3 mm. Linear trend removal was performed and the signal was temporal high-pass filtered to remove low-frequency non-linear drifts of 3 or fewer cycles per time course. Functional images were co-registered with the anatomical scan and transformed into Talairach coordinate space using the nine-parameter landmark method of Talairach and Tournoux (Talairach and Tournoux, 1988). Images were spatially smoothed with a full-width at half maximum (FWHM) Gaussian kernel of 6 mm.

Statistical analyses were performed in the context of the general linear model, including the event types of interest: informative cues preceding congruent, incongruent, and neutral targets; uninformative cues preceding congruent, incongruent, and neutral targets; congruent, incongruent, and neutral informed targets; congruent, incongruent, and neutral uninformed targets. Trials on which participants had made an error were put together as a separate event type of non-interest. Six motion parameters were included as event types of non-interest as well. The event types were modeled with a two gamma haemodynamic response function that was adjusted in such a way that it equalled the haemodynamic response function in SPM99 on the basis of which the jitter was calculated (see above). Random-effects group analyses were performed enabling generalization of the statistical inferences to the population level. A conjunction analysis with a standard 'minimal t-statistic' approach (Nichols et al., 2005) was used with the contrasts (informative cues > uninformative cues) ∩ (uninformed targets > informed targets), to assess the effect of cue type on target processing. This conjunction analysis is equivalent to a logical AND of the contrasts at the voxel level. The statistical threshold

for the group analyses was set at $p < 0.001$ at the voxel level with a minimum cluster size of 50 mm^3/14 original voxels (Forman et al., 1995), uncorrected for multiple comparisons.

To investigate differential effects of cue information in the ACC, we obtained subject-averaged beta weights (i.e., regression coefficients) for all cue conditions as indices of effect size for all voxels in the functionally defined region of the ACC showing an effect of informative cues versus uninformative cues in the random effects group analysis. To investigate the effect of cue information on target-related effects in the ACC, subject averaged beta-weights were extracted for all target conditions from ACC voxels showing an effect of informative cues versus uninformative cues in the random effects group analysis. In addition, to ensure that the observed effects were the same regardless of the contrast used to select the beta weights, subject averaged beta-weights were extracted for each event type from ACC voxels showing an effect of incongruent versus congruent targets in the uninformative condition. Regionally averaged beta-weights were analyzed in repeated-measurement ANOVAs. Specific effects were tested by applying paired *t*-contrasts to the beta weights obtained for the different event types. The regional-specific time-courses were standardized, so that beta weights reflected the BOLD response amplitude of one condition relative to the variability of the signal. An effect was called significant when $p < .05$.

Premotor cortex activity should reflect the operation of control in response to informative cues. Therefore, we expected a positive correlation between ACC and premotor activity. To test these predictions, we computed Pearson correlations between the beta-weights in the ACC and the regions differentially activated on the cues in **Table 2.1**. We mention only correlations that were significant for all three separate cue conditions and report *p*-values on a Bonferroni corrected alpha level ($p < .002$) across subjects and cue conditions ($n = 36$). Furthermore, we tested for the significance of the difference between (dependent) correlations (Chen and Popovich, 2002).

2.4 Results

2.4.1 Behavioral Data

Analysis of the reaction time data (**Figure 2.2**) showed a main effect of target condition [$F(2,22) = 69.51$, $p < .001$] and a main effect of cue condition [$F(1,11) = 45.36$, $p < .001$]. The interaction between cue condition and target condition was significant [$F(2,22) = 7.48$, $p = .003$]. A similar pattern was observed for the errors. The analysis yielded a main effect for target condition [$F(2,22) = 7.66$, $p = .003$], a marginally significant main effect for cue condition [$F(1,11) = 4.17$, $p = .066$], and a significant interaction between cue condition and target condition [$F(2,22) = 6.19$, $p = .007$].

Reaction times were slower in the incongruent than in the neutral condition [$t(11) = 5.33$, $p < .001$], and fastest in the congruent condition [compared with neutral: $t(11) = 8.97$, $p < .001$]. Most errors were made in the incongruent condition [compared with neutral: $t(11) = 2.85$, $p = .008$, one-tailed; compared with congruent: $t(11) = 2.98$, $p = .007$, one-tailed], whereas, the neutral and congruent condition did not differ [$t(11) = -0.33$, $p = .742$]. Thus, conflict and error likelihood were higher in the incongruent condition than in the other conditions.

The difference in response times between congruent and neutral targets (i.e., the facilitation effect) was larger after informative cues (83 ms) than after uninformative cues (25 ms) (**Figure 2.2**) [$t(11) = 4.47$, $p < .001$, one-tailed]. The difference between incongruent and neutral targets (i.e., the interference effect) was marginally smaller after informative cues (27 ms) than after uninformative cues (56 ms) [$t(11) = 1.52$, $p = .079$, one-tailed]. In other words, advance information tripled the Stroop-like facilitation effect and halved the interference effect.

A cue limited the target types to two. It is therefore possible that the speed up of responses to informed targets was caused by exact target expectation, which may be correct on half the trials. If so, the speed up should be present on about half the trials only. To test this, we classified the RTs from each condition as below or above the median condition RT, and tested for an interaction between cue condition and relative speed. There were no such interactions for the congruent [$F(1,11) = 1.64$, $p = .227$],

incongruent [$F(1,11) = 1.90$, $p = .195$], and neutral trials [$F(1,11) < 1$]. These results exclude that the cue-based anticipatory effects were caused by exact target expectation.

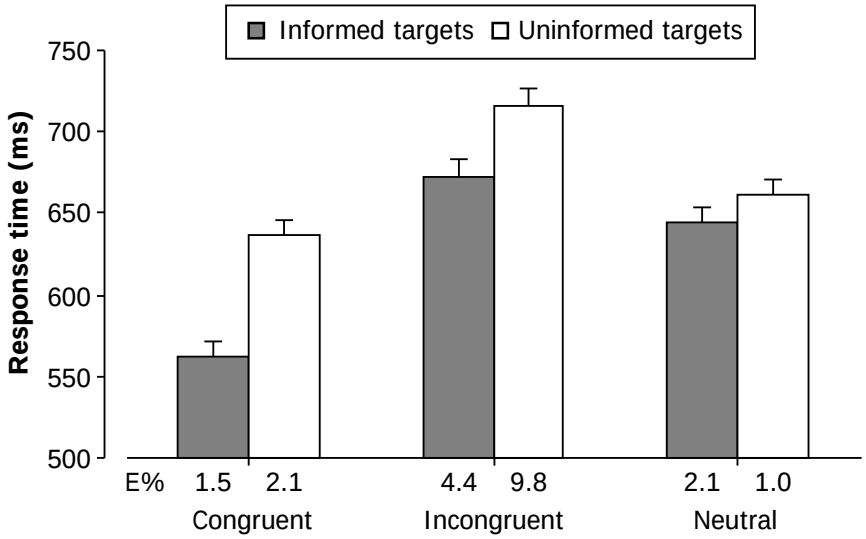

Figure 2.2 Behavioral results. Mean response times and error rates (E%) of congruent, neutral, and incongruent target condition preceded by informative and uninformative cues. Error bar is standard error of mean.

2.4.2 Neuroimaging Data

Comparing fMRI responses to informative cues with fMRI responses to uninformative cues revealed strong activity in a network of brain regions, including the ACC (**Table 2.1**).

In addition, a conjunction analysis of the contrasts [informative cue > uninformative cue] and [uninformed target > informed target] revealed that the ACC and other brain regions (listed in **Table 2.1**) showed more activity for informative than for uninformative cues, and subsequently, reduced activity for informed as compared with uninformed targets.

To further examine ACC responses to cue information, subject-averaged beta weights were extracted for all voxels in the ACC region showing increased activity for informative as compared with uninformative cues (**Figure 2.3A**). This was done for cues informative of incongruent, congruent, and neutral targets. Pair-wise comparisons of

these beta-weights showed that ACC activity was significantly larger for cues informative of incongruent and congruent targets as compared with cues informative of neutral targets [$t(11) = 2.43$, $p = .017$, one-tailed; [$t(11) = 2.74$, $p = .01$, one-tailed] (see **Figure 2.3B**). Importantly, cues informative of congruent and incongruent targets elicited similar ACC activity [$t(11) = -0.17$, $p = .869$] (**Figure 2.3B**).

Comparing fMRI responses to incongruent and congruent targets revealed increased activity in brain regions listed in **Table 2.2**. Following uninformative cues, a standard Stroop effect was observed in a network of regions including the ACC. Following informative cues, only the left dorsolateral PFC (DLPFC) and left ventrolateral prefrontal cortex (VLPFC) were more active for incongruent than for congruent targets. To further investigate this effect of cue information on target processing in the ACC, subject-averaged beta weights were extracted from the ACC region responding to informative cues (**Figure 2.3A**), separately for each of the target conditions. As can be seen in **Figure 2.3C and 2.3D**, ACC activity was significantly reduced for targets preceded by an informative cue as compared with targets preceded by an uninformative cue [$t(11) = 3.89$, $p = .002$]. Uninformed targets elicited a normal Stroop-like pattern of activity with larger responses for incongruent than for congruent targets [$t(11) = 4.77$, $p < .001$, one-tailed], and reduced responses for congruent as compared with neutral targets [$t(11) = 3.84$, $p = .002$, one-tailed]. Interestingly, for informed targets, ACC responses did not differ between target conditions (incongruent > congruent [$t(11) = -0.28$, $p = .389$, one-tailed]; congruent < neutral [$t(11) = -0.52$, $p = .307$, one-tailed]. This result shows that although a standard Stroop-like effect was obtained in the ACC for uninformed targets, this effect disappeared when a target was preceded by an informative cue.

To examine whether a similar effect of cue information on target processing was present in ACC voxels showing a strong Stroop effect for uninformed targets, subject-averaged beta-weights were obtained for all voxels in the ACC showing larger responses for incongruent as compared with congruent targets preceded by uninformative cues. Paired comparisons of the cue-related beta-weights showed that ACC responses were larger for informative than for uninformative cues [$t(11) = 4.56$, $p < .001$, one-tailed]. More specifically, ACC responses were larger for cues informative of incongruent and congruent targets as compared with cues informative of neutral targets [$t(11) = 2.29$, $p =$

.022, one-tailed; [$t(11) = 2.46$, $p = .016$, one-tailed]. Again, no difference in ACC activity was observed for cues informative of incongruent and congruent targets [$t(11) = -0.1$, $p = .911$]. Paired comparisons of target-related beta-weights obtained in this ACC region showed significantly less ACC activity for targets preceded by an informative cue than for targets preceded by an uninformative cue [$t(11) = 3.1$, $p = .005$]. Importantly, although beta weights were obtained from those ACC voxels responding more strongly to incongruent targets than to congruent targets in the uninformed condition, no such Stroop-like effects were found for targets that were preceded by an informative cue. For informed targets, ACC responses did not differ between target conditions (incongruent > congruent [$t(11) = -0.17$, $p = .43$, one-tailed]; congruent < neutral [$t(11) = -0.36$, $p = .365$, one-tailed]. Thus, the difference between incongruent and congruent targets (the Stroop effect) in the ACC was larger after uninformative cues than after informative cues [$t(11) = 1.97$, $p = .037$, one-tailed].

Further analyses showed that cue-based activity in the ACC was positively correlated for all three informative cue conditions separately with activity in the dorsal premotor cortex contralateral to the response hand (right Superior Frontal Gyrus, BA 6; overall $r = .69$, $t(34) = 5.54$, $p < .001$) and the Supplementary Motor Area (SMA, BA 6; overall $r = .75$, $t(34) = 6.65$, $p < .001$). There were no such correlations between cue-based ACC activity and any of the other regions listed in **Table 2.1**, except the Cerebellum ipsilateral to the response hand (overall $r = .74$, $t(34) = 6.47$, $p < .001$). Cue-related activity in left DLPFC, although often co-activated with the ACC (Koski and Paus, 2000) and similarly co-activated in the present study (**Table 2.1**), did not show a significant correlation with cue-related ACC activity (overall $r = .22$, $p > .1$). The correlations between activity in the ACC and the right dorsal premotor cortex and between the ACC and the SMA were significantly greater than the correlation between activity in the ACC and the left DLPFC (respectively, $t(33) = 3.39$, $p < .01$; $t(33) = 3.51$, $p < .01$). These results provide evidence that activity in premotor cortex indexes the operation of control in response to informative cues, as predicted.

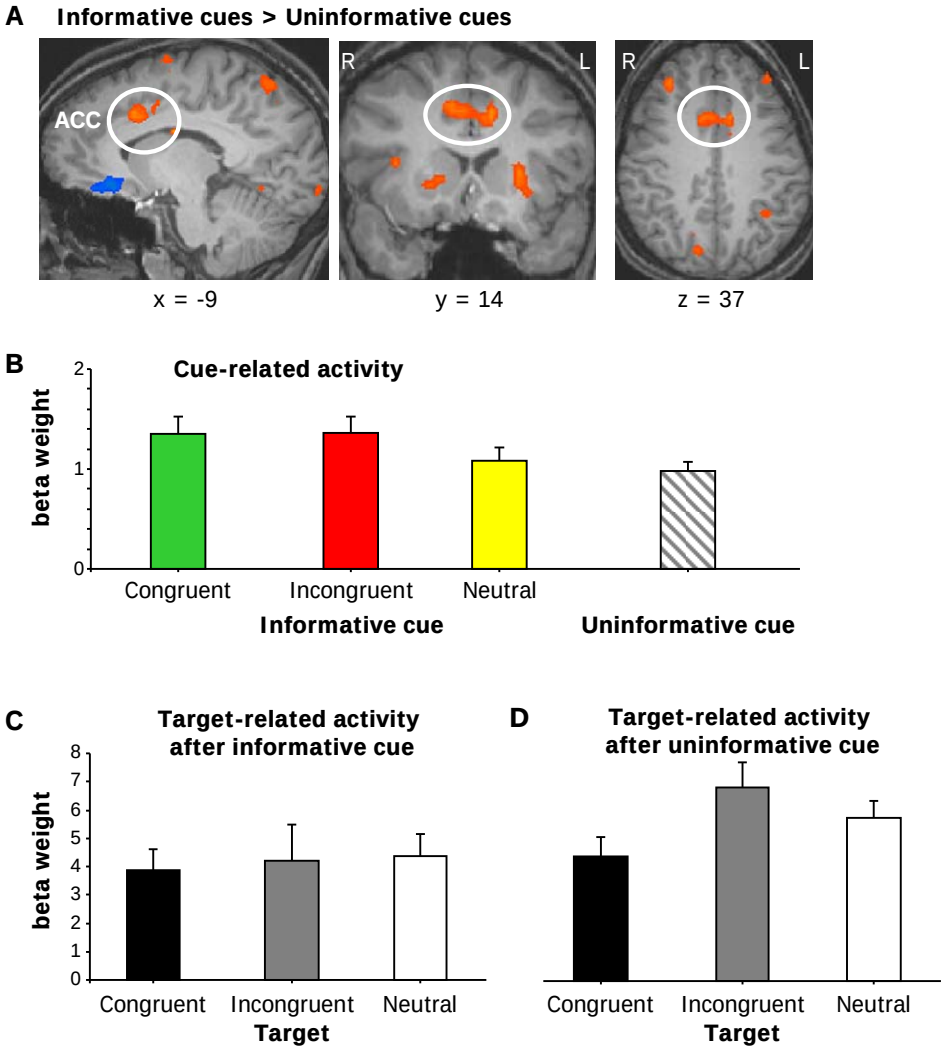

Figure 2.3 Anterior cingulate cortex (ACC) activity. **a.** Group maps showing increased ACC activity (Talairach coordinates: x = -9, y = 14, z = 37) for informative cues as compared to uninformative cues (thresholded at $p < 0.001$ and minimal cluster size of 50 mm^3). **b.** Mean beta-weights for the cues, **c.** mean beta-weights for the informed Stroop targets, and **d.** mean beta-weights for the uninformed Stroop targets in the ACC region showing an effect of informative cues versus uninformative cues.

Error bar is standard error of mean.

2.5 Discussion

In the present study, we investigated the role of the ACC in preparatory adjustments in control by using symbolic cues that informed participants about upcoming Stroop-like target conditions. Our fMRI data show that the ACC was directly involved in symbolically driven adjustments in control. ACC activity was significantly enhanced for informative cues as compared with uninformative cues. This finding is consistent with previous brain-imaging reports showing enhanced ACC activity in response to informative task- or stimulus-cues in a variety of task situations (Murtha et al., 1996; Luks et al., 2002; Weissman et al., 2005; Dosenbach et al., 2006; Parris et al., 2007). Recently, electrophysiological recordings from monkey cortex provided evidence for task-related preparatory activation in ACC neurons (Johnston et al., 2007).

Sohn et al. (2007) also demonstrated that the ACC is active during anticipatory preparation. Similar to our results, in their study, the ACC was only differentially active between low and high conflict targets when there was no opportunity to prepare. However, Sohn et al. claim that the anticipatory activity in the ACC is critically dependent upon upcoming response conflict. In their view, the ACC monitors conflict regardless of whether the source is online or anticipatory. In contrast to this view, our data show that anticipatory ACC activity can be independent of response conflict. In the present experiment, the ACC was equally active for cues indicating an upcoming incongruent target and cues indicating an upcoming congruent target, even though with congruent targets there are no competing response alternatives.

Brown and Braver (2005) presented data that also challenged the claim that anticipatory activity in the ACC reflects conflict monitoring. They showed that the ACC can be active in trials in which there is no response conflict. However, they argued that the ACC predicts error likelihood (see also Magno et al., 2006; but see Nieuwenhuis et al., 2007). In contrast to this view, we found that ACC activity was enhanced for informative cues preceding congruent as well as incongruent targets, while participants made significantly more errors in the incongruent condition than in the congruent one. Thus, although the error likelihood was higher for incongruent trials than for congruent trials, no difference in ACC activity was obtained for the cues. The independence of ACC

activity from error likelihood in the present study is also evident from comparing congruent and neutral trials in which the amount of response conflict is the same (absent in both cases) and the error likelihood is the same (see behavioral results). Despite similar conflict and error likelihood levels, the ACC was more active for cues preceding congruent trials than for cues preceding neutral trials. This clearly shows that the ACC's involvement in preparatory control is not restricted to conflict or high error-likelihood situations.

In a recent study, Luks et al. (2007) used cues to inform participants about upcoming Eriksen flanker conditions. However, unlike what we observed, Luks et al. did not find anticipatory ACC activity in response to the informative cues. The authors argued that the flanker task involves stimulus conflict rather than response conflict (but see Sanders and Lamers, 2002). Luks et al. expected to find ACC activity in preparation for response conflict. However, our data show that ACC activity is independent of upcoming response conflict. Importantly, in contrast to our findings, Luks et al. (2007) obtained no behavioral evidence for adjustments in control based on the cues. That is, the flanker effect in the RTs did not differ between informative and uninformative cues. Thus, it seems that Luks et al. (2007) did not find cue-related ACC activity simply because their participants did not adjust control in response to the cues.

If ACC activity in response to informative cues is independent of response conflict or error likelihood, what does it reflect? The behavioral data give some clues about what is happening on the cues. For both informed and uninformed targets we observed the normal Stroop pattern: Participants were slowest on the incongruent trials and fastest on the congruent trials (Baldo et al., 1998; Turken and Swick, 1999; Roelofs et al., 2006). However, participants were faster after informative cues than after uninformative cues. Moreover, the interference effect was numerically smaller after informative cues than after uninformative cues. Also, the facilitation effect was much larger after informative cues than after uninformative cues. A similar cueing benefit was observed in other studies using cues to inform participants about the upcoming target condition (Logan and Zbrodoff, 1982; Gratton et al., 1992). In these studies, the largest cueing benefit was obtained for the congruent targets, as was the case in the present study. The cues in these previous studies and in the present experiment may elicit control

adjustments aiming at optimal processing of the upcoming target (Gratton et al., 1992). An informative cue preceding an incongruent target might encourage participants to strengthen the connections between the words and their responses, because the irrelevant arrows elicit the wrong response. However, an informative cue preceding a congruent target might encourage participants to strengthen the connections between the arrows and the corresponding responses, because the irrelevant arrows also elicit the correct response. Overall, our behavioral results show that control adjustments are made on the basis of symbolic cues.

Our imaging results provide evidence for a role of the ACC in these preparatory adjustments in cognitive control. If the ACC is involved in adjusting control settings such that they are most appropriate for responding to the upcoming targets, then ACC activity should be enhanced in response to informative cues preceding both types of targets. This is indeed what we observed. In case of an upcoming neutral stimulus, control adjustments can be less because there is no incongruent arrow to ignore or congruent arrow to exploit in responding. This explains the finding of less ACC activity for informative cues preceding neutral targets as compared with informative cues preceding congruent and incongruent targets. Moreover, the advance adjustments appeared to be successful as is evident from the reaction time and imaging data. That is, the response of the ACC to the target stimuli was critically dependent upon whether the cue was informative or not. Following informative cues, there were no differences in ACC activity among target conditions, whereas in absence of advance information, a normal Stroop pattern was observed.

Previous studies have examined consequences of control adjustments by looking at the effects of control on behavioral measures and task-selective brain regions (Egner and Hirsch, 2005; Yeung et al., 2006). Specifically, effective connectivity studies provided evidence for a function of the ACC in regulating or top-down modulation of activity in modality-specific sensory areas (Crottaz-Herbette and Menon, 2006), the amygdala (Etkin et al., 2006), and the caudal cingulate (motor) zone (Fan et al., 2007). The effective connectivity from rostral ACC to caudal cingulate zone was modulated by conflict. The caudal cingulate activation extended into the SMA, a region that was functionally coupled to the rostral ACC in the present study. The present finding that

ACC activity only correlated with activity in premotor cortex/SMA following informative cues, and not with activity in any other cortical area including left DLPFC, similarly suggests that the ACC has a regulative role itself (see also Johnston et al., 2007). We are aware of the limitations of correlation analyses regarding directionality interpretations. Still, given the findings of Fan et al. (2007), it seems plausible to assume that the ACC exerts an influence over premotor cortex/SMA rather than the other way around.

Our data suggest that the ACC is actively involved in setting control parameters. This idea fits with reinforcement learning theories, according to which the ACC uses positive (reward) and negative (e.g., error) information to identify and select appropriate behaviors (Holroyd and Coles, 2002; Walton et al., 2003; Rushworth et al., 2004; Williams et al., 2004; Amiez et al., 2006; Somerville et al., 2006). Our data suggest that, in addition to rewards and errors, symbolic cues can be used to inform the ACC that it should adjust control settings. A role for the ACC in adjusting control also fits with previous neuroimaging evidence that the ACC is activated in decision making when the freedom of choice increases (Walton et al., 2004; Forstmann et al., 2006) or when a task is novel or difficult, and that activity diminishes after practice (Raichle et al., 1994; Bush et al., 1998; Milham et al., 2003b). These findings can readily be explained in terms of control adjustments. Appropriate behaviors are more easily selected after extensive training/practice or when explicitly instructed and hence control adjustments can be less.

To conclude, our results demonstrate that the ACC is involved in preparatory adjustments in control, driven by symbolic cues and independent of anticipated response conflict and error likelihood. When control can be adjusted in advance, the ACC is no longer involved in resolving Stroop-like conflict evoked by the target. The present findings argue strongly for a role of the ACC in actual control adjustments. Models of frontal cortex conflict-detection and conflict-resolution mechanisms will require modification to include consideration of these anticipatory control properties of the ACC.

Table 2.1 Peak Talairach coordinates, cluster size (in mm^3), and peak *t*-values of regions showing an effect of advance information on the cue and regions showing an effect of advance information on both the cue and the target for $p < .001$ and a threshold of 50 mm^3

		informative > uninformative cues					informative > uninformative cues AND uninformed > informed targets				
region	BA	x	y	z	size	*t*(11)	x	y	z	size	*t*(11)
activations											
ACC	32	-9	14	37	1762	6.77	9	14	40	540	5.87
		-9	-1	43	71	5.07	-9	2	37	90	5.2
DLPFC (MFG)	46	-27	26	28	316	5.45					
	9	30	32	34	901	9.16	30	32	31	192	6.99
Insula	13	33	14	13	108	5.88					
SMA (MeFG)	6	-3	-7	61	182	5.34					
PMCd (SFG)	6	-15	-10	67	240	5.60	-15	-13	64	234	5.48
		12	-7	64	216	5.35					
Precentr. g.	6	30	-13	46	58	5.75					
IPL	40	-33	-49	28	862	7.43	-30	-52	28	455	7.22
		54	-46	19	196	6.44					
SPL	7	-30	-58	55	178	5.59					
Ang. g	39	-27	-61	22	56	6.86					
Precuneus	7	-15	-58	40	65	5.24	-6	-64	55	370	5.54
		-15	-67	52	1223	7.37	-15	-67	52	120	5.51
							-9	-73	40	62	4.91
		12	-73	46	1545	7.73	12	-76	43	1065	6.46
Parahip. g.	19	18	-46	-5	61	5.39					
Ling. g.	18	-9	-94	-8	58	5.28	-6	-61	-5	142	5.86
		0	-76	1	409	5.96					
Cuneus	18/17	3	-88	19	134	4.93	0	-82	13	158	5.69
	18	15	-91	7	75	5.72					
Dors. Striatum		-21	14	10	918	6.64	-21	14	10	497	6.02
		18	11	10	1180	8.28	21	11	-2	519	6.55
Thalamus		-15	-7	13	775	6.79	-15	-7	10	76	5.34
Cerebellum		-36	-52	-29	1480	6.96	-36	-49	-29	443	6.14
							-24	-61	-17	51	5.21
		42	-49	-29	4743	8.36	21	-67	-20	2350	7.82
deactivations											
MeFG	9	-3	47	28	98	-5.11					
Subgenual area	25	-9	29	-5	486	-6.23					
		0	20	-14	55	-6.03					

BA, Brodmann area; ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; MFG, middle frontal gyrus; SMA, supplementary motor area; MeFG, medial frontal gyrus; PMCd, dorsal premotor cortex; SFG, superior frontal gyrus; Precentr. g., precentral gyrus; IPL, inferior parietal lobule; SPL, superior parietal lobule; Ang. g., angular gyrus; Parahip. g., parahippocampal gyrus; Ling. g., lingual gyrus; Dors. Striatum, dorsal striatum.

Table 2.2 Peak Talairach coordinates, cluster size (in mm^3), and peak *t*-values of regions showing more activity for incongruent than congruent targets for $p < .001$ and a threshold of 50 mm^3

region	BA	x	y	z	size	*t*(11)
uninformed targets						
ACC	24	6	8	34	1223	6.24
Insula		-30	8	1	205	5.91
Precentr. g.	6	36	-1	34	716	6.16
SMA (MeFG)	6	-6	-4	58	321	6.03
MFG	6	-24	-10	55	1125	8.07
		21	-7	58	118	5.47
CG	23	3	-22	28	1325	6.57
IPL	40	-45	-43	52	88	9.23
		-36	-43	37	156	6.24
		-54	-49	25	63	5.37
		-60	-31	34	99	5.19
		60	-31	25	502	5.92
SPL	7	-15	-64	52	3091	8.96
		15	-67	55	193	5.55
		24	-52	55	72	4.97
Precuneus	7	-24	-73	43	104	4.88
		9	-52	67	51	6.20
	31	12	-64	28	2772	7.08
Ang. g.	39	30	-55	34	153	5.65
MTG	39	45	-64	10	56	5.54
	21	-60	-49	10	152	5.80
SOG	19	-27	-67	25	253	6.60
		-24	-76	34	66	5.50
		33	-73	28	162	5.95
Cuneus	19	-3	-73	28	69	5.28
Ling. g.	18	-9	-82	-11	396	6.12
		18	-97	-8	110	8.57
		3	-85	1	287	6.08
Thalamus		-12	-19	4	352	5.76
		15	-10	4	87	6.00
Cerebellum		21	-55	-42	61	5.71
Caudate		9	5	4	61	5.43
informed targets						
DLPFC (MFG)	46	-39	41	16	73	6.69
VLPFC (IFG)	46	-48	38	7	93	5.25

BA, Brodmann area ; ACC, anterior cingulate cortex; Precentr. g., precentral gyrus; SMA, supplementary motor area; MeFG, medial frontal gyrus; MFG, middle frontal gyrus; CG, cingulate gyrus; IPL, inferior parietal lobule; SPL, superior parietal lobule; Ang. g., angular gyrus;

MTG, middle temporal gyrus; SOG, superior occipital gyrus; Ling. g., lingual gyrus; DLPFC, dorsolateral prefrontal cortex; VLPFC, ventrolateral prefrontal cortex; IFG, inferior frontal gyrus.

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3.

Control Adjustments in Anterior Cingulate Cortex Based on Probabilistic Cueing

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3.1 Abstract

In Stroop-like tasks, conflict effects in behavioral measures and anterior cingulate cortex (ACC) activity depend on the previous trial: they are smaller following a conflict trial than following a non-conflict one. These sequential effects have been explained in terms of different cognitive control mechanisms, i.e., reflecting conflict-driven adjustments in control (*conflict adaptation*) or strategic adjustments on the basis of *repetition expectancy*. In the present fMRI experiment, we specifically manipulated the expectancies by using cues predicting with 75% certainty the conflict or non-conflict targets in a Stroop-like task. Both behavioral and dorsal ACC (dACC) data replicated previous sequential effects, with conflict effects being smallest for targets following the cues that predicted conflict targets. However, these effects were not driven by conflict but by abstract cues. Furthermore, cue-related activity in the dACC was largest for the non-conflict predicting cues. These results provide evidence for an expectancy-based rather than conflict-adaptation account of sequential effects.

3.2 Introduction

Cognitive control includes the regulative processes that allow us to act according to our goals in the face of distractors. This ability is critical to normal human functioning and it is a hallmark of general intelligence (Duncan, 1995, 2005). The Stroop conflict task (Stroop, 1935) is often used to study cognitive control processes. In the original color-word version of this task, participants name the ink color of written color words or read the words aloud (MacLeod, 1991). Stimuli can be congruent (e.g., the word RED in red ink) or incongruent (e.g., the word BLUE in red ink) and the difference between these conditions in behavioral and neuroimaging measures (incongruent > congruent) is called the conflict effect. Neuroimaging studies have shown that the anterior cingulate cortex (ACC) plays a role in cognitive control, together with other areas in frontal and parietal cortex (for reviews, see Picard and Strick, 1996; Bush et al., 2000; Miller, 2000; Paus, 2001).

Conflict effects in task performance are found to be smaller following an

incongruent trial than following a congruent one (for a review, see Egner, 2007). This sequential effect is often explained as reflecting conflict-driven trial-to-trial adjustments in cognitive control (Botvinick et al., 2001), here referred to as the *conflict adaptation* account (cf. Mayr et al., 2003). Functional magnetic resonance imaging (fMRI) studies using conflict tasks (e.g., Botvinick et al., 1999; Kerns et al., 2004) have demonstrated the involvement of the ACC in these trial-to-trial adjustments (for a review, see Botvinick et al., 2004). According to these authors, conflict is detected by the ACC, which subsequently signals to the dorsolateral prefrontal cortex (DLPFC) the need to implement top-down control processes. Following this interpretation, the conflict adaptation account states that conflict effects in the ACC are greater following congruent trials than following incongruent trials because congruent trials are not associated with response conflict, and hence, the level of control is low during trials that follow a congruent trial. ACC, thus, detects more conflict and a greater need to up-regulate control on an incongruent trial following such a congruent 'low control' trial than following an incongruent, conflict trial that induced high control. Here, high control reflects increased attentional biasing of the task-relevant information (e.g., the target dimension of the Stroop stimulus) relative to the task-irrelevant information (e.g., the distractor dimension of the Stroop stimulus). Note that in the conflict adaptation account it is only (response) conflict that drives these adjustments in cognitive control.

The first to describe the sequential effect were Gratton and colleagues (Gratton et al., 1992). Their interpretation of this sequential effect, and of trial type frequency effects as well, was an expectancy-based account (see also Logan and Zbrodoff, 1979, 1982). They proposed that subjects expect a congruent trial to be followed by a congruent trial and an incongruent trial to be followed by an incongruent trial, here referred to as the *repetition expectancy* account. This should result in a more focused processing strategy when expecting an incongruent stimulus and a less focused or widened processing strategy when expecting a congruent stimulus. Hence, when expectancies are violated (e.g., on incongruent trials preceded by congruent trials), the strategic adjustments are not suitable for the present trial and performance is impaired. Thus, in the repetition expectancy account, strategic adjustments in attentional biasing are not made in response to conflict but on the basis of subjects' expectancies.

Although the conflict adaptation and the repetition expectancy account both correctly predict the behavioral sequential effects, the interpretation of the role of the ACC differs substantially. Whereas the ACC would function as a conflict detector in the conflict adaptation account, the repetition expectancy account predicts that sequential effects in the ACC reflect the rapid updating of control states when expectancies are violated. Evidence for such strategic control adjustments comes from event-related potential (ERP) P300 results of Gratton and colleagues (1992) when they specifically manipulated subjects' expectancies by using cues that predicted with 80% certainty the upcoming congruent or incongruent targets. Interestingly, this P300 component, associated with updating, was found to be larger for cues predicting congruent targets than for cues predicting incongruent targets. We have recently shown that strategic control adjustments are indeed associated with ACC activity (Aarts et al., 2008). In this fMRI study, 100% valid cues informed participants about the upcoming Stroop-like target conditions. Compared to uninformative cues, informative cues elicited ACC activity and, subsequently, a target-related conflict effect was no longer observed in this region. Importantly, ACC activity was similarly enhanced for cues predicting congruent or incongruent targets. These findings suggest that the ACC is involved in making strategic adjustments in control independent of upcoming response conflict (Aarts et al., 2008).

However, with 100% valid cues, expectancies can never be violated and, hence, the role of uncertainty that is associated with sequential effects could not be studied in the experiment of Aarts and colleagues (2008). Studying the role of the ACC in uncertain task situations is important because it more closely resembles biologically plausible situations. Therefore, in the present fMRI study, we used probabilistic cues (cf. Gratton et al., 1992) that predicted the upcoming Stroop-like targets with 75% or 50% certainty (the latter being non-predictive cues). If control adjustments are made on the basis of subjects' expectancies, we expect that target-related conflict effects, behaviorally and in the ACC, are increased following congruency-predicting cues as compared to non-predictive cues and decreased following incongruency-predicting cues as compared to non-predictive cues. We expect the attentional strategy to differ between 100% valid cues (Aarts et al., 2008) and probabilistic cues (the present study). With 100% valid cues, participants may

adopt processing strategies that are optimal for incongruent and congruent targets: a narrow-attention strategy for incongruent targets and a wide-attention strategy for congruent targets. However, with probabilistic cues, participants seem to adopt a default narrow-attention strategy, and only change to a wide-attention strategy when congruent targets are expected with great probability (Gratton et al., 1992). Thus, if ACC activity is associated with updating of control states, we expect more cue-related activity in the ACC during congruency-predicting cues than during incongruency-predicting or non-predictive cues. Moreover, if the DLPFC is implicated in implementing control, DLPFC activity should vary depending on the cue.

3.3 Materials and Methods

3.3.1 Subjects

Twenty neurologically healthy Dutch undergraduates (12 female and 8 male, mean age 21.2 years, range 19-26) participated in the experiment. All participants were right-handed and native speakers of Dutch. They were compensated for participation and gave written informed consent in a manner approved by the Dutch Central Committee on Research Involving Human Subjects (CCMO).

3.3.2 Stimuli and Paradigm

The participants were scanned while performing a manual arrow-word version of the Stroop task. As with color-word Stroop stimuli, responding in this task is usually slower on incongruent than on congruent trials (Baldo et al., 1998; Turken and Swick, 1999; Roelofs et al., 2006). The targets consisted of written words in arrows (**Figure 3.1**). The lines and letters of the targets were white on a black background. The arrows pointed to the left or to the right. The word in the arrow was the Dutch word for *right* (*rechts*) or for *left* (*links*). Participants responded manually to the words of the Stroop-like targets by pressing a left or right button on a scanner-compatible button box. Participants were told to respond as quickly and accurately as possible with the left middle finger (for *left* response) and the left index finger (for *right* response). In the congruent target condition,

the arrow and the word denoted the same direction (e.g. the word *right* in an arrow pointing to the right). In the incongruent target condition, the arrow and the word denoted a different direction (e.g., the word *left* in an arrow pointing to the right).

Every target was preceded by a cue (see **Figure 3.1**). The cue was a coloured square giving information about the upcoming target condition with a certain probability. A red cue predicted with 75 percent certainty that the upcoming Stroop-like target would be incongruent. A green cue predicted with 75 percent certainty that the upcoming Stroop-like target would be congruent. A combined red-green cue predicted with 50 percent certainty either one of the upcoming Stroop-like targets and, hence, was uninformative. Participants were told to pay explicit attention to the cues because they would be about 80 percent informative about the upcoming target. It was brought to the participants' attention that during congruent trials one could be helped by the non-relevant dimension of the target (i.e. the arrow) and that one should not be distracted by the arrow in case of an incongruent trial (cf. Logan and Zbrodoff, 1982; Gratton et al., 1992). The experiment included 350 trials, consisting of 140 incongruency-predicting, 140 congruency-predicting, and 70 non-predictive cues. The 140 incongruency-predicting cues were followed by 105 incongruent Stroop targets and 35 congruent Stroop targets. The 140 congruency-predicting cues were followed by 105 congruent Stroop targets and 35 incongruent Stroop targets. The 70 non-predictive cues were followed by 35 congruent Stroop targets and 35 incongruent Stroop targets. Predictive and non-predictive cues, as well as congruent and incongruent targets were randomly intermixed.

The target followed the cue after a variable delay of 2 - 7 s. In addition to a similar variable delay of 2-7 s between a target and the next cue, 35 null-events of 10 seconds were used. The jitter was calculated with a simulation of the BOLD response in SPM99 (Wellcome Dept. of Cognitive Neurology, London). The variable delays enabled us to reliably distinguish the BOLD response to the cue from the BOLD response to the target (Josephs et al., 1997). A random sequence with optimal delays was generated for every participant separately. Because the delay between cue and target could not be predicted, the participant needed to be ready to respond at any time. Cues and targets remained on the screen for 600 ms.

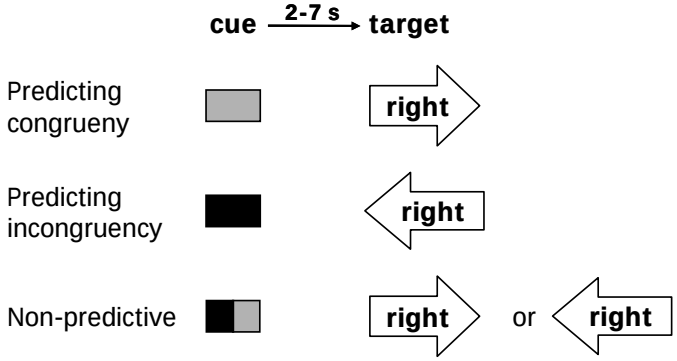

Figure 3.1. Experimental paradigm. Depicted are the predictive and non-predictive cues and examples of congruent and incongruent targets with the word 'right'. Dark green cues (here: gray) were followed by congruent targets with 75% chance, and red cues (here: black) were followed by incongruent targets with 75% chance. Combined red-green cues (here: gray-black) predicted one of the target conditions with 50% chance, and hence were uninformative. The task was to manually respond to the word.

3.3.3 Functional Imaging

Whole-brain imaging was performed on a 3 Tesla MR scanner (Magnetom Trio, Siemens Medical Systems, Erlangen, Germany). Functional data were acquired using a gradient-echo echo-planar scanning sequence (repetition time = 2100 ms, echo time = 30 ms, 33 axial slices, voxel size = 3.5 x 3.5 x 3.5 mm, field of view = 224 mm, flip angle = 70º). All functional images were acquired in a single run lasting 55 minutes. Visual stimuli were projected on a screen and were viewed through a mirror attached to the head coil. After the acquisition of functional images, a high-resolution anatomical scan (T1-weighted MP-RAGE, 192 slices) was obtained.

3.3.4 Behavioral Data Analysis

The mean latencies of the correct manual responses and the error rates were analyzed using repeated-measures analyses of variance (ANOVA) with the factors target condition (congruent, incongruent) and cue condition (congruency-predicting, incongruency-

predicting, non-predictive). All variables were tested within participants. Specific effects were tested with paired *t*-tests. An effect was called significant when $p < .05$.

3.3.5 FMRI Data Analysis

FMRI data were analysed with BrainVoyager QX (Brain Innovation, Maastricht, the Netherlands). Functional images were corrected for slice time acquisition (using sinc interpolation) and 3D motion correction was performed to detect and correct for small head movements. Linear trend removal was performed and the signal was temporal high-pass filtered to remove low-frequency non-linear drifts of 3 or fewer cycles per time course. Functional images were co-registered with the anatomical scan and transformed into Talairach coordinate space using the nine-parameter landmark method of Talairach and Tournoux (Talairach and Tournoux, 1988). Images were spatially smoothed with a full-width at half maximum (FWHM) Gaussian kernel of 6 mm.

Statistical analyses were performed in the context of the general linear model, including the event types of interest: congruency-predicting, incongruency-predicting, and non-predictive cues; congruent targets preceded by valid, invalid, and non-predictive cues; incongruent targets preceded by valid, invalid, and non-predictive cues. Trials on which participants had made an error were put together as a separate event type of non-interest. Furthermore, six motion parameters were included as event types of non-interest. The event types were modeled with a two gamma haemodynamic response function that was adjusted in such a way that it equalled the haemodynamic response function in SPM99 on the basis of which the jitter was calculated (see above). Random-effects group analyses were performed enabling generalization of the statistical inferences to the population level. The statistical threshold for the group analyses was set at $p < .05$, False Discovery Rate corrected for multiple comparisons (Genovese et al., 2002).

To further investigate effects in the regions of interest (ROIs) - anterior cingulate cortex (ACC) and left and right dorsolateral prefrontal cortex (DLPFC) - we obtained subject-averaged beta weights (i.e., regression coefficients) for all target conditions as indices of effect size for all voxels in the functionally defined ROIs showing an effect of incongruent versus congruent targets preceded by congruency-predicting cues in the

random effects group analysis. Using this contrast, we expected to find the biggest target-related differences on the basis of previous literature (Botvinick et al., 1999; Kerns et al., 2004). To investigate the effects of cue information in this region, subject averaged beta-weights were extracted for all cue conditions from the voxels in the same ROI showing an effect of incongruent versus congruent targets preceded by congruency-predicting cues in the random effects group analysis. The regional-specific time-courses were standardized, so that beta weights reflected the BOLD response amplitude of one condition relative to the variability of the signal. Regionally averaged beta-weights were analyzed in repeated-measurement ANOVAs. Specific effects were tested by applying paired *t*-contrasts to the beta weights obtained for the different event types. An effect was called significant when $p < .05$.

Moreover, to find out whether cue-related activity in the ROIs was related to subsequent behavior on the Stroop targets, we correlated (Pearson correlation) the response time effect of valid and invalid cueing (as compared to non-predictive trials) with the cue-related beta weights from the ROIs. We expected that greater cue-related activity in the ROI (as compared to non-predictive cues) would be associated with better performance for valid cues, but poorer performance for invalid cues relative to non-predictive cues.

3.4 Results

3.4.1 Behavioral Results

Reaction Times

Reaction time data showed a main effect of target condition [$F(1,19) = 92.43$, $p < .001$], no main effect of cue condition [$F(2,38) < 1$], but a significant interaction between cue condition and target condition [$F(2,38) = 9.65$, $p < .001$] (**Figure 3.2A**). There was a reliable conflict effect (incongruent > congruent targets) in the response times following all cue types [congruency-predicting cues: $t(19) = 7.48$, $p < .001$; incongruency-predicting cues: $t(19) = 4.42$, $p < .001$; non-predictive cues: $t(19) = 7.86$, $p < .001$].

Although there was a conflict effect following all cue types, the conflict effect was, as expected, greater after congruency-predicting cues than after incongruency-predicting cues [$t(19) = 3.62$, $p = .001$, 1-tailed]. The conflict effect was also greater after non-predictive cues than after incongruency-predicting cues [$t(19) = 2.49$, $p = .011$, 1-tailed]. Importantly, there was a greater conflict effect after congruency-predicting cues as compared with non-predictive cues as well [$t(19) = 2.54$, $p = .01$, 1-tailed]. Thus, conflict effects were smallest after incongruency-predicting cues and biggest after congruency-predicting cues.

If participants engage in a strategy on the congruency-predicting cues, one would expect an advantage when the cues are valid. This is indeed the case: participants were faster for congruent targets preceded by valid congruency-predicting cues than for congruent targets preceded by non-predictive cues [$t(19) = 2.43$, $p = .013$, 1-tailed]. Similarly, participants tended to be faster for incongruent targets preceded by valid incongruency-predicting cues than for incongruent targets preceded by non-predictive cues [$t(19) = 1.68$, $p = .055$, 1-tailed].

Performance did not only benefit from valid cueing but it was also impaired due to expectancy violation when the cue was invalid. Participants were slower when congruent targets were preceded by invalid incongruency-predicting cues than when preceded by non-predictive cues [$t(19) = 1.79$, $p = .045$, 1-tailed]. Similarly, incongruent targets preceded by invalid congruency-predicting cues were processed slower than incongruent targets preceded by non-predictive cues [$t(19) = 2.06$, $p = .027$, 1-tailed].

To investigate whether one of the cues would signal more (need to reduce) mental effort (Botvinick, 2007), we analyzed the difference between overall mean response times following each of the cues. Although the longest response times were observed for incongruent targets following congruency-predicting cues, overall, participants were still slower following incongruency-predicting cues (549 ms) than congruency-predicting cues (512 ms) [$t(19) = 6.23$, $p < .001$, 2-tailed] or non-predictive cues (537 ms) [$t(19) = 2.26$, $p < .036$, 2-tailed]. Independent of valid or invalid cueing, participants responded fastest to targets following congruency-predicting cues [as compared to non-predictive cues: $t(19) = 5.19$, $p < .001$, 2-tailed]. These results indicate that, overall, incongruency-predicting cues would predict the greatest effort. Thus, if control is adjusted on the basis

of expected effort (Botvinick, 2007), the greatest adjustments should be made during incongruency-predicting cues.

Error Rates

The error rates showed a main effect of target condition [$F(1,19) = 15.75$, $p = .001$], a main effect of cue condition [$F(2,38) = 6.02$, $p = .005$], and a significant interaction between cue condition and target condition [$F(2,38) = 5.42$, $p = .008$] (**Figure 3.2B**). Like in the response times, the conflict effect in the error rates was greater after congruency-predicting cues than after incongruency-predicting cues [$t(19) = 2.49$, $p = .011$, 1-tailed]. The conflict effect was not greater after non-predictive cues than after incongruency-predicting cues [$t(19) = 1.49$, $p = .077$, 1-tailed]. There was a greater conflict effect after congruency-predicting cues as compared with non-predictive cues [$t(19) = 2.76$, $p = .006$, 1-tailed]. Thus, in error rates, the conflict effect was biggest following congruency-predicting cues and comparable following incongruency-predicting and non-predictive cues.

An advantage of valid cueing could not be observed in the error rates. That is, participants did not make less errors for congruent targets preceded by valid congruency-predicting cues than for congruent targets preceded by non-predictive cues [$t(19) = 1.16$, $p = .13$, 1-tailed]. However, this might be a floor effect because the error rate in both conditions was one percent or less.

Like in the response times, invalid trials seemed to impair performance as compared to non-predictive trials. That is, incongruent targets preceded by invalid congruency-predicting cues elicited more errors than incongruent targets preceded by non-predictive cues [$t(19) = 2.86$, $p = .005$, 1-tailed]. Similarly, congruent targets preceded by invalid incongruency-predicting cues elicited more errors than congruent targets preceded by non-predictive cues [$t(19) = 2.04$, $p = .028$, 1-tailed].

To investigate whether one of the cues would signal greater error-likelihood (Brown and Braver, 2005), we analyzed the difference between overall mean error rates following each of the cues. Although most errors were observed after congruency-predicting cues when the target was incongruent, overall, participants still made a similar

amount of errors following congruency-predicting cues (4.2%) as compared to incongruency-predicting cues (5.9%) [$t(19) = 1.66$, $p = .11$, 2-tailed] or non-predictive cues (4.1%) [$t(19) = .17$, $p = .87$, 2-tailed]. Independent of valid or invalid cueing, participants made more errors following incongruency-predicting cues than following non-predictive cues [$t(19) = 2.51$, $p = .02$, 2-tailed]. These results indicate that incongruency-predicting cues rather than congruency-predicting cues would predict overall greater error-likelihood. Thus, if control is adjusted based on expected error-likelihood (Brown and Braver, 2005), the greatest adjustments should be made during incongruency-predicting cues.

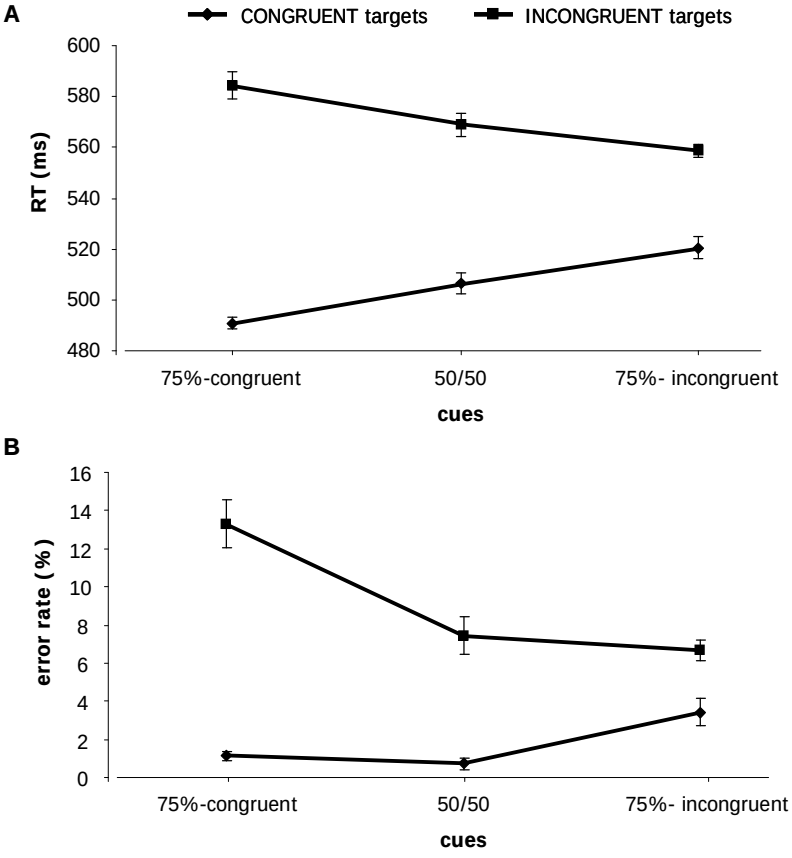

Figure 3.2 Behavioral results. **a.** Mean response times and **b.** error rates of congruent and incongruent target condition preceded by predictive and non-predictive cues. Error bar is standard error of mean.

In summary, there were differential conflict effects in the response times across cue conditions, which is to be expected when participants engage in specific strategies for both incongruency-predicting and congruency-predicting cues. Similar effects were observed in the error rates. Performance seemed to benefit from valid cueing (especially for congruent targets) and was hampered by invalid cueing. Overall, following incongruency-predicting cues, participants were slowest and made most errors because 75% of these cues were valid and, thus, preceded incongruent targets.

3.4.2 Neuroimaging Results

A conflict effect (incongruent > congruent targets) could only be observed following congruency-predicting cues in two adjacent regions in the dorsal ACC (dACC), with a peak in the ACC and peak in the pre-SMA (**Figure 3.3A**). Even after lowering the threshold to $p < .01$ (uncorrected), no ACC activity could be observed for incongruent versus congruent targets following incongruency-predicting cues or following non-predictive cues. Regions showing activation and de-activation for the conflict contrast after congruency-predicting cues are listed in **Table 3.1**.

Anterior Cingulate Cortex

To further examine dACC responses to the targets, subject-averaged beta weights were extracted for all voxels in the dACC ROI showing increased activity for incongruent as compared with congruent targets following congruency-predicting cues (**Figure 3.3A+B**). In the beta weights, there was no main effect of cue condition [$F(2,38) < 1$], but there was a significant main effect of target condition [$F(1,19) = 7.31$, $p = .014$] and an interaction between cue and target condition [$F(2,38) = 5.98$, $p = .006$]. As indicated, there was only a conflict effect after congruency-predicting cues [$t(19) = 4.94$, $p < .001$; incongruency-predicting cues: $t(19) = .65$; non-predictive cues: $t(19) = .75$]. Dorsal ACC activity was enhanced when incongruent targets were invalidly cued by congruency-predicting cues (as compared to non-predictive cues) [$t(19) = 2.57$, $p = .01$, 1-tailed]. However, a similar effect of invalid cueing could not be observed for congruent targets [$t(19) = .92$].

From the same dACC ROI (voxels showing increased activity for incongruent as compared with congruent targets following congruency-predicting cues), cue-related subject-averaged beta weights were extracted and dACC responses to cues were tested with paired-sampled t-tests (**Figure 3.3A+C**). Congruency-predicting cues elicited more activity in the dACC than non-predictive cues [$t(19) = 1.84$, $p = .041$, 1-tailed]. However, incongruency-predicting cues did not elicit more activity than non-predictive cues [$t(19) = .13$]. There was a trend towards enhanced activity for congruency-predicting cues as compared to incongruency-predicting cues [$t(19) = 1.67$, $p = .056$, 1-tailed].

Furthermore, the beta weights for congruency-predicting cues (minus non-predictive cues) in the dACC ROI correlated significantly with a response time advantage of valid cueing of congruent targets [$r = .47$, $t(18) = 2.24$, $p = .038$] and a response time disadvantage of invalid cueing of incongruent targets [$r = .52$, $t(18) = 2.59$, $p = .019$]. There were no such significant correlations for incongruency-predicting cues and valid cueing of incongruent targets [$r = -.30$, $t(18) = -1.31$, $p = .21$] or invalid cueing of congruent targets [$r = .33$, $t(18) = 1.50$, $p = .15$]. Thus, participants who showed more cue-related dACC activity for congruency-predicting cues (as compared to non-predictive cues) were also faster when the cue was valid and slower when the cue was invalid. This effect could not be observed for the incongruency-predicting cues.

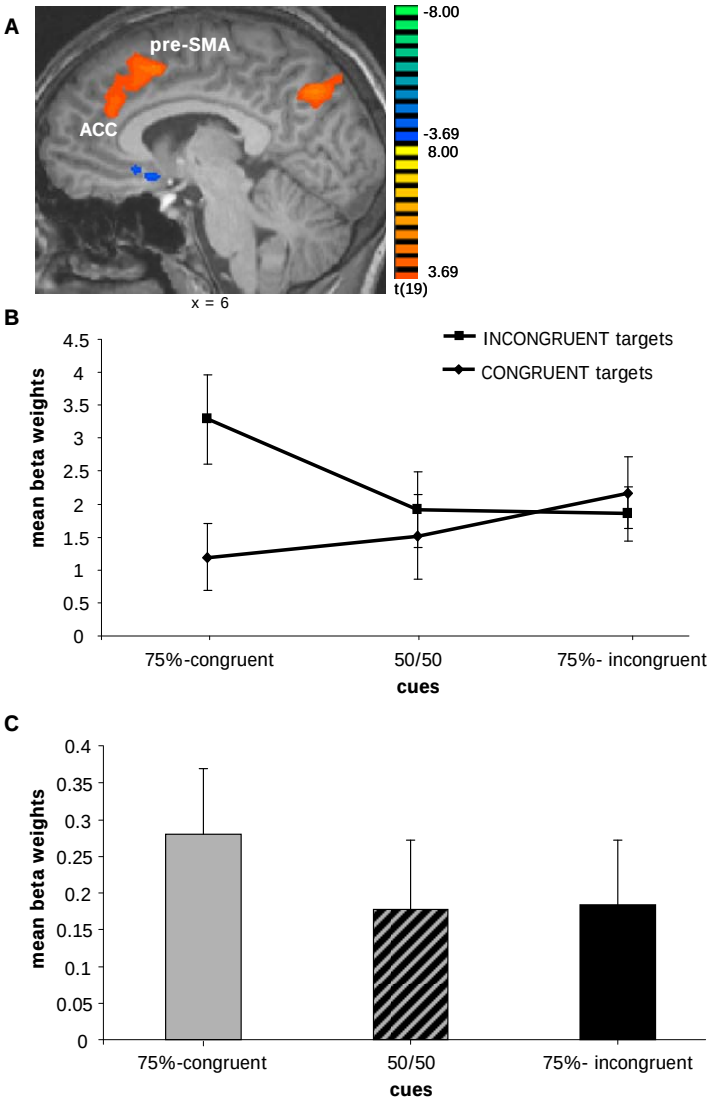

Figure 3.3 Dorsal anterior cingulate cortex (dACC) activity. **a.** Group map showing increased activity in adjacent regions in the medial frontal cortex: ACC (Talairach coordinates: x = 6, y = 32, z = 31) and pre-SMA (Talairach coordinates: x = 6, y = 14, z = 49), for incongruent as compared with congruent targets following congruency-predicting cues (thresholded at $p < .05$, False Discovery Rate corrected). **b.** Mean beta-weights for the targets, and **c.** mean beta-weights for the cues in the dACC region showing an effect of incongruent targets versus congruent targets following congruency-predicting cues.

Error bar is standard error of mean.

Dorsolateral Prefrontal Cortex

A similar ROI analysis was performed on the cue- and target-related subject-averaged beta weights of left DLPFC (BA9, Talairach coordinates: x = -54, y = 14, z = 28) and right DLPFC (BA 8/9, Talairach coordinates: x = 45, y = 11, z = 40) that showed increased activity for incongruent as compared with congruent targets following congruency-predicting cues (see **Table 3.1**). For the targets, there was a main effect of cue condition in the left DLPFC [$F(2,38) = 3.25$, $p = .05$] but not in the right DLPFC [$F(2,38) < 1$]. Activity in the DLPFC showed a significant main effect of target condition [left: $F(1,19) = 7.81$, $p = .012$; right: $F(1,19) = 11.04$, $p = .004$] and an interaction between cue and target condition [left: $F(2,38) = 7.98$, $p = .001$; right: $F(2,38) = 7.62$, $p = .002$]. The DLPFC showed a similar pattern of activity as observed in the dACC: there was only a conflict effect after congruency-predicting cues [left: $t(19) = 5.06$, $p < .001$; right: $t(19) = 6.43$, $p < .001$], not after incongruency-predicting cues [left: $t(19) = 1.18$, $p = .126$, 1-tailed; right: $t(19) < 1$] and not after non-predictive cues [left: $t(19) = 1.28$, $p = .109$, 1-tailed; right: $t(19) = 1.02$, $p = .159$, 1-tailed]. DLPFC activity was enhanced when incongruent targets were invalidly cued by congruency-predicting cues (as compared to non-predictive cues) [left: $t(19) = 2.78$, $p = .006$, 1-tailed; right: $t(19) = 2.51$, $p = .011$, 1-tailed], and a similar effect of invalid cueing could be observed for congruent targets in the left DLPFC [$t(19) = 2.81$, $p = .006$, 1-tailed], but not in right DLPFC [$t(19) = 1.02$, $p = .160$, 1-tailed].

Analysis of the cue-related beta weights showed that there were no real differences among cue conditions in the DLPFC. Congruency-predicting cues only marginally elicited more activity in the DLPFC than non-predictive cues [left: $t(19) = 1.56$, $p = .067$, 1-tailed; right: $t(19) = 1.71$, $p = .052$, 1-tailed], but there was no difference in DLPFC activity between congruency-predicting cues and incongruency-predicting cues [left: $t(19) = .76$; right: $t(19) = .56$]. Like in the ACC, incongruency-predicting cues did not elicit more activity in the DLPFC than did non-predictive cues [left: $t(19) = .67$; right: $t(19) = .96$]. Most importantly, in contrast to the observed effects in the ACC, there were no significant correlations between the cue-related beta weights in the DLPFC and response time effects of valid or invalid cueing (left: all $r < .3$; right: all $r < .4$).

3.5 Discussion

In the present fMRI study, we tested the hypothesis that the ACC is involved in making control adjustments on the basis of subjects' expectancies rather than on the basis of response conflict. To this end, we specifically manipulated participants' expectancies by using abstract cues that predicted the upcoming Stroop-like target condition with 75% certainty. Target-related results show that cues can elicit similar effects behaviorally and in the dACC as observed when looking at congruency as a function of trial-to-trial sequences, i.e., enhanced conflict effects following congruency-predicting cues compared with incongruency-predicting cues. Furthermore, cue-related activity in the dACC was more enhanced during congruency-predicting cues than during incongruency-predicting or non-predictive cues, suggesting that adjustments especially take place when expecting non-conflict trials instead of when expecting conflict. Hence, participants showing more dACC activity in response to congruency-predicting cues also showed greater response time effects of valid and invalid cueing following these cues.

These findings can better be explained by an expectancy-based theory of sequential effects than by the conflict adaptation account (for a review, see Egner, 2007). Although behavioral and dACC effects replicate those of previous studies taken as evidence in favor of the conflict adaptation account (Botvinick et al., 1999; Kerns et al., 2004), our results are driven by abstract cues instead of response conflict. Moreover, the effects are driven by cues predicting non-conflict rather than conflict. Because our cues explicitly induced expectations about the upcoming Stroop target condition, our results are more in line with the repetition expectancy account, suggesting that control adjustments are made on the basis of subjects' expectancies of the following trial (Gratton et al., 1992; Bartholow et al., 2005). Following this latter account, we suggest that participants engage in a strategy of widening of attention when expecting a congruent trial (allowing more influence of the distractor) and a focusing of attention when expecting an incongruent trial (reducing the influence of the distractor). Hence, when expectancies are confirmed, performance benefits from these strategic adjustments, as could be observed when cues were valid in the present experiment. In contrast, when expectancies are violated - like with invalid cueing - performance is impaired.

Response times, error rates, and dACC activity were most prominently enhanced when an incongruent target was invalidly cued, thus, when a congruent target was expected. In terms of strategic adjustments, an invalidly cued incongruent target is more problematic than an invalidly cued congruent target. This is because widening of attention to allow processing of the distractor leads to erroneous responses with incongruent targets, while focusing of attention on the target dimension is just a sub-optimal strategy for congruent targets. Hence, when an incongruent target is invalidly cued, the need to adjust control is most essential and activity of the dACC, implementing the control, is highest.

Although Gratton and colleagues (1992) suggested that the congruency-based strategies were quite specific for the Flanker task that they used (Eriksen and Eriksen, 1974), we show similar effects of strategic adjustments in a version of the Stroop task. Indeed, recent studies using both Stroop and Flanker tasks, show across-task effects of cueing and trial-to-trial sequence effects (Freitas et al., 2007; Fernandez-Duque and Knight, 2008). These results suggest that the strategies generalize to some extent across tasks and do not just encompass a specific strategy to allow or ignore either the Stroop distractor or the Flanker distractors (but see Magen and Cohen, 2007; Notebaert and Verguts, 2008).

In a previous study, we showed that ACC activity was similarly enhanced for (100% valid) congruency-predicting and incongruency-predicting cues as compared to uninformative cues (Aarts et al., 2008). Therefore, we suggested that the ACC is involved in making strategic adjustments in control independent of the specific processing strategies (i.e., widening or focusing of attention). However, in the present study, ACC activity seemed to be more enhanced for congruency-predicting cues than for incongruency-predicting cues. These results are in agreement with the cue-related ERP results of Gratton and colleagues (1992). Comparable to the present fMRI results, these authors found that the P300 component was increased in response to congruency-predicting cues as compared to incongruency-predicting cues. They explained these findings by suggesting that the widening of attention following a congruency-predicting cue is the adaptive strategy and needs more "reprogramming of the information-processing system" while the focusing of attention following an incongruency-predicting

cue is the default strategy (Gratton et al., 1992). Thus, the reason why we did not find any differences between incongruency-predicting and non-predictive cues in both cue- and target-related ACC activity might be because participants engage in the same default strategy on both types of cues. This reasoning is also in line with the correlation we found between cue-related ACC activity and performance, which was only significant for the congruency-predicting cues compared with non-predictive cues and not for the incongruency-predicting cues. From these results it seems that congruency-predicting cues convey the most useful information, that is, a signal to adopt the non-default strategy of widening of attention. With the 100% valid cues we obtained similar ACC activity for congruency- and incongruency-predicting cues as compared to non-predictive cues (Aarts et al., 2008), presumably because this task setting was much clearer and might have induced slight differences in strategy engagement as compared to the present probabilistic task situation. Apparently, with 100% valid cues, the most adaptive strategy would be to adjust control based on both the congruency- and incongruency-predicting cues, while the most adaptive strategy with probabilistic cues is to adjust control based only on congruency-predicting cues.

It has been suggested that anticipatory activity in the ACC reflects the expectation of conflict (Sohn et al., 2007), error likelihood (Brown and Braver, 2005), or the need to reduce mental effort (Botvinick, 2007). However, the present results show especially enhanced dACC activation when congruent targets can be expected (75%), whereas, overall, response times are slowest and error rates are biggest following incongruency-predicting cues (see behavioral results). Moreover, the DLPFC, which is often thought to receive conflict monitoring signals from the ACC to increase control, was not differentially activated for the cues in the present study and DLPFC activity also did not show any correlations with behavioral measures. Therefore, in the present study, anticipatory activity in the dACC seems to reflect strategic adjustments instead of monitoring for response conflict or error likelihood.

We have shown that the dACC is involved in expectancy-based adjustments in cognitive control based on probabilistic cues. However, we do not claim that subjects' expectancies are solely responsible for sequential effects. It is possible that conflict-driven and expectancy-driven control, or even non-control episodic memory effects

(Mayr et al., 2003; Hommel et al., 2004) all contribute to sequential effects. Moreover, to what extent these processes influence conflict resolution can differ per task situation or context (Fernandez-Duque and Knight, 2008). In any case, the present and previous data (Aarts et al., 2008) do show that expectancy-based strategic adjustments can play an important role and should be taken into account when studying sequential effects and the role of the dACC.

Table 3.1 Peak Talairach coordinates, peak t-values, and cluster size (in mm^3) of regions showing a conflict effect (incongruent > congruent trials) following congruency-predicting cues for $p < .05$ (False Discovery Rate corrected) and a threshold of 50 mm^3

region	**BA***	**x**	**y**	**z**	***t*(19)**	**size**
Activations						
pre-Supplementary Motor Area - *right* /	6	6	14	49	5.17	2715
Anterior Cingulate Cortex - *right*	32	6	32	31	4.55	
Middle Frontal Gyrus - *left*	10	-36	62	7	4.73	450
Inferior Frontal Gyrus - *right*	10	45	53	1	5.51	3899
Inferior Frontal Gyrus - *left*	47	-30	20	1	4.73	234
Inferior Frontal Gyrus - *right*	47	33	20	-2	5.52	1564
Dorsolateral Prefrontal Cortex -*left*	9	-54	14	28	5.59	2247
Dorsolateral Prefrontal Cortex - *right*	8 / 9	45	11	40	6.64	9592
Precentral Gyrus - *left*	6	-30	-10	52	4.09	57
Superior Temporal Gyrus - *right*	38	51	14	-26	5.09	561
Middle Temporal Gyrus - *right*	21	54	-28	-5	5.26	1781
Inferior Temporal Gyrus - *right*	37	57	-49	-20	4.62	99
Posterior Cingulate Gyrus - *right*	23	3	-25	31	4.32	71
Precuneus - *right*	7	3	-67	37	6.09	2230
Inferior Parietal Lobe - *right*	40	33	-52	37	10.59	13859
Inferior Parietal Lobe - *left*	40	-30	-52	37	7.30	8200
Cerebellum - *left*		-30	-55	-35	6.01	3590
Cerebellum - *right*		30	-55	-32	4.59	143
Deactivations						
Middle Frontal Gyrus - *left*	11	-18	29	1	-4.42	69
Subgenual Area - *right*	25	6	23	-2	-4.53	369
Cingulate Gyrus - *left*	24	-3	2	28	-4.07	70
Superior Frontal Gyrus - *right*	6	18	-7	67	-4.99	66
Insula - *left*	13	-42	-4	1	-4.34	129
Insula - *left*	13	-42	-13	13	-4.39	249
Insula - *right*	13	36	-13	22	-5.05	1775
Posterior Cingulate Gyrus - *left*	30	-15	-52	16	-4.79	422
Posterior Cingulate Gyrus - *right*	31	15	-34	40	-4.88	406
Inferior Parietal Lobe - *left*	40	-57	-28	19	-4.35	606
Parahippocampal/Fusiform Gyrus - *right*	37	33	-40	-8	-5.44	617
Parahippocampal/Fusiform Gyrus - *left*	37	-33	-40	-11	-5.47	102

* BA = Brodmann Area

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4.

Cognitive Control over Task and Response in Lateral and Medial Frontal Cortex: Brain Activity and Reaction Time Distributions

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4.1 Abstract

It is unclear whether task conflict is reflected in the anterior cingulate cortex (ACC) or in more dorsal regions of the medial frontal cortex (MFC). When participants switch between tasks involving incongruent, congruent, and neutral stimuli, it is possible to examine both response conflict (incongruent vs. congruent) and task conflict (congruent vs. neutral). Here, we report an event-related functional magnetic resonance imaging (fMRI) study that examined which areas in frontal cortex, including MFC, are implicated in response conflict, task conflict, or both. Stimuli were incongruent and congruent arrow-word combinations, or arrows and words only in a neutral condition. Participants responded manually to the arrow or word. The task varied every second trial. The behavioral data revealed response conflict (incongruent > congruent) and task conflict (congruent > neutral) in mean reaction times and ex-Gaussian latency distribution components. The imaging data revealed activity in both the ACC and a more dorsal region in the MFC (the medial superior frontal gyrus) related to response conflict as well as task conflict. These conflict effects were observed independent of the task performed (arrow or word) or the trial type (repeat or switch). In lateral prefrontal cortex (LPFC), response conflict was associated with activity in ventral LPFC, whereas task conflict activated both ventral and dorsal regions. Thus, whereas the type of conflict (response vs. task) was differentiated in LPFC, no such differentiation was found in MFC, including the ACC. Models of ACC functioning may require modification to take account of these findings.

4.2 Introduction

Cognitive control refers to the regulatory processes that ensure that our actions are in accordance with our goals. Cognitive control implies flexibility to switch rapidly between tasks and the ability to resolve conflict when stimulus dimensions are competing for control of the output. Previous research has implicated regions in the dorsal medial

frontal cortex (MFC) and the anterior cingulate cortex (ACC, Brodmann area [BA] 24 and 32) in cognitive control (for reviews, see Posner and Raichle, 1994; Bush et al., 2000; Miller and Cohen, 2001; Paus, 2001; Ridderinkhof et al., 2004a). The exact role of these areas has remained unclear, however.

A task often used in studying cognitive control is the Stroop task (Stroop, 1935). In the original color-word version of this task, participants name the ink color of written color words or read the words aloud (MacLeod, 1991). Stimuli can be congruent (e.g., the word RED in red ink), incongruent (e.g., the word BLUE in red ink), or neutral (e.g., a row of Xs in red ink for color naming or the word RED in black ink for word reading). In a blocked-task design, only the color-naming task elicits interference effects, that is, participants are slower when naming the color of incongruent Stroop stimuli compared with neutral or congruent stimuli, whereas there are no effects in word reading. Throughout neuroimaging history, the ACC is typically found to be more active for the incongruent than the congruent or neutral conditions in Stroop color naming, implying a role of the area in dealing with response conflict (Pardo et al., 1990; Bench et al., 1993; Carter et al., 1995; MacDonald et al., 2000; Kerns et al., 2004).

Regions in MFC have also been implicated in conflict at the level of tasks. In Stroop paradigms, the difference between word reading and color naming is less when the tasks are mixed than when they are blocked. In particular, when tasks are blocked, Stroop interference is absent in word reading, but when word reading and color naming are mixed, or participants switch between tasks, Stroop interference occurs in word reading (Allport and Wylie, 2000; Gilbert and Shallice, 2002; Yeung and Monsell, 2003): the so-called reverse Stroop effect. Woodward and colleagues have conducted several experiments to elucidate the role of the ACC in Stroop task-switching (Ruff et al., 2001; Woodward et al., 2006; Woodward et al., 2008). In particular, they have demonstrated that the ACC/pre-supplementary motor area (pre-SMA) not only reflects Stroop conflict in color naming, but also the reverse Stroop conflict in word reading when participants switch between the tasks (Ruff et al., 2001). Furthermore, they have shown that the ACC/pre-SMA activation for the reverse Stroop effect decreased as a function of the number of trials since a task switch, suggesting a role for this MFC region in resolving competition between tasks (Woodward et al., 2006). However, in these studies, the

authors contrasted incongruent with neutral stimuli, that is, a bivalent stimulus containing conflicting response and task dimensions (i.e., a color word in a conflicting ink color) with a univalent stimulus containing no conflicting response and task dimensions (i.e., a color word in black ink). This contrast not only involves task conflict but also response conflict in the word reading task. Thus, it is unclear whether brain activity related to task or response conflict was measured in these studies.

In a more recent study, Woodward and colleagues (2008) contrasted neutral trials in an univalent block context with neutral trials in a bivalent block context. This contrast revealed dorsal ACC (dACC, which was actually medial BA 9) activity, interpreted as a role for dACC in signaling a break in task inertia. Although this is convincing evidence for a role of the MFC in task conflict, the exact locus of the effect is still unclear because the activation in the dACC included the ACC (BA 32) and the medial superior frontal gyrus (BA 8). In the previously mentioned studies, Woodward and colleagues (Ruff et al., 2001; Woodward et al., 2006) also found activity for the reverse Stroop effect in ACC/pre-SMA voxels that were located more in the pre-SMA than in the ACC. Thus, the question arises whether the task-conflict effect is actually located in the ACC, in more dorsal regions of the MFC, or both. This question is especially important in light of the results of Milham and Banich (2005). They used congruent, incongruent, and neutral (color-unrelated) color-word Stroop stimuli, which made it possible to contrast bivalent (incongruent and congruent) with univalent (neutral) stimuli and to contrast stimuli involving conflict (incongruent) with stimuli not involving conflict (congruent and neutral). The authors found that for the valency contrast (i.e., congruent > neutral and incongruent > neutral) a region nearby the pre-SMA was activated, while for the conflict contrast (i.e., incongruent > congruent = neutral) a more anterior and ventral region in the ACC was active (Milham and Banich, 2005). Hence, the activity in the ACC was suggested to be conflict specific, while the activity nearby the pre-SMA was suggested to be more generally related to valency (i.e., task conflict). However, although this latter dorsal (and caudal) region in MFC was more active for congruent than for neutral stimuli, participants responded still faster to congruent than neutral stimuli (i.e., an RT facilitation effect was found). Thus, it is not clear whether the manipulation really induced reliable task conflict, which may explain the absence of an effect in the ACC. To conclude, from

the studies of Woodward and colleagues (2006; 2008) and Milham and Banich (2005) it is unclear whether task conflict is reflected in the ACC or in more dorsal regions of the MFC. In several studies, Banich and colleagues (Milham et al., 2001; Milham et al., 2003a; Liu et al., 2006) compared performance on incongruent and neutral Stroop trials. However, the neutral stimuli used were colored non-color words (e.g., the word 'lot' in green ink), affording both color naming and word reading. Thus, it remains unclear to what extent the neutral stimuli evoked response conflict, task conflict, or both in these studies.

To resolve these issue, we used a design with incongruent, congruent, and neutral Stroop-like stimuli, in which participants switched between responding to the two dimensions of the stimuli (**Figure 4.1**) (see also, Aron et al., 2004). Switching between tasks creates conflict at the level of the whole task set and at the level of individual responses (e.g., Rogers and Monsell, 1995; Allport and Wylie, 2000; Monsell, 2003). Incongruent and congruent stimuli afford both tasks in an experiment (i.e., they are bivalent), whereas our neutral stimuli afford only one task (i.e., they are univalent) (Allport and Wylie, 2000; Pashler, 2000). When people switch between tasks involving incongruent, congruent, and neutral stimuli, it is possible to examine both response- and task-related activity evoked by the stimuli (Aron et al., 2004). Because incongruent and congruent stimuli are equally associated with the two tasks, slower responding to incongruent than to congruent stimuli must reflect response conflict. Congruent stimuli create no conflict at the response level but are associated with both tasks, whereas neutral stimuli are associated with only one task. Therefore, slower responding to congruent than to neutral stimuli can only reflect conflict at the task level (Rogers and Monsell, 1995; Aron et al., 2004; Monsell, 2005): “In task-switching experiments, competition from stimulus→task associations is revealed by a pattern Rogers & Monsell (1995) observed: RTs substantially shorter for neutral (N) than for congruent (C) stimuli. ... Hence we argued that observing a positive C-N contrast (i.e. C slower than N) is a marker for competition at the task-set level" (Monsell, 2005, p. 184).

Our use of the term 'response conflict' refers to conflict at the level of individual response tendencies as opposed to conflict at the level of task set ('task conflict'), which by definition involves multiple stimulus-response mappings. Conflict at the individual

response level may occur at one or more processing stages, including conceptual processing, response selection, and motor programming of the manual response (Roelofs and Hagoort, 2002; see Roelofs, 2003; Roelofs et al., 2006, for a computational model of performance on Stroop-like tasks). Milham and colleagues (2001) provided evidence that the ACC and right dorsal lateral prefrontal cortex (LPFC) are specifically involved in conflict during response selection, whereas left dorsal LPFC is implicated in conflict at other processing levels. Our design (i.e., the contrast between incongruent and congruent trials) does not allow a distinction between response selection and other processing stages, although the findings of Milham and colleagues (2001) make it likely that conflict relates to response selection in our experiment as well.

We employed an arrow-word Stroop task, allowing for manual responding in the scanner with non-arbitrary mapping of responses onto buttons (see also, Baldo et al., 1998; Turken and Swick, 1999; Roelofs et al., 2006; Aarts et al., 2008). Participants were presented with incongruent or congruent combinations of left- or right-pointing arrows and the words left or right (e.g., a right-pointing arrow combined with the word left) or arrows and words only in a neutral condition (e.g., a right-pointing arrow combined with a row of Xs). A task cue presented on each trial reminded the subjects whether they had to respond to the direction denoted by the arrow or by the word. Although the tasks switched predictably every two trials, we used external cues to not make the task too difficult to perform with long inter-trial intervals. We were, however, only interested in the stimulus-related activity.

We hypothesized that response conflict is indexed by the difference in performance between incongruent and congruent conditions, while task conflict is indexed by the difference between the congruent and neutral conditions. To obtain converging evidence for this assumption in our experiment, we performed ex-Gaussian distribution analyses on the response times (Ratcliff, 1979). The ex-Gaussian is a mathematical model used to describe response time distributions. Ex-Gaussian functions provide good fits of empirical response time distributions and have been widely adopted (e.g., Hohle, 1965; Luce, 1986; Heathcote et al., 1991; Spieler et al., 1996; Yap and Balota, 2007). The ex-Gaussian distribution is a convolution of a Gaussian and an exponential distribution, and it has three parameters: μ, σ, and τ. The μ and σ parameters

reflect, respectively, the mean and standard deviation of the Gaussian portion, and τ reflects both the mean and standard deviation of the exponential portion. Theoretically, the sum of μ and τ is equal to the mean of the overall distribution (Hohle, 1965; Luce, 1986). Ex-Gaussian analyses allow differences between conditions to be separated into distributional shifting, reflected in μ, and distributional skewing, reflected in τ. Whereas μ has been associated with the process of resolving response competition in Stroop-like tasks (e.g., Kane and Engle, 2003; Roelofs, 2008b), τ has been associated with processes at the level of task set, such as goal maintenance (Duncan et al., 1996; Kane and Engle, 2002, 2003; Schmiedek et al., 2007). Thus, according to our assumptions, response conflict (i.e., incongruent > congruent) should be reflected in μ, and task conflict (congruent > neutral) should be apparent in τ in our experiment.

The present design allowed us to directly test whether the ACC region typically involved in response conflict (incongruent > congruent) is also involved in task conflict (congruent > neutral) or whether task conflict is associated with a more dorsal region in MFC. We also assessed these effects in lateral prefrontal cortex (LPFC), where processes at the level of response selection are often associated with ventral regions and processes at the level of task set with dorsal regions, although the distinction need not be absolute (for reviews, see Thompson-Schill et al., 1997; Kane and Engle, 2002; Roelofs, 2008a).

4.3 Materials and Methods

4.3.1 Participants

Twelve neurologically healthy Dutch subjects (10 female, mean age 21.2 years, range 19-25) participated in the experiment. All participants were right-handed and native speakers of Dutch. They were compensated for participation and gave written informed consent in a manner approved by the Dutch Central Committee on Research Involving Human Subjects (CCMO).

4.3.2 Design and Procedure

The participants were scanned while performing a manual arrow-word version of the Stroop task. The stimuli consisted of written words superimposed onto arrows, or arrows and words only (**Figure 4.1**). The lines and letters of the stimuli were white on a blue background. The arrows pointed to the left or to the right. The words were the Dutch words for *right* (*rechts)* and for *left* (*links*). Participants responded manually to the Stroop-like stimuli by pressing a left or a right button on a scanner-compatible button box. Participants responded either to the direction of the arrow (arrow task) or to the direction indicated by the word (word task). Participants were told to respond as fast and accurately as possible with the left middle finger (for left response) and the left index finger (for right response). This button-box response was executed with the left hand (right motor cortex) because the stimuli themselves were language-related (left hemisphere). In the congruent Stroop condition, the arrow and the word denoted the same direction (e.g. the word right in an arrow pointing to the right). In the incongruent Stroop condition, the arrow and the word denoted a different direction (e.g., the word left in an arrow pointing to the right). In the neutral Stroop condition, the stimuli consisted of words (left or right) in rectangles without arrow heads or rows of five or six Xs in arrows. In both tasks, each of the three conditions included 40 stimuli (240 trials in total). Congruent, incongruent, and neutral stimuli were presented randomly intermixed.

The task switched predictably every two trials (order: arrow arrow word word arrow arrow, etc.), following the alternate runs paradigm (Rogers and Monsell, 1995). Half of the participants started the experiment with the arrow task, the other half with the word task. Although the task switched predictably, a cue at the beginning of each trial indicated what task to perform next. The cue was the Dutch word for *word* (*woord*), which instructed the subjects to respond to the word, or the Dutch word for *arrow* (*pijl*), instructing them to respond to the arrow. The Stroop stimulus followed the cue after a variable delay of minimally 2 and maximally 7 s long. Similarly, a variable delay of 2-7 s was used between a Stroop stimulus and the next task cue, in which participants made their response. Participants were not limited in their response times. The jitter between cue and stimulus and the inter-trial interval was calculated with a simulation of the blood oxygenation level-dependent (BOLD) response in SPM99 (Wellcome Dept. of Cognitive

Neurology, London). The variable delays enabled us to characterize the hemodynamic responses at a fine temporal resolution (Josephs et al., 1997) and thus allowed us to reliably distinguish the BOLD response to the cue from the BOLD response to the Stroop stimulus (see for a similar procedure: Toni et al., 1999; Mars et al., 2005). This calculation was repeated several times, generating a random sequence with appropriate delays for every participant separately. Because the delay between cue and Stroop stimulus could not be predicted, the participant needed to be ready to respond at any time. Stimuli remained on the screen for 600 ms.

Conflict processes were indexed by differences in activity among incongruent, congruent, and neutral Stroop stimuli. As indicated, bivalent incongruent and bivalent congruent stimuli afford and activate both tasks in an experiment, whereas univalent neutral stimuli afford and activate only one of the tasks. Thus, more activity for incongruent than congruent stimuli indexes response conflict, whereas more activity for congruent than neutral stimuli indexes conflict between task sets. These contrasts are closely related to, respectively, the conflict contrast and the valency (or 'competition') contrast of Milham and Banich (2005).

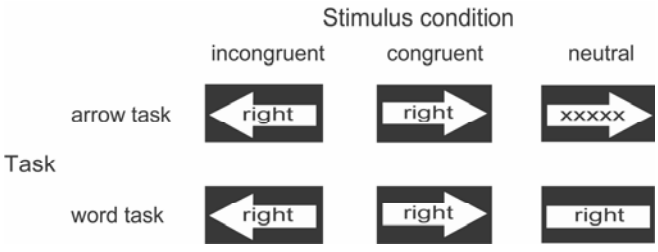

Figure 4.1 Examples of incongruent, congruent, and neutral stimuli in the arrow and the word tasks. Incongruent and congruent stimuli are both bivalent, whereas neutral stimuli are univalent. In the study, the words were given in the participants' native language, i.e. Dutch.

4.3.3 FMRI Data Acquisition

Whole-brain imaging was performed on a 3T Siemens Trio MRI system. Functional data were acquired using a gradient-echo echo-planar scanning sequence (30 axial slices, 3.5 mm thick, interslice gap = 0.35 mm, repetition time = 2210 ms, echo time = 40 ms, voxel size = 3.5 mm x 3.5 mm x 3.5 mm, field of view = 224 mm, flip angle = 70º). All functional images were acquired in a single run with a duration of 40 minutes. Visual stimuli were projected on a screen and were viewed through a mirror attached to the head coil. After the acquisition of functional images, high-resolution anatomical images were acquired using an MP-RAGE sequence (192 saggital slices, repetition time = 2300 ms, echo time = 3.03 ms, voxel size = 1.0 x 1.0 x 1.0 mm, field of view = 256 mm).

4.3.4 Behavioral Data Analysis

Mean Response Times and Error Rates

The mean latencies of the correct manual responses to the arrows and words in the two tasks (arrow task, word task) and error rates were analyzed using repeated-measures analyses of variance (ANOVA) with the factors STROOP CONDITION (congruent, incongruent, neutral), TASK (word, arrow), and TRIAL TYPE (switch, repeat). All variables were tested within participants. T-tests were performed one-tailed unless mentioned otherwise.

Ex-Gaussian Parameters

In addition, the data were examined at the level of distributional characteristics using ex-Gaussian analyses. These analyses characterize a response time distribution by assuming an explicit function for the shape of the distribution. The ex-Gaussian function consists of a convolution of a Gaussian and an exponential distribution and it has three parameters, μ and σ (characterizing the Gaussian distribution) and τ (characterizing the exponential distribution). Previous research has associated μ with the process of resolving response competition in Stroop-like tasks and τ has been associated with processes at the level of task set. The distributional parameters of the present data were estimated using the quantile maximum likelihood estimation method proposed by Brown and Heathcote

(2003). The ex-Gaussian parameters (μ, σ, and τ) were obtained per condition for each participant individually using the program of Brown and Heathcote. All estimations converged within 31 iterations. Condition differences in the parameters were then examined by conducting analyses of variance.

4.3.5 FMRI Data Analysis

Image Processing

Data were analyzed using SPM2 (Wellcome Dept. of Cognitive Neurology, London). The first five volumes of each participant's data set were discarded to allow for T1 equilibrium. Functional images were corrected for differences in slice acquisition timing, followed by motion correction. Structural and functional data were co-registered and spatially normalized to a standard stereotactic space (Montreal Neurological Institute (MNI) template), using a 12-parameters affine transformation. After normalization, voxels were resampled with a 2 x 2 x 2 mm^3 voxel size. Images were spatially smoothed with a 6 mm full-width at half-maximum (FWHM) isotropic Gaussian kernel. High-pass filtering (128 secs) was applied to the time series of the functional images to remove low-frequency drifts.

Statistical Model

Statistical analyses were performed in the context of the general linear model in SPM2. On the first level, all event-types were modeled. Stimulus-related predictors included word congruent, neutral, and incongruent, and arrow congruent, neutral, and incongruent stimuli for each trial type (switch and repeat). Trials on which participants had made an error were put together as a separate regressor of non-interest. All predictors of interest were modeled as a stick function (duration = 0) convolved with a canonical HRF (Friston et al., 1998) and its temporal derivative to account for variance due to different slice timings as well as to different HRF delays/shapes for different regions. The first derivatives of the six motion parameters were included as covariates. Effects were estimated using a subject-specific fixed-effects model.

Consistent effects across subjects were tested using a random effects analysis. A within-subject ANOVA was performed on the second level with first-level contrast images for every subject, corresponding to the 12 cells of the 3 x 2 x 2 design [STROOP CONDITION (congruent, incongruent, neutral) x TASK (word, arrow) x TRIAL TYPE (switch, repeat)]. We report the results of this random effects analysis with the statistical threshold set at $p < .001$ at the voxel level and a minimum cluster size of 10 voxels (Forman et al., 1995). We also mention the false discovery rate (FDR) corrected p-value at the voxel level in the text for the ROIs in MFC and in **Table 3.1**.

Contrasts

First, we looked at the contrasts for task conflict (congruent > neutral stimuli) and response conflict (incongruent > neutral stimuli) separately. However, we specifically wanted to test whether a region in the ACC typically involved in response conflict is also involved in task conflict. To that end, we specified the contrast congruent > neutral (i.e., task conflict) inclusively masked (at $p = .01$) by the contrast incongruent > congruent (i.e., response conflict). This way, we could identify regions that were responsive to both types of conflict.

Region-of-Interest Analysis

To test whether the effects of response and task conflict in the MFC regions were influenced by task or trial type, we performed a ROI analysis using MarsBaR (Brett et al., 2002). From the 2nd level group analysis ($P_{FDR} < .05$), we chose the regions within the MFC and LPFC (with a minimum cluster size of 10 voxels) that responded to both response and task conflict, determined with the contrast specified above (congruent > neutral, masked inclusively by incongruent > congruent [at $p = .01$]). Mean beta weights from all voxels in these regions were extracted for all event types and all subjects. These regionally averaged beta-weights were analyzed in repeated-measurement ANOVAs.

To ascertain whether or not task conflict would activate more dorsal levels of the MFC and response conflict more ventral levels, we also used anatomically defined AAL ROIs (Tzourio-Mazoyer et al., 2002). To investigate conflict effects in MFC, we performed analyses on the left and right anterior cingulum ROIs and left and right medial

superior frontal ROIs. With a repeated-measurement ANOVA on the regionally averaged beta-weights, we investigated region by conflict effects. To establish a possible dissociation between task conflict and response conflict in lateral prefrontal cortex (LPFC), a similar analysis was done with LPFC ROIs. We used the left and right middle frontal ROIs (dorsal LPFC), and left and right inferior frontal pars triangularis and inferior frontal pars orbitalis ROIs (ventral LPFC). The dorsal LPFC is often associated with processes at the level of task set, and the ventral LPFC with processes at the level of response selection.

4.4 Results

4.4.1 Behavioral Data

Figure 4.2 shows the mean response latencies and error rates for each Stroop condition on switch and repeat trials, separately for each task.

Mean Response Times

Response times were longer on switch than on repeat trials and longer in the incongruent condition than in the other conditions (**Figure 4.2**). There were main effects of TRIAL TYPE [$F(1,11) = 70.45$, $p<0.001$] and STROOP CONDITION [$F(2,22) = 38.92$, $p < .001$]. There was, however, no main effect of TASK [$F(1,11) = 2.95$, $p > .1$]. There was no TRIAL TYPE x TASK interaction [$F(1,11) = 1.86$, $p > .1$], but there was a TRIAL TYPE x STROOP CONDITION interaction [$F(2,22) = 3.98$, $p = .03$] and a TASK x STROOP CONDITION interaction [$F(2,22) = 4.91$, $p = .02$]. There was no TRIAL TYPE x TASK x STROOP CONDITION interaction [$F(2,22) = 2.38$, $p > .1$].

In the arrow task, responses were slower for incongruent than for congruent stimuli on both repeat [$t(11) = 3.9$, $p < .001$] and switch trials [$t(11) = 5.09$, $p < .001$], and slower for congruent than for neutral stimuli on repeat trials [$t(11) = 3.3$, $p = .004$], and there was a trend towards this effect on switch trials [$t(11) = 1.66$, $p = .06$]. The difference between incongruent and congruent trials was greater on switch than on repeat trials [$t(11) = 3.3$, $p = .007$. The congruent and neutral conditions did not differ between switch and repeat trials [$t(11) < 1$]. In the word task, responses were slower for

incongruent than for congruent stimuli on both repeat [$t(11) = 2.96$, $p = .007$] and switch trials [$t(11) = 2.51$, $p = .01$]. Response times did not differ between congruent and neutral stimuli on repeat trials [$t(11) = 1.03$, $p > .1$], but they were slower for congruent than for neutral stimuli on switch trials [$t(11) = 1.82$, $p = .05$]. The difference between the incongruent and congruent conditions, and between the congruent and neutral conditions, did not differ between switch and repeat trials [both $t(11) < 1$].

To summarize, responding was slower on switch than repeat trials for both tasks, replicating the standard switch cost in the literature. Moreover, response times differed among the Stroop conditions in both tasks, indicating effects of both response conflict and task conflict.

Error Rates

Figure 4.2 (error rates between brackets) shows that more errors were made on switch than on repeat trials. Also, more errors were made in the incongruent condition than in the other conditions. The error rates exhibited main effects of TRIAL TYPE [$F(1,11) = 7.65$, $p < .018$] and STROOP CONDITION [$F(2,22) = 18.78$, $p < .001$], but there was no TRIAL TYPE x STROOP CONDITION interaction [$F(2,22) = 1.42$, $p = .26$]. For the error rates, there was no main effect of TASK [$F(1,11) = 1.61$, $p = .23$], and there was no TASK x STROOP CONDITION interaction [$F(2,22) = 1.70$, $p = .21$]. Also, the TRIAL TYPE x TASK x STROOP CONDITION interaction was not significant [$F(2,22) < 1$].

Overall, participants made more errors when there was response conflict, i.e. incongruent versus congruent Stroop stimuli [$t(11) = 4.33$, $p = .001$]. However, there was no difference between the congruent and neutral condition [$t < 0$], so no effect of task conflict in the error rates.

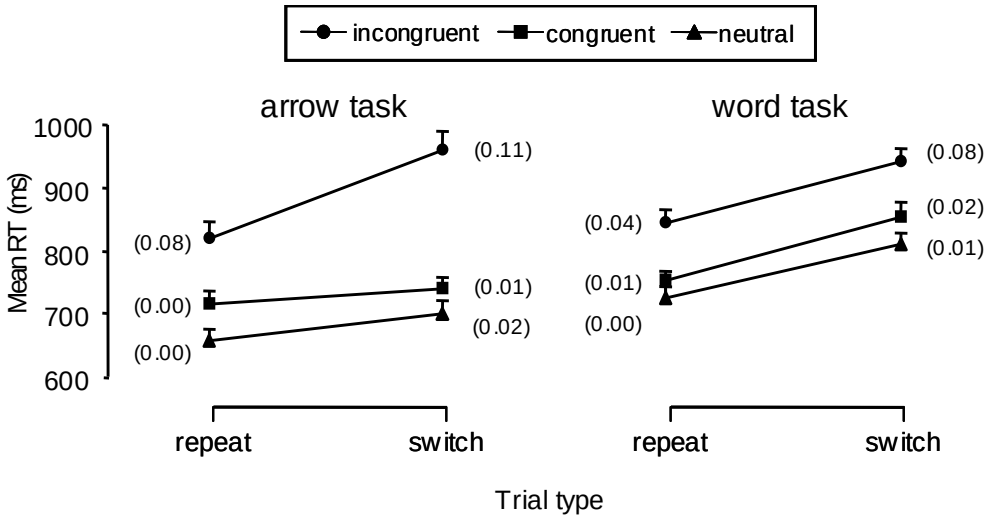

Figure 4.2 Mean reaction times (RT) for the three Stroop conditions on repeat and switch trials in the arrow and word tasks. Error rates are given between parentheses. Error bars represent the standard error of the mean.

Ex-Gaussian Parameters

We also investigated the conflict effects on the three ex-Gaussian parameters, μ, σ, and τ. The values of these parameters for the incongruent, congruent, and neutral conditions are shown in **Figure 4.3**. Note that the congruent condition was slower than the neutral condition in the mean RTs (765 vs. 723 ms, respectively), but the congruent condition was numerically faster than the neutral condition in μ. For μ, there was a main effect of STROOP CONDITION [$F(2,22) = 7.96$, $p = .003$]. This effect on μ was caused by a difference between the incongruent and congruent conditions [$F(1,11) = 8.13$, $p = .016$] and not by the congruent and neutral conditions [$F(1,11) = 2.25$, $p = .162$]. There was an interaction of STROOP CONDITION and TRIAL TYPE in μ [$F(2,22) = 5.12$, $p = .015$], revealing that the difference between incongruent and congruent trials in μ was greater on switch trials (160 ms) than repeat trials (67 ms), like in the mean RTs (see **Figure 4.2**). There was no interaction of STROOP CONDITION and TASK in μ [$F(2,22) = 1.70$, $p = .21$]. For σ, there was also a main effect of STROOP CONDITION [$F(2,22) = 4.32$, $p = .026$], which was also caused by a difference between incongruent and congruent trials

[$F(1,11) = 5.9$, $p = .033$] and not by congruent and neutral trials [$F(1,11) < 1$]. There was no interaction of STROOP CONDITION and TRIAL TYPE in σ [$F(2,22) = 1.63$, $p = .28$]. STROOP CONDITION interacted with TASK in σ [$F(2,22) = 5.55$, $p = .011$], which occurred because σ was larger for the incongruent condition in the arrow task than in the other conditions. For τ, there was again a main effect of STROOP CONDITION [$F(2,22) = 13.4$, $p < .001$]. However, in contrast to the effects on μ and σ, the effect on τ was caused by a difference between congruent and neutral trials [$F(1,11) = 20.1$, $p = .001$] and not by incongruent and congruent trials [$F(1,11) = 1.53$, $p = .242$]. There was no interaction of STROOP CONDITION and TRIAL TYPE in τ [$F(2,22) = 1.30$, $p = .29$] and also not of STROOP CONDITION and TASK [$F(2,22) < 1$, $p = .66$].

To summarize, the difference in performance between the incongruent and congruent conditions in the experiment was uniquely associated with the μ and σ parameters of the ex-Gaussian distribution. In contrast, the difference in performance between the congruent and neutral conditions was uniquely associated with the τ parameter. Given that earlier research has associated μ with the process of resolving response competition, and τ with processes at the level of task set (such as goal maintenance), the results of the ex-Gaussian analyses provide converging evidence for our hypothesis that response conflict is indexed by the difference in performance between the incongruent and congruent conditions, and that task conflict is indexed by the difference between the congruent and neutral conditions.

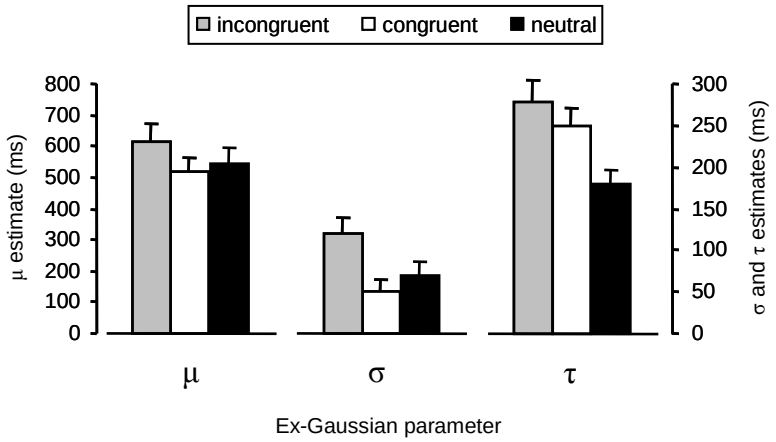

Figure 4.3 Mean ex-Gaussian parameter estimates as a function of Stroop condition. Error bars represent the standard error of the mean.

4.4.2 Imaging Data

Areas activated by response conflict, task conflict, or both are shown in **Table 4.1** and **Figure 4.4**. Response conflict and task conflict both activated areas in dorsal and ventral MFC and in ventral LPFC (inferior frontal gyrus), while areas in dorsal LPFC (middle frontal gyrus) seemed to be primarily activated by task conflict. In the MFC, two regions showed an effect for response conflict and were also activated for conflict at the task level, as revealed by the masking contrast used (**Figure 4.5**). This was the ACC (BA 32; MNI: -6, 38, 28; *p*(FDR corrected) = .009) and a more dorsal and caudal region in the medial superior frontal gyrus (meSFG, BA 8; MNI: -2, 26, 44; *p*(FDR corrected) = .002). To examine whether these conflict effects were influenced by the task that had to be performed (arrow or word) or by the trial type (repeat or switch), we performed an ANOVA on the regionally averaged beta weights of these two MFC regions (see **Figure 4.5**). As can be seen in **Table 4.2**, the effects of response and task conflict were independent of task or trial type in both regions of the MFC (ACC and meSFG). We performed a similar functional ROI analysis with regions in LPFC (BA 44-47) activated by both response conflict and task conflict (see **Table 4.1**). **Table 4.2** shows that in these LPFC regions, conflict effects were also not considerably influenced by the task that had to be performed (arrow, word). In the inferior frontal gyrus (IFG) pars triangularis (BA 45), there were only trends towards interaction effects of task by response conflict [$F(1,11) = 3.43$, $p = .091$] and task by task conflict [$F(1,11) = 3.7$, $p = .081$]. In the IFG pars orbitalis (BA 47), there was no interaction of task by task conflict [$F(1,11) < 1$], but only an interaction of task by response conflict [left: $F(1,11) = 7.94$, $p = .017$; right: $F(1,11) = 3.36$, $p = .094$]. This occurred because these regions in ventral LPFC were more activated for the incongruent condition in the arrow task than in the word task. Similar to the regions in MFC, trial type (switch or repeat) did not interact with Stroop condition in the functionally defined regions in LPFC.

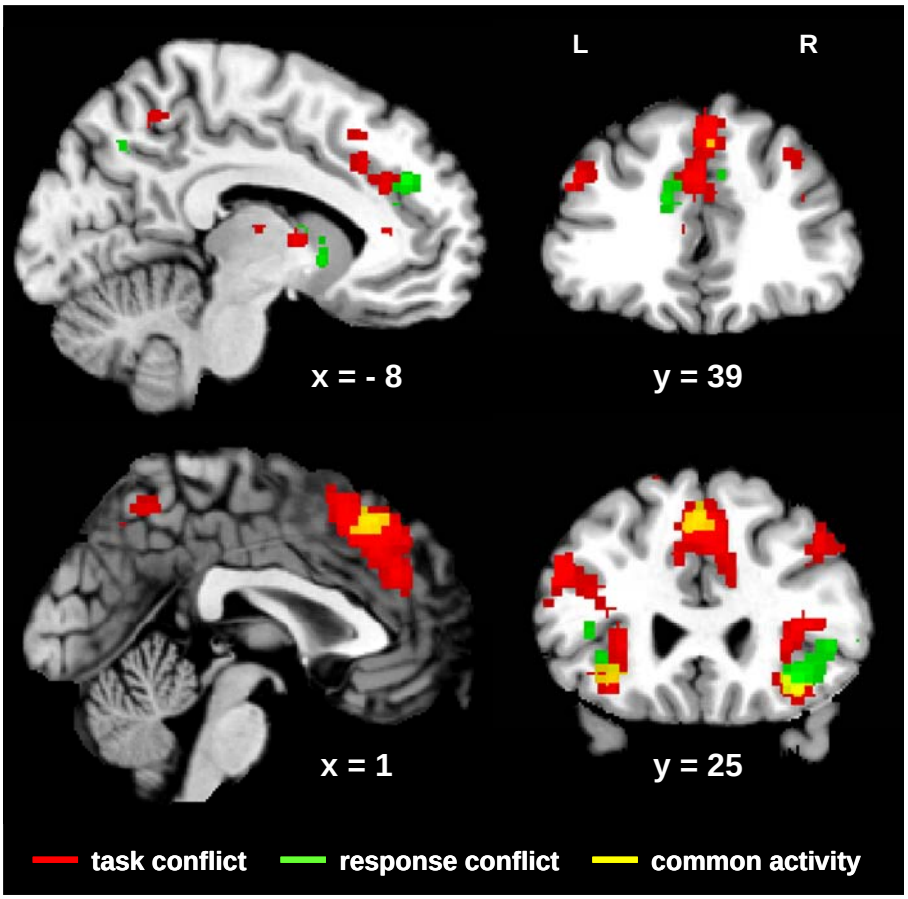

Figure 4.4 Contrasts of response and task conflict overlaid on two sagittal (left) and two coronal sections (right), thresholded at t = 3.16 at the voxel level. Red denotes activity for the task conflict contrast (congruent > neutral stimuli). Green denotes activity for the response conflict contrast (incongruent > congruent stimuli). Yellow denotes common activity for task and response conflict. The sagittal sections show adjacent and overlapping activity for task and response conflict in the anterior cingulate cortex (ACC; top) and in the medial superior frontal gyrus (meSFG; bottom). The coronal sections show effects of task conflict in dorsal parts of the lateral prefrontal cortex (LPFC), and common activity for task and response conflict in ventral parts of LPFC (bottom).

To investigate conflict effects with functionally unbiased ROIs, we performed similar analyses on anatomical (AAL) ROIs in dorsal and ventral MFC and LPFC (see **Table 4.2**). In MFC, especially the left anterior cingulum ROI showed effects of both response and task conflict. On a more dorsal level in MFC, the medial superior frontal ROI showed effects of task conflict and a trend towards a response conflict effect on the left (p = .053, 2-tailed). Both dorsal and ventral ROIs in LPFC showed effects of task conflict, while response conflict was clearly associated with ventral instead of dorsal LPFC (**Table 4.2**). Again, whether participants had to perform the arrow or word task only interacted with the Stroop condition in left ventral LPFC regions (inferior frontal pars triangularis and pars orbitalis), but task and trial type (switch or repeat) did not interact with Stroop condition in the MFC regions.

To investigate whether task conflict and response conflict could be dissociated in dorsal and ventral MFC and LPFC, we directly compared these conflict effects between the left-lateralized (most activated) anatomically defined ventral and dorsal regions. Although more dorsal levels of the MFC (medial superior frontal ROIs) showed only a marginally significant response conflict effect, there was no region by response conflict effect when comparing the left medial superior frontal ROI with the left anterior cingulum ROI [$F(1,11) < 1$], and no region by task conflict effect either [$F(1,11) < 1$]. Similarly, between the functionally defined regions in ACC and meSFG, there was no difference in response conflict [$F(1,11) < 1$] or task conflict effect [$F(1,11) = 2.32$, p = .156]. Thus, although it seems apparent from **Figure 4.4** and **Table 4.1** that task conflict more extensively activates dorsal regions in MFC than the ACC, we do not find any differences for either measure of conflict between anatomically and functionally defined ROIs in MFC. The anatomically defined LPFC regions, on the other hand, demonstrated a clear dissociation in conflict effects. The dorsal LPFC regions showed less response conflict than the ventral regions in LPFC [left middle frontal vs. left inferior frontal pars triangularis: $F(1,11) = 18.47$, p = .001; left middle frontal vs. left inferior frontal pars orbitalis: $F(1,11) = 41.01$, $p < .001$], while there was no difference between regions within ventral LFPC [left inferior frontal pars triangularis vs. left inferior frontal pars orbitalis: $F(1,11) < 1$]. In contrast, task conflict was equally associated with dorsal and

ventral regions in LPFC [left middle frontal vs. left inferior frontal pars triangularis: $F(1,11) = 1.39$, $p = .263$; left middle frontal vs. left inferior frontal pars orbitalis: $F(1,11) < 1$].

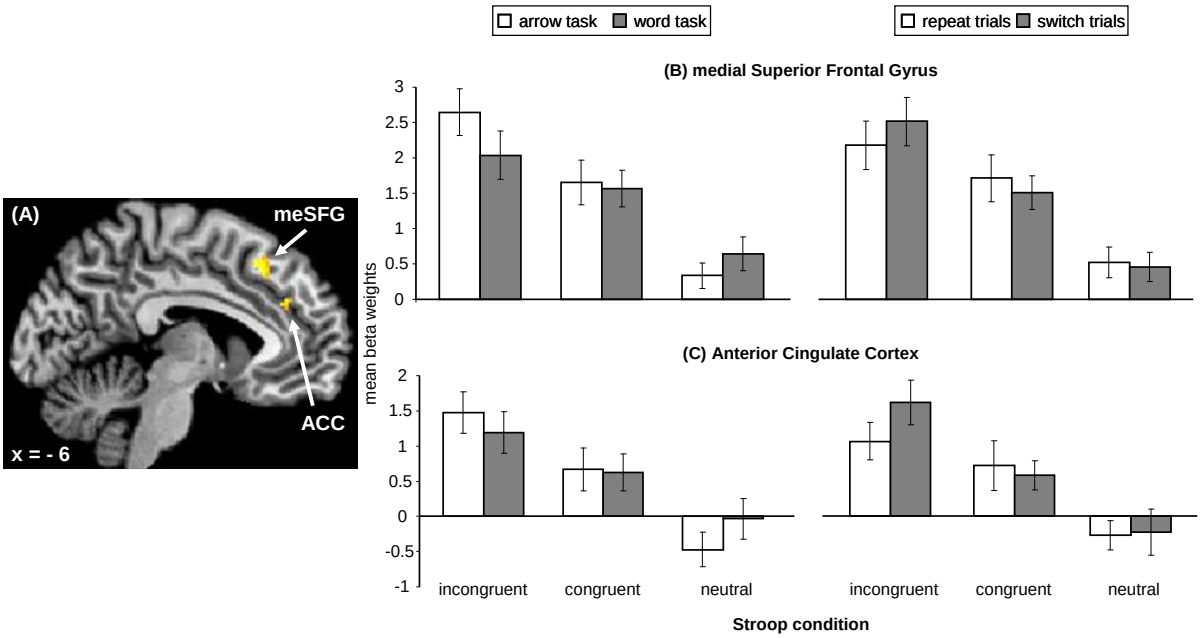

Figure 4.5 Response and task conflicts in medial frontal cortex.

a. Sagittal section showing increased medial Superior Frontal Gyrus activity (meSFG / BA 8; MNI: x = -2, y = 26, z = 44) and increased anterior cingulate activity (ACC / BA 32; MNI: x = -6, y = 38, z = 28) for the contrast congruent vs. neutral stimuli (thresholded at $p < .001$ and 10 contiguous voxels), inclusively masked by the contrast incongruent vs. congruent stimuli (at $p < .01$) in the random effects group analysis. **b.** Mean beta weights of all active voxels in meSFG and **c.** ACC are plotted separately for the three Stroop conditions in the arrow and word task (left) and in repeat and switch trials (right). There were no interactions of task or trial type with Stroop condition.

BA = Brodmann area. MNI = coordinates of the peak voxel in the random effects group average. Error bar represents the standard error of the mean.

4.5 Discussion

The present fMRI study examined the role of the ACC in cognitive control during response conflict and conflict at the level of task sets. We mixed arrow-word Stroop tasks with incongruent, congruent, and neutral stimuli. Our behavioral data yielded the expected patterns of switch costs and measures of both response conflict and task conflict in the mean RTs. Furthermore, the ex-Gaussian analyses of the response times demonstrated that our measure of response conflict (incongruent > congruent) was uniquely associated with the μ and σ parameters, which have previously been linked to the resolution of response competition. Moreover, our measure of task conflict (congruent > neutral) was uniquely associated with the τ parameter, which has previously been linked to processes at the level of task set. The fMRI findings indicate that the ACC is activated by both response conflict and task conflict, independent of the particular task (word or arrow task) and trial type (repeat or switch). Using anatomical ROIs, there was no difference in conflict effects between ventral and dorsal MFC regions. In contrast, there was a difference between ventral and dorsal LPFC regions: Response conflict was associated with ventral rather than dorsal LPFC, whereas there was no such regional dissociation for task conflict.

4.5.1 Behavioral Data

We found reliable effects of response and task conflict in the mean RTs. Converging evidence that we correctly measured response conflict and task conflict came from the ex-Gaussian analyses that we performed. In these analyses, response conflict was reflected in the Gaussian parameters of the distribution (μ and σ), while task conflict was reflected in the exponential parameter τ, which has previously been associated with processes at the level of task set (e.g., Kane and Engle, 2003; Schmiedek et al., 2007).

This conclusion was further corroborated by comparing the direction of the difference between the congruent and neutral conditions in μ and τ. Numerically, the congruent condition was faster than neutral in μ, but the congruent condition was slower

than neutral in τ. Thus, the slower responding on congruent than neutral trials in the mean RTs was driven by the slower responding on congruent than neutral trials in τ. For μ, there was Stroop facilitation. The pattern of numerical facilitation in μ and interference in τ replicates previous results obtained with standard Stroop color naming (Heathcote et al., 1991; Spieler et al., 1996). When participants only perform the Stroop color naming task, the magnitude of the facilitation in μ tends to equal the interference in τ, which leads to a null effect in the mean RTs. In the current task switching experiment, where there was presumably much more competition between tasks, the interference in τ was much larger than the facilitation in μ, yielding a net interference effect in the mean RTs. Relative to neutral trials in a task switching situation, congruent trials yield both task competition (because they activate the competing task) and response facilitation (because they activate the appropriate response). In the mean RTs, we found faster responses on neutral trials than on congruent trials, indicating that a lack of task conflict on neutral trials outweighed the response facilitation on congruent trials.

To conclude, the results of the ex-Gaussian analyses provide converging evidence for our hypothesis that response conflict is indexed by the difference in performance between the incongruent and congruent conditions, and that task conflict is indexed by the difference between the congruent and neutral conditions. Moreover, a tradeoff between task competition and response facilitation on congruent trials was observed in the ex-Gaussian parameters: The congruent condition was faster than neutral in μ (reflecting response facilitation), but slower than neutral in τ (reflecting task competition).

Task conflict (congruent > neutral) in RTs did not differ between switch and repeat trials in either task. This may come as a surprise given the presence of an RT switch cost, which seems to suggest greater competition at switch than repeat trials. However, Monsell (2005) argued that the task conflict caused by stimulus-task associations cannot account for the type of residual switch cost that we observed. When a small number of bivalent stimuli occur in both task contexts (in our experiment, there were only two stimuli per task), they soon become asymptotically associated with both task sets. Consequently, the task conflict caused by stimulus-task associations will not differ between repeat and switch trials, exactly as we (and Aron et al., 2004) observed.

To conclude, our behavioral data yielded the expected patterns of switch costs and Stroop-like effects. The difference in response time among all three Stroop conditions and the additional ex-Gaussian analyses suggest that the stimuli evoked response conflict as well as conflict at the level of task sets.

4.5.2 Task Conflict in the MFC

We found effects of both response and task conflict in the ACC and in the meSFG. An anatomical ROI analysis confirmed that response and task conflict were equally associated with more ventral regions of the MFC (ACC) and more dorsal regions of the MFC (meSFG). Our finding of task conflict in the meSFG replicates previous studies (Milham and Banich, 2005; Woodward et al., 2008). Woodward and colleagues found a region in meSFG when they contrasted neutral trials in a univalent context with neutral trials in a bivalent context. Milham and Banich found a region close to the pre-SMA when contrasting bivalent versus univalent Stroop stimuli (congruent > neutral and incongruent > neutral). However, in both studies no effects of task conflict were found in the ACC, whereas we did find such an effect in the present study.

The differences between these previous studies and ours might be related to differences in experimental design. Woodward and colleagues (2008) did not compare bivalent and univalent trials directly, but looked at block-context effects, which may have been weaker than the effects from our direct comparisons. Thus, we may have observed differential ACC activity because of greater experimental power. The explanation of the discrepancy with the results of Milham and Banich (2005) might reflect the fact that the authors used unrelated words as neutral stimuli instead of the row of Xs that were used in the present experiment. In contrast to a row of Xs, an unrelated word still evokes the word reading task (Monsell et al., 2001). This diminishes or removes the task conflict difference between neutral and congruent stimuli. Furthermore, the experiment of Milham and Banich did not use task switching, i.e. the only task was to name the color of the word. Hence, they observed a behavioral facilitation effect (i.e., faster responding to congruent than to neutral stimuli). In the present task-switching design, both tasks were active, resulting in a behavioral task conflict effect (i.e., faster responding to neutral than

to congruent stimuli). Thus, we found faster responses and less ACC activity on neutral trials than on congruent trials, indicating that a lack of task conflict on neutral trials outweighed the response facilitation on congruent trials. The fact that we did find a behavioral index for task conflict might be related to our observation of task conflict activity in the ACC.

4.5.3 The Role of the ACC in Cognitive Control

It is often claimed that the ACC is a response conflict monitor, signaling other brain regions - like the lateral prefrontal cortex - to execute control when conflict is detected (Carter et al., 1999; MacDonald et al., 2000; Botvinick et al., 2001; Miller and Cohen, 2001). The present findings show that ACC activity was not only greater for incongruent than for congruent stimuli (i.e., response conflict), but also greater for congruent than for neutral stimuli (i.e., task conflict), in the absence of response conflict. That ACC activity can be independent of response conflict was also observed by Roelofs and colleagues (2006) using a version of the arrow-word Stroop paradigm in which the trials were blocked by task. Others have also observed increased ACC activity in contexts requiring increased cognitive control, where the level of response conflict was kept the same (Badre and Wagner, 2004).

Recent evidence indicates that the ACC is differentially active for decision conflict even before a response is made (Pochon et al., 2008). Similarly, the ACC was demonstrated to be differentially active in anticipation of Stroop stimuli, again when no response had to be given yet (Aarts et al., 2008). Importantly, this anticipatory ACC activity was independent of upcoming response conflict. In contrast to a conflict monitoring role, effective connectivity studies provided evidence for a function of the ACC in regulating or top-down modulation of activity in modality-specific sensory areas (Crottaz-Herbette and Menon, 2006), the amygdala (Etkin et al., 2006), and the caudal cingulate (motor) zone (Fan et al., 2007). These findings are in agreement with monkey electrophysiology studies. While two studies have failed to identify populations of neurons in the ACC specialized for monitoring response conflict (Ito et al., 2003; Nakamura et al., 2005), a recent study found differential preparatory activity in ACC

neurons in a task-switching task (Johnston et al., 2007). The authors argued for a role of the ACC in the implementation of top-down control. In line with above mentioned evidence, it is plausible to assume that our results of response and task conflict in the ACC reflect regulatory processes that resolve conflict rather than merely detect conflict. Our results then suggest that the ACC is implicated in the resolution of conflict evoked both by stimulus-response associations (i.e., response conflict, indexed by the positive incongruent-congruent contrast) and stimulus-task associations (i.e., task conflict, indexed by the positive congruent-neutral contrast), following the reasoning of Monsell and colleagues (Rogers and Monsell, 1995; Aron et al., 2004; Monsell, 2005).

Although task and response conflict both engaged the ACC, it is not clear from the present study whether these types of conflict are associated with different sub-regions in the ACC. **Figure 4.4** (at x = -8) shows that the clusters for response conflict and task conflict within the ACC are non-overlapping, with response conflict activating a more anterior region of the ACC and task conflict activating a bordering posterior region. However, when comparing response conflict activity from numerous other studies, clusters are found throughout the whole ACC region (Ridderinkhof et al., 2004a). Future studies may further test whether functional heterogeneity exists within the ACC. Important for now is that both task and response conflict activate the ACC.

4.5.4 ACC vs. meSFG

The present results indicate a role for both the ACC and a more dorsal (and caudal) region in the MFC, the meSFG (z = 46), in conflict tasks. Others have suggested that conflict is better associated with activations at a more dorsal level (z > 45) in the SFG than activations in the ACC (Ullsperger and von Cramon, 2001; Rushworth et al., 2004). Indeed, several studies found regions rostral to the pre-SMA in meSFG for conflict processing (Ullsperger and von Cramon, 2001; Nachev et al., 2005). This is in line with our findings of meSFG activity for response and task conflict. Yet, our present experiment and previous studies have consistently found the ACC to be differentially active in conflict tasks (Roelofs et al., 2006; Aarts et al., 2008).

Rushworth and colleagues (2004) proposed that the meSFG is involved in task control and selection of action sets, whereas the ACC guides decisions while taking the reward history into account (see also Rushworth and Behrens, 2008). During response or task conflict both types of processes could actually play a role, which would explain the present finding of the involvement of both MFC regions in conflict.

4.5.5 Conflict-Related Processes in the LPFC

In contrast to the MFC, we did find a dissociation regarding conflict-related processes in LPFC. While task conflict was observed in both ventral and dorsal LPFC, response conflict was only observed in ventral LPFC. The inferior frontal gyrus (ventral LPFC) has been shown to be involved in Go/NoGo tasks (Konishi et al., 1998; Menon et al., 2001; Rubia et al., 2001) and lesions in the inferior part of the frontal cortex cause utilization behavior. This impulse-control disorder is characterized by a lack of goal-directed behavior (Lhermitte, 1983; Shallice et al., 1989). Therefore, it seems that ventral LPFC regions have a role in the suppression of inappropriate responses in case of response conflict and in the suppression of inappropriate task sets in case of task conflict. Furthermore, some findings suggest that the left VLPFC plays an important role in controlled retrieval and selection processes (Thompson-Schill et al., 1997; Badre et al., 2005; Crone et al., 2006). It is no surprise that task conflict was also associated with dorsal regions of the LPFC. Dorsal LPFC has typically been associated with goal maintenance and working memory (e.g., D'Esposito et al., 2000), see Kane and Engle (2002) for a review. Banich and colleagues (2000a; 2000b) have argued that dorsal LPFC regions are involved in imposing an attentional set (i.e., task set). The association in our study of the dorsal LPFC with task conflict, but not with response conflict, provides further converging evidence that the congruent > neutral contrast indexes task conflict.

4.5.6 Conclusion

Our behavioral data showed that we were successful in manipulating response and task conflict within one paradigm. The imaging data revealed that the ACC is not only active for response conflict but also for conflict at the level of task sets. Whereas the LPFC

showed a functional dissociation in conflict effects when comparing ventral and dorsal regions, such dissociation between ventral and dorsal regions could not be observed in the MFC. That is, like in the ACC, a more dorsal region in the MFC, the meSFG, was activated by both response and task conflict. Models of cognitive control should take account of these key properties of the ACC and meSFG.

Table 4.1 Regions showing an effect of both task conflict and response conflict determined by the contrast congruent > neutral stimuli inclusively masked (at p = .01) by the contrast incongruent > congruent stimuli, and regions activated for either task conflict or response conflict.

	task + response conflict					**task conflict (con > neu)**					**response conflict (inc > con)**				
	size	T-value	MNI coordinates			size	T-value	MNI coordinates			size	T-value	MNI coordinates		
Region			x	y	z			x	y	z			x	y	z
ACC (32/24)	13	3.84*	-6	38	28	10	3.67*	-6	34	10	91	4.41	-10	42	26
meSFG (8)	460	5.80*	-2	26	44	1295	5.80*	-2	26	44	116	3.87	2	30	46
IFG-L (47)	161	4.23*	-32	26	-14						150	4.14	-40	22	-14
IFG-R (47)	56	4.41*	36	24	-18						308	5.13	34	24	-14
IFG-L (45)	72	4.49*	-44	22	24						31	3.67	-42	28	6
											10	3.62	-42	20	14
IFG-R (45)						271	4.65*	36	24	8					
IFG-L (44)	149	5.21*	-36	10	28	1591	5.32*	-34	8	30					
IFG-R (44)						25	3.50*	58	16	28					
MFG-L (10)						10	3.67*	-40	60	2					
MFG-R (10)						574	4.40*	32	58	4					
MFG-R (8)	22	4.28*	44	6	44	26	3.43*	26	16	42					
MFG-R (6)						1287	5.26*	38	2	48					
preCG-L (6)											19	3.86	-54	4	38
											22	3.45	-46	4	30
STG-L (22)						15	3.45*	-60	-50	8					
Ang G-L (39)											44	4.26	-28	-60	36
IPL-L (40)	426	4.91*	-32	-54	44	857	4.91*	-32	-54	44	118	4.25	-36	-38	40
											176	4.12	-48	-52	30
IPL-R (40)						450	4.55*	36	-48	44					
SPL-L											20	3.66	-32	-64	54

(7)										
						16	3.53	-26	-66	46
SPL-R (7)	10	3.50*	32	-68	52					
preCun-R (7)	454	4.88*	12	-64	58					
Caud-L	63	4.15*	-8	0	4	18	3.74	-8	10	-2
Caud-R	53	3.68*	14	2	6	42	3.73	10	12	6
Thal-L	27	3.47*	-8	-14	10					
Cerebel-R	15	3.46*	34	-64	-36					

Note: This table presents the results of the 2nd level random effects group analysis. Brodmann areas are listed between brackets. The *T* values represent the voxel *T* value for local maxima at $p < .001$(only one peak per activated cluster is shown here). The size refers to the total number of (2 x 2 x 2 mm) voxels included in the cluster (minimum of 10 voxels). The MNI coordinates are measured in mm. con = congruent stimuli; neu = neutral stimuli; inc = incongruent stimuli; ACC = anterior cingulate cortex; meSFG = medial superior frontal gyrus; IFG = inferior frontal gyrus; MFG = middle frontal gyrus; preCG = precentral gyrus; STG = superior temporal gyrus; Ang G = angular gyrus; IPL = inferior parietal lobule; SPL = superior parietal lobule; preCun = precuneus; Caud = caudate nucleus; Thal = thalamus; Cerebel = cerebellum; L = left; R = right.

* = voxel p-value is < .05 (False Discovery Rate corrected)

Table 4.2 Main effects, interaction effects and effects of task conflict and response conflict in functionally and anatomically defined regions in medial and lateral frontal cortex.

region	Stroop condition	task	trial type	task x Stroop condition	trial type x Stroop condition	task-set conflict	response conflict
	F(2,22)	*F*(1,11)	*F*(1,11)	*F*(2,22)	*F*(2,22)	*t*(11)	*t*(11)
ACC (-6, 38, 28)	25.37 ***	< 1	1.03	1.33	< 1	4.17 **	3.68 **
A: Cing Ant L	9.4 **	< 1	< 1	1.49	1.29	2.67 *	2.33 *
A: Cing Ant R	8.93 **	< 1	< 1	1.33	1.07	2.83 *	1.86
meSFG (-2, 26, 44)	38.98 ***	< 1	< 1	2.76	< 1	5.19 ***	4.22 **
A: Front Sup Med L	14.32 ***	< 1	< 1	1.21	< 1	4.25 **	2.17
A: Front Sup Med R	8.23 **	1	< 1	1.74	1.31	3.11 *	1.43
IFG-L (-32, 26, -14)	25.18 ***	< 1	2.60	6.80 **	1.51	14.45 **	33.27 ***
A: Front Inf Orb L	20.26 ***	< 1	< 1	5.02 *	1.33	4.00 **	3.55 **
IFG-R (36, 24, -18)	24.90 ***	< 1	3.27	3.60 *	1.69	14.04 **	25.92 ***
A: Front Inf Orb R	14.98 ***	< 1	< 1	2.47	< 1	3.66 **	2.69 *
IFG-L (-44, 22, 24)	22.79 ***	3.63	< 1	6.40 **	< 1	13.99 **	11.96 **
A: Front Inf Tri L	20.69 ***	1.13	< 1	7.32 **	< 1	3.75 **	3.69 **
A: Front Inf Tri R	12.37 ***	< 1	1.14	2.67	< 1	3.06 *	2.29 *
A: Front Mid L	9.21 **	1.71	2.6	2.25	< 1	3.64 **	< 1
A: Front Mid R	9.65 **	1.12	2.58	1.17	< 1	3.64 **	< 1

ACC = anterior cingulate cortex (MNI coordinates x, y, z); meSFG = medial superior frontal gyrus (MNI coordinates x, y, z); IFG = inferior frontal gyrus (MNI coordinates x, y, z); A = "AAL" ROI (Tzourio-Mazoyer et al., 2002); Cing Ant = anterior cingulum; Front Sup Med = medial superior frontal; Front Mid = middle frontal; Front Inf Tri = inferior frontal (pars triangularis); Front Inf Orb = inferior frontal (pars orbitalis); L = left; R = right.

* $p < .05$; ** $p < .01$; *** $p < .001$

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5.

Parsing the Role of Dopamine in Human Reward and its Cognitive Consequences Using Genetic Imaging

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5.1 Abstract

Dopamine has been hypothesized to provide the basis for the interaction between motivation and cognition. However, there is no evidence for this hypothesis in humans. We fill this gap by using a novel behavioral paradigm and a common polymorphism in the *DAT1* gene (*SLC6A3*) in an event-related fMRI study. Carriers of the 9-repeat allele in the *DAT1* 3' UTR VNTR, associated with high striatal dopamine levels, exhibited smaller task-switch costs in anticipation of high reward relative to low reward than did homozygotes for the 10-repeat allele. This effect was accompanied by increased neural activity in the ventral striatum during the anticipation, but not receipt, of reward as well as altered activity in the prefrontal cortex during rewarded switching. These data establish a critical role for human striatal dopamine in preparatory reward-directed processes and their influence on cognitive flexibility, thereby providing a neurochemical mechanism of one instance of the motivation-cognition interface.

5.2 Introduction

Mesolimbic dopamine has long been implicated in reward and motivation. Specifically, animal studies have highlighted a role of dopamine in learned preparatory or appetitive behavior (related to "wanting" and reward anticipation) in response to reward, as opposed to innate consummatory behavior (related to "liking" and reward receipt) (Robbins and Everitt, 1992; Berridge and Robinson, 1998; Ikemoto and Panksepp, 1999; Schultz, 2002; Baldo and Kelley, 2007). Besides signaling reward, evidence suggests that the ventral striatum (VS), a key structure in the mesolimbic reward pathway, also serves to mediate interactions between the anticipation of reward and cognitive processing (Mogenson et al., 1980; Cardinal et al., 2002). For instance, previous animal work has suggested that preparatory reward processes potentiate behavioral and cognitive flexibility (Marshall and Teitelbaum, 1977; Baldo and Kelley, 2007), a function classically associated with striatal dopamine (Lyon and Robbins, 1975; Cools, 1980; Cools et al., 1984; Oades, 1985). Furthermore, anatomical evidence suggests that dopamine might mediate this interaction between motivational reward and cognitive flexibility (Haber et al., 2000;

Haber, 2003). Specifically, Haber and colleagues (2000) have established striatonigrostriatal spiraling loops that would be perfectly suited to subserve a mechanism by which dopamine can direct information flow between ventromedial (limbic), central (associative), and dorsolateral (motor) striatal regions, thus providing an anatomical basis for the limbic/cognitive/motor interface via the ventral midbrain.

Accumulating evidence indicates that dopamine is also implicated in human reward processing. For example, a pharmacological neuroimaging study found that dopamine-enhancing drugs had opposite effects on reward prediction error activity in the striatum and on subjects' behavioral choices compared with dopamine reducing drugs (Pessiglione et al., 2006). Genetic imaging studies (for reviews, see Goldberg and Weinberger, 2004; Green et al., 2008) can also elucidate the role of dopamine in human brain function. For example, it has been shown that variants of the dopamine transporter gene, associated with striatal dopamine levels, predict interindividual variability in reward-related activity in ventral striatum (Forbes et al., 2007) (see also reward-related effects in studies investigating polymorphisms in the DRD2 gene: Cohen et al., 2005; Kirsch et al., 2006; Cohen et al., 2007; Klein et al., 2007). However, these studies have generally employed blocked designs and do not enable the disentangling of effects on the subcomponents processes of reward anticipation and receipt. Critically, there is also no functional evidence that the influence of motivational aspects of reward on cognitive processes is mediated by dopamine.

In the present event-related fMRI study, we sought to determine the necessary role of dopamine in the component processes of reward, and its consequences for cognitive flexibility, i.e. a specific instance of the motivation-cognition interface. We employed a task-switch design (see Monsell, 2003) with reward cues preceding each trial and feedback following each response on incongruent arrow-word targets (see **Figure 5.1**). We investigated brain activity during motivational (i.e., reward-related) processing and cognitive flexibility (i.e., switch versus repeat trials) as a function of inter-individual variation in the 40-bp variable number of tandem repeats (VNTR) polymorphism in the 3′-untranslated region (UTR) of the dopamine transporter gene (*DAT1*, *SLC6A3*). The 10-repeat allele (10R) has been associated with increased gene expression and presumably lower levels of synaptic dopamine in the striatum relative to the 9-repeat (9R) allele

(Heinz et al., 2000; e.g., Fuke et al., 2001; Mill et al., 2002; but see van Dyck et al., 2005). In keeping with the animal literature reviewed above, we predicted selective effects of genetic variation on reward anticipation-related but not reward receipt-related activity. Consistent with this prediction we demonstrate a specific role for striatal dopamine in human preparatory rather than consummatory aspects of reward, i.e. its anticipation rather than its receipt. Furthermore, our data also show that dopamine is a critical modulator of the interaction between these motivational processes and cognitive flexibility. This result provides the first test in humans of a hypothesis put forward based on anatomical data by Haber and colleagues (2000). Specifically, the anticipation of high reward, which activated the ventral striatum, enhanced task-switch performance, associated with dorsal frontal brain regions, compared with the anticipation of low reward. Most critically, this motivation-cognition interaction was dependent on *DAT1* genotype. Importantly, unlike most genetic imaging studies, we corrected for differences in striatal volumes between the genotype groups, meaning that the functional results we observed are unlikely to reflect structural differences. Furthermore, the effects of the *DAT1* genotype were corrected for the effects of genetic variation in frontal dopamine, as indexed by the common polymorphism in the gene coding for catechol-O-methyltransferase (*COMT*), which catabolizes dopamine in the prefrontal cortex. Accordingly, our data demonstrate a key role for striatal as opposed to frontal dopamine in the interface between preparatory reward and cognitive flexibility.

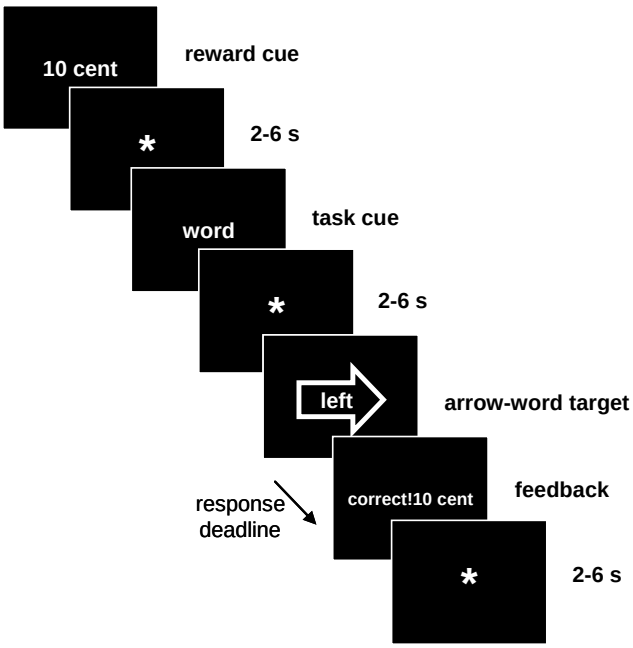

Figure 5.1 Example trial from the experimental paradigm. In this trial, the reward cue indicated that the participant could earn 10 cents with a correct and sufficiently quick response. The task cue told the participant to respond to the word of the incongruent arrow-word Stroop-like target. Immediately after the response, feedback was given with the amount of reward the participant had earned for this specific trial. There was a variable delay of two to six seconds between cues and targets.

5.3 Materials and Methods

5.3.1 Participants

Twenty neurologically healthy Dutch undergraduates (10 female and 10 male, mean age 21.6 years, range 18-27) participated in the experiment. All participants were right-handed and native speakers of Dutch. Participants were screened for psychiatric and neurological disorders, were compensated for participation, and gave written informed consent in a manner approved by the local ethics committee on research involving human subjects. Exclusion criteria were claustrophobia, medication for treating hypertension, cardiac arrhythmia, allergy, asthma, diabetes, a renal or blood disease, any neurological or psychiatric symptom or disorder, family history of epilepsy, and metal parts in body.

Initially, 24 participants were scanned. One participant was excluded due to technical problems during scanning, one participant's saliva sample was not collected, genotyping of one participant's saliva sample failed, and one participant had a *DAT1* allele different from the two alleles we were interested in. The remaining sample size was 20.

5.3.2 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 (UTR) of the *SLC6A3/DAT1* gene encoding the dopamine transporter has been described before (Kooij et al., 2008). For *DAT1*, two genotype groups were established: 11 participants (55% female, mean age: 21.6) were homozygous for the common 10-repeat allele (10R/10R) and 9 participants (44% female, mean age: 22.4) were heterozygous for the 9-repeat allele (9R/10R).

We also genotyped the catechol-*O*-methyltransferase gene *COMT* rs4680 ($Val^{108/158}Met$) single nucleotide polymorphism. Genotyping was performed using Taqman analysis (assay ID: Taqman assay: C__25746809_50; reporter 1: VIC-A-allele; Applied Biosystems, Nieuwerkerk a/d Ijssel, The Netherlands). Genotyping was carried out in a volume of 10 ul containing 10 ng of genomic DNA, 5 ul of ABgene Mastermix (2x; ABgene Ltd., Hamburg, Germany), 0.125 ul of the Taqman assay and 3.875 ul of H_2O. Amplification was performed on a 7500 Fast Real-Time PCR System starting with 15 minutes at 95ºC, followed by 50 cycles of 15 seconds at 95ºC, 1 minute at 60ºC. Genotypes were scored using the algorithm and software supplied by the manufacturer (Applied Biosystems). To investigate the random genotyping error rate, the lab included 5% duplicate DNA samples, which had to be 100% consistent. In addition, 4% blancs were included, which were required to be negative. For *COMT*, participants were classified as having two (Met/Met; n = 2), one (Val/Met; n = 13), or no Met-alleles (Val/Val; n = 5). The *DAT1* 10R/10R group consisted of 2 Met/Met subjects, 7 Val/Met

subjects, and 2 Val/Val subjects. The *DAT1* 9R/10R group consisted of 6 Val/Met subjects and 3 Val/Val subjects.

5.3.3 Task

Participants were scanned while performing a pre-cued task-switching task (**Figure 5.1**). The targets to which participants had to respond were incongruent arrow-word combinations (see also Roelofs et al., 2006; Aarts et al., 2008). The targets consisted of written words in arrows. The lines and letters of the targets were white on a black background. Participants responded manually to the Stroop-like stimuli by pressing a left button (with their left middle finger) or a right button (with their left index finger) on a scanner-compatible button box. This button-box response was done with the left hand (right motor cortex) because the stimuli themselves were language-related (left hemisphere). Participants responded either to the direction of the arrow (arrow task) or to the direction indicated by the word (word task), which were always conflicting. A task cue indicated which task to perform. The cues for the arrow task were the Dutch words for *arrow* (*pijl*) and *shape* (*vorm*). The cues for the word task were the Dutch words for *word* (*woord*) and *letter* (*letter*). The task cue switched every trial, while the task itself switched or was repeated in a random fashion. This way, a task switch was never confounded with a task-cue switch (Logan and Bundesen, 2003).

In addition, a reward cue (reward anticipation) preceded each task cue, telling the participants whether 1 cent (low reward) or 10 cents (high reward) could be earned with a correct and quick response, denoted by the words *1 cent* or *10 cent*. After the participant's response, feedback was given (reward receipt). Positive feedback was given for a correct response and depended on the preceding reward cue at the beginning of the trial: *correct! 1 cent* or *correct! 10 cents*. Negative feedback was given for an incorrect response (*wrong! 0 cent*) or a missed response (*too late! 0 cent*). The feedback for correct responses was given in green, the feedback for incorrect responses in red, and the feedback for misses in blue. A white asterisk was displayed during the variable intervals between reward cue and task cue and between task cue and target. In the inter-trial interval, a blue asterisk was displayed. Participants were told to fixate on the asterisks.

The intervals between reward cue and task cue, task cue and target, and feedback and reward cue of the next trial were jittered with a variable delay between 2 and 6 seconds. Feedback was given immediately after the participant's response. Cues and feedback stayed on the screen for 600 ms. Targets remained on the screen until a response was made or until the end of the individually determined response window. This response deadline was calculated for each participant separately on the basis of their performance in two practice blocks in the scanner during the anatomical scan. Both practice blocks consisted of 12 word-task trials and 12 arrow-task trials, half of which were repeat trials and half of which were switch trials. In the practice block, no reward cues appeared and no feedback was given. Each practice block lasted for about 4 minutes. Before the second practice block, participants were instructed to respond as quickly (yet accurately) as possible. The mean response times (RT) of the correct trials per trial-type (arrow-repeat, arrow-switch, word-repeat, word-switch) from the second practice block were taken as a response deadline in the main experiment. When participants responded faster for a certain trial-type in the first practice block, this mean RT was taken instead of the one from the second practice block.

The main experiment consisted of 160 trials. The factors reward (high/low), task (arrow/word), trial-type (switch/repeat), and response (right/left) were equally distributed over the trials in a random fashion, resulting in 40 trials per condition when taking the factors reward and trial-type into account (e.g. 40 high reward switch trials, 40 low reward switch trials, 40 high reward repeat trials, 40 low reward repeat trials). The whole experiment lasted for about 40 minutes with a 30 second break after every 32 trials. In the break, the amount of money the participant had earned thus far in the experiment was displayed on the screen. The maximum amount of money a participant was able to win was 8.80 euros. At the end of the experiment, the total amount of awarded money was shown on the screen and this was transferred to the participant's bank account together with the standard compensation that was earned for participating in the fMRI experiment (15 euros). On average, the participants won 7 euros extra.

5.3.4 fMRI Data Acquisition

Whole-brain imaging was performed on a 3 Tesla MR scanner (Magnetom Trio Tim, Siemens Medical Systems, Erlangen, Germany). Functional data were acquired using a gradient-echo echo-planar scanning sequence (30 axial slices, repetition time = 2020 ms, echo time = 31 ms, voxel size = 3.5 mm x 3.5 mm x 3.0 mm, interslice gap = 0.5 mm, field of view = 224 mm, flip angle = 80º). All functional images were acquired in a single run lasting ~40 minutes. Visual stimuli were projected on a screen and were viewed through a mirror attached to the head coil. Before the acquisition of functional images, a high-resolution T1-weighted MP-RAGE anatomical scan was obtained (192 saggital slices, repetition time = 2300 ms, echo time = 3.03 ms, voxel size = 1.0 mm x 1.0 mm x 1.0 mm, field of view = 256 mm).

5.3.5 Behavioral Data Analyses

The mean latencies of the correct manual responses and the proportion of errors were analyzed using a repeated-measures general linear model (GLM) with the factors reward (high, low), task (arrow, word), trial-type (repeat, switch) and the between-subject factor *DAT1* genotype. Specific effects were tested with paired *t*-tests. An effect was called significant when $p < .05$.

5.3.6 fMRI Data Analyses

Data were pre-processed and analyzed using SPM5 (Wellcome Dept. of Cognitive Neurology, London). The first four volumes of each participant's data set were discarded to allow for T1 equilibrium. First, functional EPI images were spatially realigned using a least squares approach and a 6 parameter (rigid body) spatial transformation. Subsequently, the time-series for each voxel was realigned temporally to acquisition of the middle slice. Images were normalized to a standard EPI template centered in MNI space (Ashburner and Friston, 1997) by using 12 linear parameters and resampled at an isotropic voxel size of 2 mm. The normalized images were smoothed with an isotropic 8 mm full-width-at-half-maximum (FWHM) Gaussian kernel. Anatomical images were spatially coregistered to the mean of the functional images (Ashburner and Friston, 1997)

and spatially normalized by using the same transformation matrix applied to the functional images.

The resulting pre-processed fMRI time series was analyzed at the first level using an event-related approach in the context of the general linear model (GLM). Our statistical model on the first (subject-specific) level considered the factors reward (high, low), task (arrow, word), trial-type (repeat, switch), and feedback (correct-1cent, correct-10cents, miss-0cents, error-0cents). This resulted in 22 regressors of interest: 2 regressors for the reward cues, 8 regressors for the task cues (reward by task by trial-type), 8 regressors for the targets (reward by task by trial-type), and 4 regressors for the feedback. All regressors of interest were modeled as a stick function (duration = 0) convolved with a canonical HRF (Friston et al., 1998). Additionally, the breaks (with a duration of 30 seconds) and 6 motion parameters were modeled as regressor of non-interest. High-pass filtering (128 seconds) was applied to the time series of the functional images to remove low-frequency drifts. Parameter estimates for all regressors were obtained by maximum-likelihood estimation, modeling temporal autocorrelation as an AR(1) process.

Contrast images from the first level were entered into second level random-effect analyses to test consistent effects across participants. We calculated 4 different analyses of variance (ANOVAs) corresponding to the 4 phases of the experiment (reward cue, task cue, target, feedback) with *DAT1* genotype as a between-group factor in each of them. Furthermore, each of the full factorial designs included each participant's number of MET alleles (0, 1, or 2) of the COMT $Val^{108/158}$Met polymorphism as covariate of non-interest. For the factorial design on the reward cues, we included 2 contrast images (high reward cues, low reward cues) for each participant of the *DAT1* 10R/10R versus the DAT1 9R/10R group (4 regressors in total + 1 *COMT* covariate). For the factorial design on the task cues, we included 8 contrast images corresponding to the 8 cells of the 2 x 2 x 2 design (reward by task by trial-type) for each participant of the *DAT1* 10R/10R versus the *DAT1* 9R/10R group (16 regressors in total + 1 *COMT* covariate). For the factorial design on the targets, we included 8 contrast images corresponding to the 8 cells of the 2 x 2 x 2 design (reward by task by trial-type) for each participant of the *DAT1* 10R/10R versus the *DAT1* 9R/10R group (16 regressors in total + 1 *COMT* covariate). Finally, for the factorial design on the feedback, we included 4 contrast images (correct-1cent,

correct-10cents, miss-0cents, error-0cents) for each participant of the *DAT1* 10R/10R versus the *DAT1* 9R/10R group (8 regressors in total + 1 *COMT* covariate).

In a whole brain analysis, we investigated the effects of reward anticipation and its modulation by *DAT1* genotype by contrasting high versus low reward trials on reward cues, task cues, and targets. We investigated the effects of reward receipt and its modulation by *DAT1* genotype by contrasting positive versus negative feedback and vice versa. We investigated the effects of task switching and its modulation by *DAT1* genotype by contrasting switch versus repeat trials on task cues and targets. Furthermore, we specifically tested for interaction effects between reward and trial-type and its modulation by *DAT1* genotype on task cues and targets. For illustration purposes, we have plotted the mean beta weights of all voxels in the regions reaching significance in these whole brain analyses, using MarsBaR (Brett et al., 2002). Results of the random effects analyses were considered statistically significant when effects reached a threshold of 0.05 (family wise error [FWE] corrected for multiple comparisons at the voxel level). However, for completeness, we also report higher-order interaction effects (e.g. between reward, trial-type and genotype) at $p < .001$ (uncorrected for multiple comparisons at the voxel level and a minimum cluster size of 10 voxels).

Our *a priori* hypotheses allowed us to further investigate the effects of reward anticipation and reward receipt in regions-of-interest (ROIs) in left and right ventral striatum (VS). These ROIs were defined from the above mentioned main contrasts of reward on task and reward cues (high > low reward) and feedback (positive > negative feedback) using a FWE corrected $p < .05$. With MarsBaR, we combined left and right VS ROIs and extracted mean beta weights from all voxels in these regions for the cells in the relevant factorial design. These regionally averaged beta-weights were analyzed using a repeated-measures GLM to investigate interaction effects with the between-group factor *DAT1* genotype. It is important to note that the main contrast that we used to localize the VS was always orthogonal to the subsequent contrasts that were tested in the VS (i.e., interactions between reward and *DAT1* genotype).

5.3.7 Structural MRI Analysis

Because we were specifically interested in functional differences, we also investigated potentially confounding structural differences in the striatum between the two *DAT1* genotype groups as measured with the anatomical scan. First, an automatic subcortical segmentation method was applied to the structural MRI scans using FSL 4.1 First v1.1 software (FMRIB, Oxford, UK). After automatic segmentation, volume information of the subcortical structures of interest (left and right nucleus accumbens, left and right caudate nucleus, and left and right putamen) was extracted from the segmentation results using a script written in Matlab7.2. To correct the volume of the subcortical structures for total brain volume, we performed a standard segmentation of the anatomical data into grey matter, white matter, and cerebrospinal fluid using SPM. Total brain volume was defined as the grey matter plus white matter volume and used to express the subcortical volumes as percentages. Independent t-tests were performed on these striatal volumes to test for differences between the groups.

5.4 Results

5.4.1 Behavioral Results

Response time data showed a main effect of reward [$F(1,18) = 10.14$, $p = .005$] and trial-type [$F(1,18) = 13.99$, $p = .001$]. Participants responded faster on high reward (mean = 441 ms) than on low reward trials (mean = 459 ms), thus revealing a reward benefit (**Figure 5.2, *top***). Participants also responded faster on repeat (mean = 437 ms) than on switch trials (mean = 462 ms), thus revealing a switch cost. Reward and trial-type did not interact [$F(1,18) = 2.2$, $p = .15$]. There was no main effect of *DAT1* genotype on RTs [$F(1,18) = 1.8$, $p = .20$] and no interaction between reward and genotype, or trial-type and genotype, or a reward by trial-type by genotype interaction (**Figure 5.2, *top***) [all $F(1,18) < 1$].

In the error rates, there was no main effect of reward [$F(1,18) = 2.5$, $p = .1$], but there was an interaction between reward and *DAT1* genotype [$F(1,18) = 5.7$, $p = .03$]. As can be observed in **Figure 5.2** (*bottom*), only carriers of the *DAT1* 9-repeat allele (with presumably higher striatal dopamine levels) demonstrated a reward benefit in error rates.

Participants made more errors on switch trials (mean error rate = 13.6 %) than on repeat trials (mean error rate = 7.6 %) [$F(1,18) = 16.5$, $p = .001$], but this switch cost did not interact with reward [$F < 1$]. Critically, there was a marginal interaction between *DAT1* genotype, reward and trial-type [reward x trial-type x genotype: $F(1,18) = 3.25$, $p = .088$]. Our prediction allowed us to break down this three-way interaction into two-way simple interaction effects. This analysis revealed that the reward by genotype interaction was present only on switch trials [$F(1,18) = 7.6$, $p = .01$], and not on repeat trials [$F(1,18) < 1$].

To summarize, anticipation of high reward caused faster response times and less errors compared with the anticipation of low reward. This reward benefit depended on *DAT1* genotype with the difference between genotype groups being restricted to the cognitively demanding switch trials, not extending to the repeat trials.

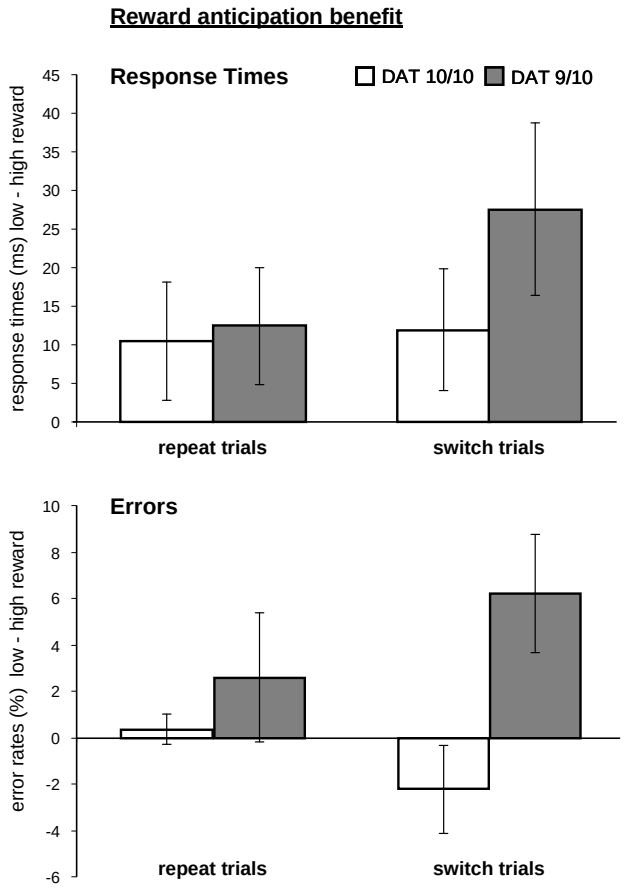

Figure 5.2 Behavioral performance. Plotted is the reward benefit (low - high reward trials) in the response times (*top*) and error rates (*bottom*) for the *DAT1* 10-repeat homozygotes (DAT 10/10) and the *DAT1* 9-repeat allele carriers (DAT 9/10) on repeat and switch trials. The difference in reward benefit between the two *DAT1* genotype groups was restricted to the switch trials. Error bars represent standard errors of the difference (SED) between low and high reward.

5.4.2 Imaging Results: Reward Anticipation and Receipt

In **Tables 5.1 and 5.2** we present all cortical and subcortical regions that were more active for high than for low reward, during reward cues, task cues and feedback. We first assessed neural activity and its modulation by *DAT1* genotype during reward anticipation. At our stringent statistical threshold of $P_{FWE} < 0.05$, the bilateral ventral striatum (VS, centered on the nucleus accumbens) was among the regions activated for reward

anticipation on both reward cues and task cues (**Figure 5.3A, *left* + *middle***). For the targets, which followed the task cues, there was no difference between high and low reward trials on a whole-brain corrected threshold ($P_{FWE} < 0.05$). Whole-brain analyses did not reveal significant main or interaction effects of *DAT1* genotype as a function of reward, at least at our stringent statistical threshold ($P_{FWE} < 0.05$). However, our *a priori* hypotheses enabled us to conduct region of interest analyses, which revealed an interaction effect in the VS between reward and genotype during the reward cue [$F(1,18) = 6.49$, $p = .02$]. As shown in **Figure 5.3B** (*left*), the *DAT1* 9R/10R group demonstrated a greater reward effect (high - low) [$F(1,8) = 21.95$, $p = .002$] than did the *DAT1* 10R/10R group [$F(1,10) = 7.25$, $p = .023$]. During the task cues, we observed a similar interaction effect between reward and genotype [$F(1,18) = 7.41$, $p = .014$], due to the *DAT1* 9R/10R group demonstrating greater VS activity after high reward cues relative to low reward cues [$F(1,8) = 38.15$, $p < .001$] than did the *DAT1* 10R/10R group [$F(1,10) = 5.41$, $p = .042$].

Next we assessed neural activity and its modulation by *DAT1* genotype during reward receipt or feedback. During reward receipt, the bilateral VS (ventral putamen) was more active during positive than during negative feedback (**Table 5.2; Figure 5.3A, *right***). Conversely, negative feedback induced more activity in a frontal and temporal-parietal network than did positive feedback; no striatal activity was observed for this contrast (**Table 5.2**). *DAT1* genotype seemed to affect VS activity during reward receipt in the opposite direction as during reward anticipation. Thus, the *DAT1* 9R/10R group showed a *smaller* reward receipt effect [effect of reward in the 9R/10R group: $F(1,8) = 13.31$, $p = .007$] than did the *DAT1* 10R/10R group [effect of reward in the 10R/10R group: $F(1,10) = 68.23$, $p < .001$], resulting in a strong tendency towards a reward x *DAT1* genotype interaction [$F(1,18) = 4.00$, $p = .061$] (**Figure 5.3B, *right***). A direct comparison between the reward by genotype effects in the VS during reward anticipation (reward cues) and reward receipt (feedback) confirmed this dissociation by revealing a significant 3-way interaction of phase (anticipation / receipt) by reward by genotype [$F(1,18) = 9.43$, $p = .007$].

To summarize, we observed VS activity for both reward anticipation and reward receipt. However, there was a dissociation between the effects of *DAT1* genotype on VS

activity depending on task period: Whereas the *DAT1* 9R/10R group - with presumably more striatal dopamine - showed *greate*r reward-related VS activity than did the *DAT1* 10R/10R group during *anticipation* of reward, the same *DAT1* 9R/10R group showed marginally *less* reward-related VS activity than did the *DAT1* 10R/10R group during the *receipt* of reward.

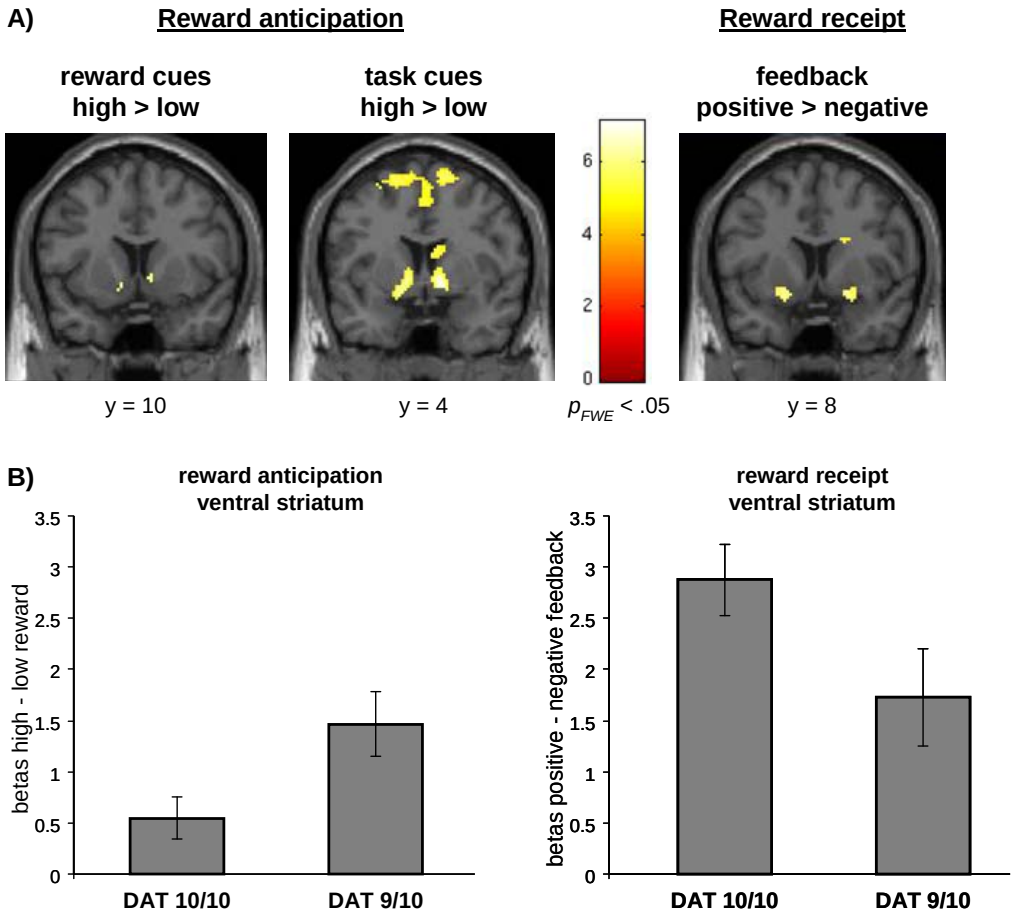

Figure 5.3 Reward anticipation and reward receipt in the ventral striatum (VS).

a. Coronal sections showing increased bilateral VS activity during high versus low reward cues (nucleus accumbens; *left*), high versus low reward on task cues (nucleus accumbens; *middle*), and positive versus negative feedback (ventral putamen; *right*) in the random effects group analysis ($p < .05$, FWE corrected). Color bar represents the voxel *T*-value.

b. The mean beta weights of all active voxels in VS for reward anticipation on reward cues (betas high - low reward; *left*) and for reward receipt (betas positive -negative feedback; *right*) are

plotted for the *DAT1* 10-repeat homozygotes (DAT 10/10) and the *DAT1* 9-repeat allele carriers (DAT 9/10). The *DAT1* 9R/10R group (with presumably more striatal dopamine) demonstrated a larger reward anticipation effect in VS, but a smaller reward receipt effect than the *DAT1* 10R/10R group. Error bars represent standard errors of the difference (SED) between high and low reward (*left*) or between positive and negative feedback (*right*).

5.4.3 Imaging Results: Task-Switch Effects

Whole brain analyses did not reveal significant effects of task switching at our stringent statistical threshold of $P_{FWE} < 0.05$. However, contrasts between switch versus repeat task cues and switch versus repeat targets at $P_{uncorrected} < .001$ revealed a cortical fronto-parietal network of activity consistent with prior studies (e.g., Ruge et al., 2005; Yeung et al., 2006) (**Table 5.3; Figure 5.4A**). No subcortical activity was observed.

Because we hypothesized that dopamine would provide the basis for a motivation-cognition interface, we specifically tested for an interaction between *DAT1* genotype (9R/10R > 10R/10R), reward (high > low & low > high), and trial-type (switch > repeat) on task cue-related and target-related activity (**Table 5.4**). During the targets, at whole-brain level $P_{uncorrected} < .001$, we observed a region in ventral anterior cingulate cortex (vACC, BA 32; **Figure 5.4B, *left***) and a region in left dorsolateral prefrontal cortex (DLPFC, BA 46; **Figure 5.4C, *left***), showing opposite effects. Below, we break down these interaction effects into its simple (interaction and main) effects for illustration purposes only. For the *DAT1* 9R/10R genotype group, a reward effect (high - low activity) in vACC was only evident on switch trials, not on repeat trials. On the contrary, the *DAT1* 10R/10R genotype showed more reward-related activity during repeat trials than during switch trials in vACC (**Figure 5.4B, *right***) (significant simple reward by trial-type interaction effect in the vACC of 10R/10R subjects: $F(1,10) = 11.42$, $p = .007$). Thus, in other words, in the vACC, reward-related activity was only present for trials in which the subjects had to perform a task-switch but not during repeat trials, and this effect was specific for subjects with high levels of striatal dopamine (9/10 DAT). On the other hand, subjects with low levels of striatal dopamine (10/10 DAT) showed more reward-related activity during repeat trials. Conversely, in the lDLPFC reward-related

activity was present only for repeat trials but not for switch-trials, and again this effect was specific for subjects with high levels of striatal dopamine (9R/10R genotype) (significant simple reward by trial-type interaction effect in the DLPFC of *DAT1* 9R/10R subjects: $F(1,8) = 23.08$, $p = .001$). The *DAT1* 10R/10R group did not show a reward effect in either switch or repeat trials in lDLPFC. Note that this pattern of cortical activity resembles that seen in the performance data: The greater behavioral reward benefit on switch relative to repeat trials in the *DAT1* 9R/10R group paralleled the enhanced reward-related activity on switch relative to repeat trials in the vACC in this group compared with that in the *DAT1* 10R/10R group. By contrast, the greater reward benefit in terms of error rates on switch relative to repeat trials in the *DAT1* 9R/10R group mirrored the pattern in the DLPFC, i.e. reduced (i.e. perhaps more efficient) reward-related activity on switch relative to repeat trials in the *DAT1* 9R/10R group compared with that in the *DAT1* 10R/10R group. There were no additional meaningful effects during the task cue (see **Table 5.4**).

To summarize, switch effects were observed in fronto-parietal cortical, but not subcortical regions. Target-related activity in the ventromedial (vACC) and dorsolateral (DLPFC) frontal regions depended on motivational and cognitive task-demands as well as *DAT1* genotype. The activity pattern of this three-way interaction in the vACC was opposite to that seen in the DLPFC.

5.4.4 Imaging Results: Structural Differences

Using the anatomical data, we tested whether structural differences in striatal volumes between the *DAT1* genotype groups could possibly account for the functional differences in brain activity we observed between the groups. There were no differences between the groups in the volumes of the left or right nucleus accumbens (both $p > .89$), left and right caudate nucleus (both $p > .49$), left and right putamen (both $p > .14$), or total striatal volume ($p > .53$). Thus, it is unlikely that the functional differences we observed between the *DAT1* genotype groups are caused by volumetric differences in the striatum.

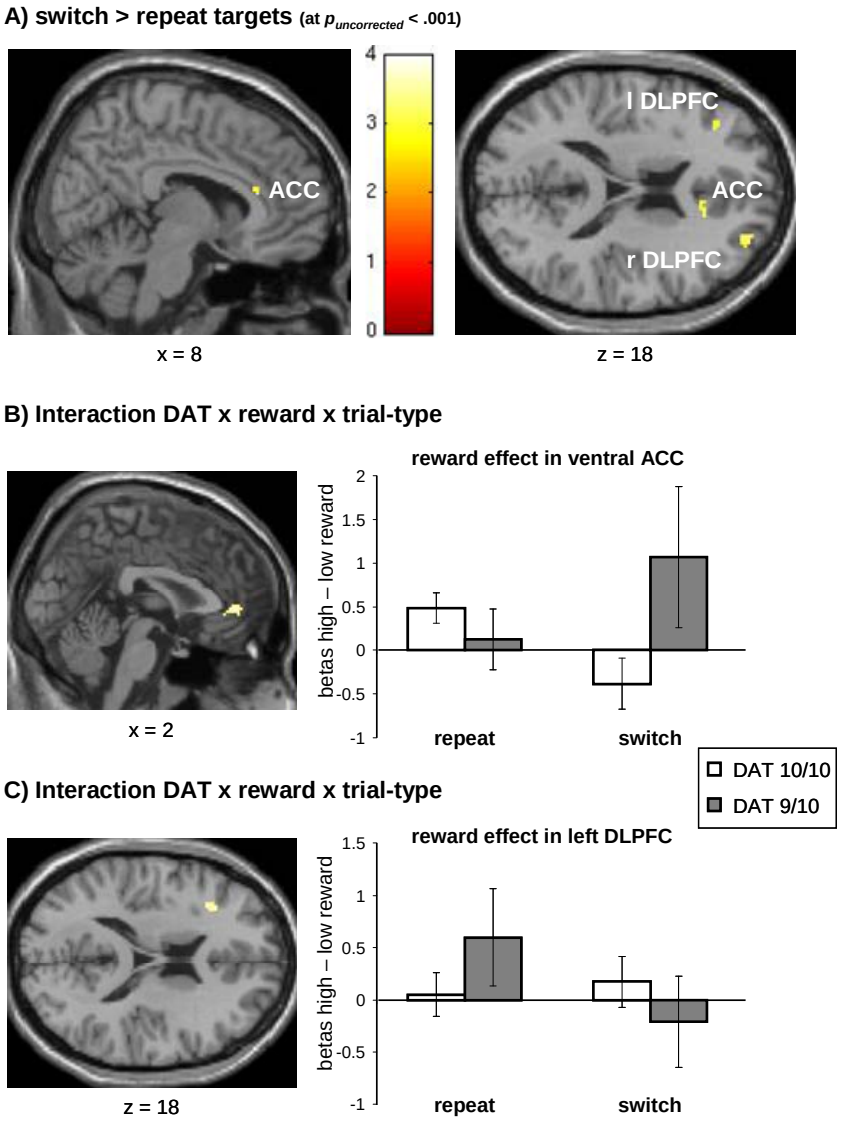

Figure 5.4 Target-related switch effects in frontal cortex.

a. Sagittal section (*left*) showing the anterior cingulate cortex (ACC, BA 24) and transversal section (*right*) showing the ACC and bilateral dorsolateral prefrontal cortex (DLPFC, BA 46) more active for switch than repeat targets in the random effects group analysis ($P_{uncorrected} < .001$ and > 10 contiguous voxels). Color bar represents the voxel *T*-value. BA = Brodmann area.

b. Sagittal section (*left*) showing a region in ventral ACC activated for the three-way interaction of *DAT1* genotype, reward, and trial-type. The reward effect in the mean beta weights (high – low) of all active voxels in this ventral ACC region are plotted (*right*) for the *DAT1* 10-repeat

homozygotes (DAT 10/10) and the *DAT1* 9-repeat allele carriers (DAT 9/10) on switch and repeat trials. Error bars represent standard errors of the difference (SED) between high and low rewarded trials.

c. Transversal section (*left*) showing a region in left DLPFC activated for the three-way interaction of *DAT1* genotype, reward, and trial-type. The reward effect in the mean beta weights (high - low) of all active voxels in this left DLPFC region are plotted (*right*) for the *DAT1* 10-repeat homozygotes (DAT 10/10) and the *DAT1* 9-repeat allele carriers (DAT 9/10) on switch and repeat trials. Error bars represent standard errors of the difference (SED) between high and low rewarded trials.

Activity patterns of the *DAT1* 10R/10R and *DAT1* 9R/10R groups show opposite effects in ventral ACC and left DLPFC.

5.5 Discussion

In the present event-related fMRI study, reward-related and switch-related brain activity was measured across groups displaying different variants of the dopamine transporter gene (*DAT1* or *SLC6A3*). The results provide evidence in support of two separate, but related and pervasive hypotheses regarding the role of dopamine in reward.

First, consistent with our prediction, we found that activity in the VS depended on the *DAT1* genotype, but only during reward anticipation: 9R-carriers, presumably characterized by genetically determined higher striatal dopamine levels, exhibited greater activity than did 10R/10R homozygotes during reward anticipation, but not during reward receipt. In fact, if anything, the opposite pattern was obtained for activity during reward receipt. Second, by manipulating both motivation (i.e., reward) and cognitive flexibility (i.e., task switching) within the same paradigm, we demonstrated that the interaction between motivation and cognition can be dopamine-dependent. Specifically, in our behavioral results, an interaction between preparatory reward and cognitive flexibility was obtained, but only as a function of *DAT1* genotype, and these behavioral effects paralleled activity patterns in ventromedial and dorsolateral frontal areas.

5.5.1 Parsing Human Reward

Reward-related activity in the VS depended both on *DAT1* genotype and on task phase (reward anticipation vs. reward receipt). The *DAT1* 9R/10R group, with presumably higher levels of striatal dopamine, displayed more VS activity during reward anticipation than did the *DAT1* 10R/10R group; the latter group, on the other hand, displayed marginally more VS activity during reward receipt than did the *DAT1* 9R/10R group. These findings in the *DAT1* 9R/10R group replicate findings from a recent genetic imaging study, in which *DAT1* genotype influenced VS activity during reward anticipation, but not receipt in a similar fashion (Dreher et al., 2009). Such replication of genetic imaging findings is rare (Green et al., 2008) and thus adds significant value. The results are also in line with behavioral neuroscience studies indicating that effects of manipulating dopamine in the VS are more readily observed on preparatory than on consummatory behaviors (Robbins and Everitt, 1992; Salamone et al., 2007). In fact some studies have reported that consummatory responses are attenuated rather than potentiated by increases in mesolimbic dopamine transmission, e.g. after amphetamine administration in the nucleus accumbens of rats (but see Kelley et al., 1989; e.g., Bakshi and Kelley, 1991). Furthermore, decreases in mesolimbic dopamine transmission by 6-OHDA lesions in the ventral striatum of rats can increase consummatory processes in rats (Koob et al., 1978). These findings lend credence to our observation that reward-related activity was marginally *decreased* in the VS during reward receipt of 9R-allele carriers (high striatal dopamine). Future imaging studies with larger sample sizes should test the hypothesis, derived from work with experimental animals and supported by the current observations, that the relationship between these dopamine-dependent preparatory and consummatory reward processes is antagonistic (Baldo and Kelley, 2007).

The present findings might shed a different light on recent findings of Forbes and colleagues (2007), who investigated neural effects of the same polymorphism in the *DAT1* gene. The authors found that 9R-allele carriers showed increased reward-related VS activity. However, in contrast to the present event-related study, Forbes and colleagues used a blocked design that did not allow them to disentangle the subcomponent reward process modulated by *DAT1* genotype. The present data reveal that this enhanced reward-related activity in the VS is restricted to reward anticipation, while

a marginal opposite effect is seen for reward receipt, a finding in line with previous studies (see above).

Furthermore, the present results resolve some apparently conflicting results from recent genetic imaging studies, investigating DRD2 polymorphisms. Specifically, in these studies, genetically determined reduced DRD2 receptor density (which might be linked with enhanced dopamine synthesis and release through presynaptic D2 autoreceptors (Cooper et al., 2003)) was associated with increased VS activity during reward prediction (Kirsch et al., 2006) but decreased activity during reward receipt (Cohen et al., 2007; Klein et al., 2007). Our data indicate that the increased and decreased VS activity as a function of genetic variation may be obtained in a single study.

Our findings of reward-related activity in ventral striatum, medial frontal cortex, and orbitofrontal cortex (see **Tables 5.1 and 5.2**) are in accordance with previous neuroimaging studies investigating reward processing (for reviews, see O'Doherty, 2004; Knutson and Cooper, 2005). Specifically, activity in the ventral striatum has been observed during both the anticipation and the receipt of reward, e.g. as function of the reward prediction error (e.g., Knutson et al., 2001; O'Doherty et al., 2004). Furthermore, Pessiglione and colleagues (2006) have recently reported that receipt-related striatal activity associated with the reward prediction error during reinforcement learning was modulated by dopaminergic drugs. This finding is consistent with evidence from pervasive neurophysiological evidence for prediction error learning carried by dopamine neurons (Schultz, 2002). The present study, in which there were no demands for learning, demonstrates that these prediction-related effects of dopamine are not restricted to the domain of learning, and more likely reflect preparatory motivational processes that affect flexible performance in general rather than learning specifically.

5.5.2 Interfacing between Preparatory Reward and Cognitive Flexibility

This is the first neuroimaging study demonstrating a dopamine-dependent motivation-cognition interface in humans. Previously, such an interaction has been hypothesized on the basis of neuro-anatomical evidence for spiraling dopamine projections between ventral and dorsal striatum in primates (Haber et al., 2000; Haber, 2003). Note that in the

present behavioral results, a motivation-cognition interaction was only observed as a function of *DAT1* genotype. These results show the importance of dopamine in providing the basis for a motivation-cognition interface.

Behaviorally, we found that the *DAT1* 9R/10R group, with supposedly more striatal dopamine, showed a greater benefit from reward than did the *DAT1* 10R/10R group, which was evident from the more accurate performance on high than low rewarded trials. Importantly, this difference in sensitivity to reward was especially pronounced on the switch trials compared with the repeat trials (see **Figure 5.2*, bottom***). In line with these behavioral findings, we found a similar pattern of results in a ventromedial region of the frontal cortex, the vACC, a region strongly connected to the VS (e.g., Devinsky et al., 1995; Carmichael and Price, 1996). In the vACC, the two genotype groups differed in reward-related activity especially during switch trials; the *DAT1* 9R/10R group showing more reward-related activity than did the *DAT1* 10R/10R group (see **Figure 5.4B, *right***). The finding of a dopamine-dependent motivation-cognition interface in the ACC is generally in line with theories stating that the ACC encodes gains, costs, and effort of an action to guide decision making (Walton et al., 2007; Rushworth and Behrens, 2008).

In a dorsolateral region of PFC, the left DLPFC, the activity pattern was exactly opposite to the pattern observed in the error rates and in the vACC: The reward effect was more pronounced on trials where the behavioral benefit was least apparent, i.e., more on repeat than on switch trials in the *DAT1* 9R/10R group (see **Figure 5.4C, *right***). The DLPFC is often found to be differentially active in task-switching studies (e.g., Luks et al., 2002; Cools et al., 2004; Crone et al., 2006) and such task-related DLPFC activity has been previously found to be influenced by reward manipulations (Leon and Shadlen, 1999; Pochon et al., 2002; Gilbert and Fiez, 2004; Taylor et al., 2004; Krawczyk et al., 2007; Locke and Braver, 2008). Here we show that this motivation-cognition interface in the DLPFC depends on the *DAT1* genotype. This is generally in agreement with previous genetic imaging studies showing that genetically determined dopamine levels (as a function of the COMT genotype) are associated with increased cognitive performance and decreased, perhaps more efficient task-related frontal cortex activity (e.g., Egan et al., 2001; Mattay et al., 2003). However, we found that these effects in the PFC changed as a

function of genetically determined levels of the dopamine transporter, which is much more abundant in the striatum than in the frontal cortex (Sesack et al., 1998; Lewis et al., 2001), even after correcting for genetic variation in *COMT*. Similar effects were not seen as a function of genetic variation in *COMT*, although it should be noted that the distribution of *COMT* alleles was perhaps suboptimal for detecting such effects (see methods). Together these findings suggest that the three-way interactions likely reflect an indirect modulation of flow through cortico-striatal circuitry rather than a direct modulation of frontal activity. Indeed, *DAT1* expression in the striatum has been previously hypothesized to influence signal-to-noise ratio in PFC indirectly (see, Bertolino et al., 2006) by modulating activity of the cortico–striato–thalamo–cortical pathways (Wichmann and DeLong, 1996).

5.5.3 Limitations and Implications

It is important to note that we did not measure dopamine concentrations or release directly. Furthermore, since dopaminergic function has been shown to influence brain structure and plasticity, variation in *DAT1* genotype might contribute to individual differences in brain morphometry. However, in the present study in young healthy volunteers, we could not find volume differences in basal ganglia structures between the two genotype groups. Thus, it is unlikely that our functional findings are caused by structural differences between the groups.

The present results have implications for neuro-psychiatric disorders implicating dopaminergic dysfunction. For instance, our data are relevant to attention deficit hyperactivity disorder (ADHD), which is characterized not only by abnormal interactions between motivation and cognition (Sonuga-Barke, 2003), but also by abnormal levels of the dopamine transporter (Dougherty et al., 1999; Krause et al., 2003). Indeed the most effective medication (e.g., methylphenidate) acts by blocking the dopamine transporter and in keeping with this observation is the finding of an association between the 10R allele of the *DAT1* genotype and ADHD (e.g., Cook et al., 1995; Gill et al., 1997; Waldman et al., 1998; Madras et al., 2002). However the motivational and cognitive effects of methylphenidate in this disorder are highly variable. Future study should

address the obvious next question whether these effects can be predicted by the *DAT1* genotype.

To conclude, our genetic imaging study indicates a critical role for human striatal dopamine in preparatory reward-directed processes and their influence on cognitive flexibility. In doing so, our results provide direct support for a previously hypothesized neurochemical mechanism for the human motivation-cognition interface.

Table 5.1 Regions activated for reward anticipation (high > low reward) during reward cues and task cues

	size	T-value	x	y	z
Reward cues:					
right nucleus accumbens	11	5.94	10	8	-4
left nucleus accumbens	27	5.83	-10	10	-6
left supplementary motor area	31	6.44	-2	16	46
right precentral gyrus	19	6.14	44	2	42
left thalamus	62	6.82	-12	-20	16
right thalamus	14	6.25	8	-22	16
left cerebellum	23	5.99	-10	-72	-12
left superior occipital gyrus	332	7.12	-20	-76	32
left middle occipital gyrus		6.03	-34	-70	30
right superior occipital gyrus	36	6.43	20	-78	30
left middle occipital gyrus	270	6.72	-30	-84	6
left lingual gyrus		6.56	-14	-92	-2
right lingual gyrus	25	5.98	10	-76	-6
left cuneus	11	6.12	-6	-82	30
right cuneus	186	6.87	10	-84	24
right calcarine gyrus	45	6.98	14	-94	-4
Task cues:					
right nucleus accumbens	1127	7.14	12	4	-4
right thalamus		6.5	2	-22	16
left ventral putamen		6.48	-14	10	-4
right insula	90	5.71	34	28	0
right inferior frontal gyrus (p. triang.)		5.42	42	26	0
left superior frontal gyrus	891	6.68	-18	10	64
right superior frontal gyrus		6.02	14	6	66
right supplementary motor area		5.87	4	10	50
left midbrain	70	6.11	-6	-22	-18
right midbrain	62	5.66	8	-26	-16
left inferior parietal lobe	284	5.9	-36	-56	56
right superior parietal lobe	136	5.57	14	-62	56
left precuneus	148	5.69	-10	-72	46

Note: This table presents the results of the 2nd level random effects group analysis. The *T* values represent the value for local maxima at $p < .05$ (FWE corrected). The size refers to the total number of (2 x 2 x 2 mm) voxels included in the cluster (minimum of 10 voxels). x, y, z are MNI coordinates measured in mm. No areas were more active during low relative to high reward.

Table 5.2 Regions activated for reward receipt (positive > negative and negative > positive) during feedback

	size	T-value	x	y	z
Positive > negative[1]:					
right ventral putamen	67	6.03	22	8	-14
left ventral putamen	84	7.11	-20	6	-12
Negative > positive:					
right medial superior frontal gyrus	1049	6.84	4	42	48
left supplementary motor area		6.79	-2	24	54
right anterior cingulate cortex		6.05	8	32	26
left inferior frontal gyrus (p. triang.)	97	5.84	-48	22	22
right inferior frontal gyrus (p. orb.)	763	8.11	38	22	-20
left inferior frontal gyrus (p. orb)		5.96	-46	20	-12
right middle frontal gyrus	247	6.01	42	20	32
right inferior frontal gyrus (p. triang.)		5.24	56	26	28
left middle frontal gyrus	46	5.67	-42	12	36
left insula	404	7.66	-32	18	-18
right middle temporal gyrus	337	6.8	54	-26	-12
right supramarginal gyrus	520	7.01	58	-46	28
left supramarginal gyrus	56	5.69	-60	-48	30

Note: This table presents the results of the 2nd level random effects group analysis. The *T* values represent the value for local maxima at $p < .05$ (FWE corrected). The size refers to the total number of (2 x 2 x 2 mm) voxels included in the cluster (minimum of 10 voxels). x, y, z are MNI coordinates measured in mm.

[1] Only when lowering the threshold to an uncorrected p-value of .001, a region in orbitofrontal cortex (OFC; MNI coordinates: x = 6, y = 44, z = -16) was more active for positive than negative feedback.

Table 5.3 Regions activated for task switching (switch > repeat trials) during task cues and targets

	size	T-value	x	y	z
Task cues:					
left middle frontal gyrus	26	3.56	-32	2	52
left superior parietal lobe	15	3.41	-26	-62	48
Targets:					
right dorsolateral prefrontal cortex	27	3.69	30	54	20
left dorsolateral prefrontal cortex	55	4.43	-30	44	10
	22	3.76	-36	36	20
right anterior cingulate cortex	11	3.31	8	28	18
left superior parietal lobe	35	3.81	-24	-48	44
right angular gyrus	14	3.74	38	-56	22

Note: This table presents the results of the 2nd level random effects group analysis. The *T* values represent the value for local maxima at $p < .001$ (uncorrected). The size refers to the total number of (2 x 2 x 2 mm) voxels included in the cluster (minimum of 10 voxels). x, y, z are MNI coordinates measured in mm.

Table 5.4 Regions activated and deactivated for the reward by trial-type by *DAT1* genotype interaction during task cues and targets

	size	T-value	x	y	z
Task cues (activations):					
right middle frontal gyrus[1]	64	4.03	26	44	2
Targets (activations):					
right medial superior frontal gyrus	29	3.97	8	54	24
ventral anterior cingulate cortex	88	3.64	2	46	0
right inferior temporal gyrys	13	3.66	58	-36	-20
right angular gyrus	15	3.34	42	-60	36
Targets (deactivations):					
left dorsolateral prefrontal cortex	24	3.56	-34	22	18
left inferior parietal lobe	14	3.51	-50	-36	36
right supramarginal gyrus	58	3.94	28	-44	46

Note: This table presents the results of the 2nd level random effects group analysis. The *T* values represent the value for local maxima at $p < .001$ (uncorrected). The size refers to the total number of (2 x 2 x 2 mm) voxels included in the cluster (minimum of 10 voxels). x, y, z are MNI coordinates measured in mm.

[1]Note that this activation during task-cues was more ventral and medial than that located in the dorsolateral PFC during targets. Consistent with this observation is the finding that the pattern resembled that seen in the vACC and not in the DLPFC.

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6.

Discussion

The studies reported in this thesis aimed to elucidate the role of the anterior cingulate cortex (ACC) and strongly connected structures in adjusting cognitive control. I have manipulated adjustments in control by using cues that enabled participants to prepare for the upcoming Stroop-like target condition (chapters 2 and 3) and by using cues that introduced switching between the two tasks associated with the Stroop-like stimuli (chapters 4 and 5). In addition, in chapter 5, I have investigated how motivational control interacts with cognitive control and the role of dopamine in modulating this interaction.

In this final chapter, I discuss the main findings in light of current theories about the areas shown to be involved in adjustments in control, with a focus on the ACC. Furthermore, I speculate on the relevance of these results for neuropsychiatric disorders.

6.1 Cognitive Control

6.1.1 Anterior Cingulate Cortex: Control Adjustments

Much of the research described in this thesis has focused on the role of the dorsal ACC (also including parts of pre-supplementary motor area [pre-SMA, BA 6] and medial superior frontal gyrus [meSFG, BA 8]), situated in the medial frontal cortex (MFC). Replicating numerous other imaging studies investigating conflict processing, I have found the ACC to be active for response conflict (chapters 2-4). However, throughout this thesis I have clearly demonstrated that the role of the ACC is not confined to the processing of response conflict. For example, chapter 2 has revealed that the ACC is not activated during response conflict when informative cues provide the opportunity to prepare for the Stroop-like target condition beforehand (see **Figure 2.3C**), even in the presence of a behavioral conflict effect. Furthermore, chapter 3 has revealed ACC activity for incongruent targets relative to congruent targets only after congruency-predicting cues. Critically such a Stroop effect was absent in the ACC after incongruency-predicting or non-predictive cues (see **Figure 3.3B**). This is actually not different from what has been observed previously in trial-to-trial adjustment studies. For example, Carter and colleagues (2000) have found no differential ACC activity for congruent and incongruent Stroop trials in mostly incongruent blocks, despite a

behavioral effect (44 ms). Similarly, using an Eriksen flanker task, Botvinick and colleagues (1999) have found a response time difference between incongruent and congruent flanker trials not only following congruent trials (290 ms), but also following incongruent trials (243 ms), even though no differential ACC activity was found in the latter comparison. The absence of ACC activity in the presence of a behavioral conflict effect is problematic for the conflict monitoring hypothesis, which states that the ACC monitors for response conflict (e.g., MacDonald et al., 2000; Botvinick et al., 2004). However, these findings can be explained if the ACC has a more general role in adjusting control.

To investigate the role of the ACC in these control adjustments, I have used cues preceding the Stroop targets. A major advantage of this approach is that it enabled me to investigate what happens in between Stroop trials without confounding processes related to the previous target with processes on the current target. This is in contrast to trial-to-trial adjustment studies, in which sequential effects are investigated on the current target as a function of the previous one. Consistent with the adjustment hypothesis, the ACC was differentially active in preparation for the upcoming Stroop target condition, on both deterministic cues (chapter 2) and probabilistic cues (chapter 3). Importantly, this ACC activity during the cues - which did not convey any response conflict themselves - was independent of *upcoming* response conflict (Sohn et al., 2007), high error likelihood (Brown and Braver, 2005), or increased mental effort (Critchley et al., 2003). Interestingly, the ACC responded similarly to deterministic cues predicting incongruent or congruent targets (see **Figure 2.3B**) and even more to probabilistic cues predicting congruent targets than to cues predicting incongruent targets (see **Figure 3.3C**). My findings suggest that the ACC is involved in *strategic* adjustments in control. Moreover, I claim that these adjustments are not solely triggered by response conflict, but can also be based on abstract cues that influence participants' expectations (see also, Logan and Zbrodoff, 1982; Gratton et al., 1992). Most importantly, the data show that strategic adjustments do not just serve to reduce conflict during incongruent targets (i.e., by employing a narrow-attention strategy), but also to increase facilitation effects during congruent targets (i.e., by employing a wide-attention strategy).

In a deterministic situation (chapter 2), participants can easily adopt the most optimal strategy for each target. This was shown by similar ACC activation for cues predicting incongruent and congruent targets compared with cues predicting neutral targets that do not elicit the need for a specific strategy. By contrast, in a probabilistic task (chapter 3), activity in the ACC was more enhanced for cues predicting congruent targets than for cues predicting incongruent targets and non-predictive cues, whereas ACC activity for the latter two types of cues was similar. This led to the conclusion that the narrow-attention strategy is the default strategy, which is then also employed when participants do not know what to expect, i.e. on non-predictive cues. This is probably because a narrow-attention strategy (i.e., focusing on the relevant dimension) does not lead to erroneous responses in any target condition. Only when a congruent target is expected with great probability, do participants employ a wide-attention strategy, leading to increased ACC responses on the congruency-predicting cues (see also, Gratton et al., 1992). Similarly, in a normal probabilistic Stroop situation without cues, participants will engage in a wide-attention strategy (i.e., also paying attention to the distractor dimension) only when the previous trial was a congruent one as well. However, a wide-attention strategy is not suitable for every kind of trial and, hence, results in the need for new adjustments when expectancies are not met (i.e., on incongruent trials). Thus, by using cues, I have demonstrated why Stroop effects in the ACC are only observed after congruent trials (see above). Together, the findings in chapters 2 and 3 show the involvement of the ACC in strategic adjustments in control on the basis of abstract cues independent of the need to reduce high mental effort on the following target (Botvinick, 2007). Thus, adjustments accompanied by ACC activity lead to cognitively more efficient processing strategies not only on high conflict, high error likelihood and high mental effort (i.e., incongruent) trials (see **Table 1.1**), but also on low conflict, low error likelihood and low mental effort (i.e., congruent) trials. In other words, the ACC seems to be involved whenever adjustments in control can lead to more efficient processing strategies; this can be in response to novel or effortful situations or after errors, but also in response to informative cues signaling the need to adjust control settings.

In chapters 4 and 5, I have used a task-switching Stroop paradigm to investigate whether adjustments in the ACC could also be elicited at a different level than the

response level. Specifically, I have studied task conflict (chapter 4) and switch effects (chapter 5) to look at control adjustments at the task-set level. I have found that the ACC was indeed involved in control adjustments at the level of task sets (see **Figure 4.5** and **Figure 5.4A**), independent of response conflict. This is in accordance with other studies that demonstrated the involvement of the ACC in task-switching (e.g., Yeung et al., 2006; Leber et al., 2008) and suggests that control adjustments in the ACC contribute to cognitive flexibility. Below, I discuss the involvement of the ACC in cognitive flexibility which is influenced by the anticipation of reward. This reward-related activity further strengthens the idea that ACC activity can be independent of conflict or errors.

6.1.2 Anterior Cingulate Cortex: Anatomical Considerations

In chapters 2-4, I have consistently found multiple peaks of activation in MFC when looking at target-related activity as a function of conflict (see **Table 2.2**, **Table 3.1**, **and Table 4.1**), and in chapter 5 when looking at negative versus positive feedback (see **Table 5.2**). That is, peaks were obtained both in the ACC and in a more dorsal and caudal region: meSFG (BA 8) or (pre) SMA (BA 6). It has been suggested that conflict is associated more strongly with those dorsal regions in the MFC than with the ACC proper (Ullsperger and von Cramon, 2001; Rushworth et al., 2004), in accordance with the absence of neurons coding for response conflict in the ACC of monkeys (see Schall and Boucher, 2007). However, in the studies presented in this thesis, the ACC and the SFG were consistently co-activated during conflict. The ACC was even shown to be functionally connected to the SMA during cues informing participants about the upcoming Stroop target condition (chapter 2). Moreover, a direct test between the two medial regions could not reveal any differences in activity for either response conflict or task conflict (chapter 4). Hence, a functional dissociation cannot be discerned from our data in chapters 2-4. Others have proposed that the meSFG is involved in task control and selection of action sets (Rushworth et al., 2004), whereas the ACC guides decisions while taking the reward history into account (see also Rushworth and Behrens, 2008). The finding of a dopamine-modulated interaction between motivation and cognition in ventral

ACC but not in BA 8 or BA 6 (chapter 5), seems to be in accordance with this suggestion (see below).

However, the region in ACC (BA 32), which was activated for the motivation-cognition interface in chapter 5 was clearly located more ventrally than the regions activated in the ACC (BA 32/24) for the cognitive measures in chapters 2-5. This is in line with suggestions of a dorsal cognitive division and a ventral 'limbic' division in the ACC (Bush et al., 2000; Koski and Paus, 2000). Others have further divided the cognitive part of the ACC dependent on response modality, i.e. oculomotor, vocal, or manual responses (Paus et al., 1993; Picard and Strick, 1996; but see Barch et al., 2001). Although the responses were all manual in our experiments, when comparing the results, slightly different peaks of activation were seen throughout the ACC that were not confined to the 'arm' region of the ACC (see Picard and Strick, 1996). Nevertheless, all peaks of activation for the cognitive measures were within the rostral cingulate zone (RCZ), similar to the results of a meta-analysis focusing on the role of the MFC in cognitive control (Ridderinkhof et al., 2004a).

6.1.3 Anterior Cingulate Cortex Versus Lateral Prefrontal Cortex

The ACC is strongly connected to the dorsolateral prefrontal cortex (DLPFC), both anatomically (Bates and Goldman-Rakic, 1993; Van Hoesen et al., 1993) and functionally (Koski and Paus, 2000). In keeping with this evidence, I have often found the DLPFC to be co-activated with the ACC. However, there were also some marked differences that can shed light on the potential division of labor between the ACC and DLPFC.

In chapter 2, I found the ACC to be differentially active during informative cues but not during informed targets, whereas regions in LPFC (a ventral and a dorsal region) were still active for response conflict on informed targets (see **Table 2.2**). In chapter 3, I observed differential cue-related ACC activity, whereas the DLPFC was not differentially activated during the cues. Furthermore, while cue-related ACC activity was correlated with behavioral performance on the targets that followed, cue-related DLPFC activity did not show such correlations. These findings are opposite to the pattern observed by

MacDonald and colleagues (2000), who found differential DLPFC activity on task cues and differential ACC activity on the Stroop targets. On the basis of these findings, the authors concluded that the engagement of the DLPFC in the preparatory period is consistent with a role in the implementation of control, while the selective activation of the ACC for conflict during the response period would be consistent with a role in conflict monitoring. Do our findings point to an exact opposite division of labor? Naturally, the task cues in the study of MacDonald and colleagues differ from the condition cues I used in chapter 2 and 3. However, in chapter 4 and 5, I have demonstrated that not only the DLPFC but also the ACC is involved in processes at the task-set level (see **Figure 4.4** and **Figure 5.4A**). Moreover, the fact that the preparatory activity in chapter 2 and 3 in the ACC was independent of response conflict (see above), seems to be more in line with a role of implementing control instead of monitoring for response conflict. An opposite division of labor has been suggested before; i.e., that the DLPFC signals to the ACC to implement control (Paus et al., 1993; Posner and DiGirolamo, 1998; Turken and Swick, 1999) (see **Table 1.1**). However, evidence for a direct relationship, in either direction, could not be observed in chapter 2 because no significant correlations were found between the ACC and DLPFC. Instead, in accordance with anatomical connections (Picard and Strick, 1996; Paus, 2001), the ACC was functionally connected to premotor areas, which is in line with a role for implementing control without the intervention of another control region such as the DLPFC.

6.2 Motivational Control and Dopamine

The frontal cortex is highly sensitive to its dopaminergic environment and the ACC is one of the parts of the frontal cortex that is most richly innervated by dopaminergic neurons from the midbrain (Crino et al., 1993; Williams and Goldman-Rakic, 1998). Dopamine is well known to be implicated in the adjustment of cognition and behavior by motivation. Accordingly, the role of the ACC in cognitive adjustment might depend on its modulation by dopamine and reward. This hypothesis is strengthened by the observation of abundant connections of the ACC with other limbic regions, like the ventral striatum. Together these lines of evidence have led to suggestions that the ACC

can use motivational input to guide decision making, perhaps in a dopamine-dependent fashion (e.g., Pandya et al., 1981; Vogt et al., 1993; Morecraft and Van Hoesen, 1998; Holroyd and Coles, 2002; Williams et al., 2004; Amiez et al., 2006; Walton et al., 2007; Rushworth and Behrens, 2008). To investigate whether the ACC can use motivational information to make adjustments in control, I have employed a reward-cued task-switching paradigm in chapter 5. In agreement with the above mentioned suggestions, the results provided evidence for a motivation-cognition interface in (ventral) ACC, which was modulated by striatal dopamine. Again, these reward-related findings support the suggestion that adjustments in the ACC can be independent of negative consequences or conflict.

6.2.1 Ventral Striatum and Ventral ACC

Consistent with previous studies, the results reported in this chapter 5 revealed that both the anticipation and receipt of reward activated the ventral striatum (see **Figure 5.3**). By looking at brain activity as a function of inter-individual variation in the dopamine transporter gene (*DAT1*, *SLC6A3*), I could determine that striatal dopamine is especially involved in the anticipation of reward, while having no significant effects on reward receipt (cf. Baldo and Kelley, 2007). Such a mechanism of dopamine-dependent reward anticipation in the ventral striatum might well mediate the hypothesized interface between motivation and cognitive adjustment in the ACC. The results were consistent with this hypothesis. I have found that participants with supposedly higher striatal dopamine levels were better in switching to the other task on high compared with low rewarded trials (see **Figure 5.2**).

Whereas the dorsal ACC was activated during Stroop performance and task switching (see paragraph 6.1), the interaction between motivational and cognitive measures elicited activity in ventral instead of dorsal ACC. The activation pattern in this region (see **Figure 5.4B**) followed the behavioral interaction effect seen in the error rates (see **Figure 5.2**). Ventral ACC (vACC) is part of the ventromedial prefrontal cortex (VMPFC) (Ongur et al., 2003; Vogt et al., 2005), and is strongly connected to limbic areas like the ventral striatum and the amygdala as well as other more dorsal regions in

the ACC and the medial frontal cortex (e.g., Devinsky et al., 1995; Carmichael and Price, 1996). Thus, the vACC is ideally located for a motivation-cognition interface. VMPFC has been shown to encode reward value representations in several neuroimaging studies (e.g., McClure et al., 2004; Knutson et al., 2005; Daw et al., 2006; Kable and Glimcher, 2007; Knutson et al., 2007). Here, I have shown that the vACC can use cues that predict reward value to aid flexible behavior.

Several theories have incorporated a (dopamine-modulated) interaction between motivation and cognition to explain ACC functioning (see **Table 1.1**). Most of these authors have implicated the ACC in (reinforcement) learning processes (e.g., Holroyd and Coles, 2002; Brown and Braver, 2005; Rushworth and Behrens, 2008). However, in chapter 5 we have demonstrated a motivation-cognition interface in the ACC without specifically focusing on learning processes. We have shown that dopamine-dependent *reward anticipation* mediates this interface in the ACC. This finding is in accordance with the theory that both *positive* and negative information of *prediction* or outcome values is coded in the ACC (Walton et al., 2007; Rushworth and Behrens, 2008). Although we find these interaction effects in vACC instead of dACC, in macaque monkeys, vACC is heavily connected to dACC and other regions in MFC, and less so to other regions in its ventral neighboring area, the orbital frontal cortex (Carmichael and Price, 1996). Hence, dACC and vACC might be nodes in the same network "where motor control, drive and cognition interface" (Paus, 2001), with vACC being closer connected to limbic areas and dACC to motor/cognitive areas. Throughout this thesis, I have shown that the ACC can use value information to select-for-action on the basis of preceding abstract cognitive cues and reward cues, thus not necessarily predicting a negative event (e.g., Botvinick, 2007 and see **Table 1.1**).

6.2.2 Lateral PFC

In chapter 5, I have also found evidence for a motivation-cognition interface in a region of the dorsal fronto-striatal circuit, the DLPFC. The DLPFC was consistently activated during cognitive control measures (see paragraph 6.1), similar to the dorsal striatum (see **Table 2.1**, **Table 2.2**, and **Table 4.1**) and other regions connected to the dorsal striatum,

like regions in the parietal cortex (inferior parietal lobe [IPL, BA 40] and superior parietal lobe [SPL, BA 7]). Activity of the DLPFC is repeatedly demonstrated to be modulated by dopamine using genetic imaging, particularly during working memory tasks (for reviews, see Goldberg and Weinberger, 2004; Green et al., 2008). Most of these genetic imaging studies examined effects of a polymorphism in the gene coding for catechol-O-methyltransferase (COMT), which catabolizes dopamine in the prefrontal cortex. In contrast to the findings in the vACC in chapter 5, but similar to previous findings with the COMT gene, I have found that genetically determined dopamine levels are associated with increased cognitive performance and more efficient (i.e., decreased) task-related DLPFC activity. These previous studies have investigated effects of prefrontal dopamine by making use of the COMT polymorphism. I have extended this prior work by making use of the *DAT1* polymorphism, which affects dopamine primarily in the striatum. Specifically, control-related DLPFC activity was modulated by striatal dopamine as a function of reward anticipation. This dopamine-dependent interaction between a motivational ventral circuit and a cognitive dorsal circuit is the first functional evidence in humans of what has only been hypothesized before on the basis of neuro-anatomical data (Haber et al., 2000; Haber, 2003).

6.3 Clinical Relevance

The research discussed in this thesis might be of relevance to neuro-psychiatric disorders, like attention deficit hyperactivity disorder (ADHD) and Parkinson's disease (PD), which are both characterized by failures of cognitive adjustment.

6.3.1 Attention Deficit Hyperactivity Disorder

ADHD is characterized by structural and functional differences in fronto-striatal and frontal-parietal networks (Dickstein et al., 2006; Valera et al., 2007), probably underlying the executive and attentional dysfunction observed in this disorder. Specifically, the present results of the 10R homozygous group (chapter 5) can be of importance for ADHD research since there is evidence of higher levels of the striatal dopamine transporter in

ADHD subjects than healthy controls (Dougherty et al., 1999; Krause et al., 2003). Indeed, an association has been found between the 10R allele and ADHD (e.g., Cook et al., 1995; Gill et al., 1997; Waldman et al., 1998; Madras et al., 2002). Furthermore, stimulant drugs (e.g., methylphenidate), which are effective in the treatment of ADHD, block the dopamine transporter. Importantly, the ACC has shown reduced volume (Seidman et al., 2006), decreased cortical thickness (Shaw et al., 2006; Makris et al., 2007), and functional hypo-activation (Bush et al., 1999; Bush et al., 2005; Dickstein et al., 2006) in ADHD. Altered ACC structure and function could be partly due to disrupted striatal dopaminergic signaling, contributing to both the executive dysfunction and altered reward processes in ADHD (see Sonuga-Barke, 2003). Further research is needed to investigate the dopamine-modulated motivation-cognition interface in ADHD and the effects of stimulant drugs on this interaction.

6.3.2 Parkinson's Disease

PD is characterized by cell loss in the substantia nigra, resulting in severely depleted striatal dopamine levels, which are associated with motor dysfunction but also cognitive decline (Cools et al., 2001). Specifically, it has been shown that disrupted striatal outflow impairs cognitive functioning that relies on a fronto-striatal circuit (Owen et al., 1998). Importantly, in early stages of PD, dopamine levels in dorsal striatum are severely depleted, whereas ventral striatal dopamine levels are still rather intact (Kish et al., 1988). Hence, motivational processes, relying on the relatively intact - or even up-regulated (van Oosten et al., 2005) - ventral fronto-striatal circuit, might be able to compensate for the cognitive deficits, induced by dopamine loss in the dorsal fronto-striatal circuit (see also Pessiglione et al., 2004). Such compensatory processes early in the disease might be observed in the ACC, as early PD patients had higher dopamine receptor binding in the ACC (but not in the DLPFC) than advanced PD patients (Kaasinen et al., 2000). Indeed, ACC hyper-activity was found in presymptomatic Parkinson-gene carriers during internally generated movements (Buhmann et al., 2005). Furthermore, activity in the ACC was enhanced during complex movement sequences in PD as compared to controls, while DLPFC activity was decreased (Sabatini et al., 2000). This indicates that ACC

function may be relatively preserved in the mild stages of the disease, and that this region may fulfill a compensatory role in PD, at least in motor tasks. It remains to be investigated whether a similar region in the ACC will show compensatory activity when studying the interaction between motivation and cognition in PD.

6.4 Conclusions

In this thesis, I have shown that the ACC, as part of a dopamine-modulated fronto-striatal circuit, implements control adjustments on the basis of motivational and cognitive information in order to select the most efficient processing strategy on response or task-set level. Importantly, these control adjustments are not only made on the basis of negative outcomes, like response conflict or errors. Specifically, our results suggest that the ACC is engaged whenever specific adjustments can or should be made in order to engage in an optimal processing strategy. The ACC probably fulfills this role by encoding reward or goal value on the basis of previous and present motivational and cognitive information that it receives from other regions in the dopamine-sensitive fronto-striatal network.

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Nederlandse Samenvatting

De verleiding weerstaan:
De rol van de anterieure cingulate cortex in het aanpassen van cognitieve controle

We staan constant bloot aan verleidingen en hebben doelgericht gedrag nodig om deze verleidingen te weerstaan. De regulatieve processen die hierbij een rol spelen noemen we 'cognitieve controle'. Ik heb onderzocht in hoeverre een gebied in het midden van de voorhersenen (frontale cortex), de anterieure cingulate cortex (ACC), betrokken is bij het weerstaan van verleidingen. Over de exacte rol van de ACC in cognitieve controle bestaan vele theorieën. Het werk in dit proefschrift toont aan dat dit gebied inderdaad nauw betrokken is bij het weerstaan van verleidingen. Bij de voorbereidingen op het weerstaan van verleiding vinden er al controleaanpassingen plaats in de ACC, maar het opmerkelijke is dat de ACC ook betrokken blijkt te zijn bij de voorbereiding op situaties waar geen verleiding is. De kennis die is verworven in dit onderzoek kan mogelijk een bijdrage leveren aan verder onderzoek naar bijvoorbeeld ADHD en de ziekte van Parkinson.

De Stroop taak

Om cognitieve controle te onderzoeken wordt vaak de zogenaamde Stroop taak gebruikt. In deze taak zien proefpersonen stimuli die uit twee dimensies bestaan, bijvoorbeeld een kleurwoord ("rood") in een bepaalde kleur. Deze twee dimensies kunnen elkaar tegenspreken (bijvoorbeeld het woord "rood" in groene letters); deze stimulus wordt 'incongruent' genoemd. Het woord en de kleur kunnen ook overeenkomen (bijvoorbeeld het woord "rood" in rode letters); deze stimulus wordt 'congruent' genoemd. Als proefpersonen de kleur moeten benoemen van het woord worden ze afgeleid door de betekenis van het woord. Bij incongruente stimuli (met een afleidend woord) blijken proefpersonen langzamer te reageren op de kleur dan als er geen afleidend woord is (een neutrale stimulus, bv. een rijtje x'en in een bepaalde kleur). Proefpersonen moeten bij incongruente stimuli dus de verleiding weerstaan het woord op te lezen als het doel is de

kleur te benoemen. Bij congruente stimuli kan de betekenis van het woord het kleuren benoemen juist helpen, omdat kleur en woord overeenkomen. Het verschil tussen (traag) reageren op incongruente Stroop stimuli en (snel) reageren op congruente Stroop stimuli wordt gebruikt als maat voor 'response conflict'; het soort conflict dat dus wel bij incongruente stimuli, maar niet bij congruente stimuli voorkomt. In mijn onderzoek heb ik steeds pijl-woord combinaties gebruikt als een soort van Stroop stimuli. Hierbij kon een naar links- of rechtswijzende pijl dezelfde richting aangeven als de betekenis van het woord "links" of "rechts" in de pijl, of de richtingen konden tegengesteld zijn. Er werd bijvoorbeeld een links-wijzend pijltje getoond dat was gecombineerd met het woord "rechts" (incongruent) of het woord "links" (congruent). De proefpersonen moesten de richting van de pijl (de pijltaak) of de betekenis van het woord (de woordtaak) aangeven door op een linker of rechter knop te drukken (zie **Figuur 1.1** vooraan dit proefschrift).

Hersenactiviteit

In het onderzoek dat beschreven is in dit proefschrift hebben de proefpersonen de pijl-woord Stroop taak gedaan in een magnetic resonance imaging (MRI) scanner. De MRI scanner heeft een groot constant magneetveld en steeds wisselende elektromagnetische velden, zodat er beelden gereconstrueerd kunnen worden van het brein. Met *functionele* MRI (fMRI) wordt de verandering van zuurstofvoorziening in het bloed gemeten, wat een correlaat is van activiteit van zenuwcellen (neuronen). Hierdoor kan neuronale activiteit gemeten worden op de millimeter en enkele seconden nauwkeurig. Deze techniek is daarom uitermate geschikt om de rol van de ACC te meten in cognitieve controle processen, opgeroepen door bijvoorbeeld de Stroop taak.

In vroege studies naar hersenactiviteit werd gevonden dat de ACC meer actief is voor incongruente dan voor congruente Stroop stimuli. Later werd bovendien gevonden dat de ACC vooral meer actief is voor incongruente stimuli (ook wel 'trials' genoemd) als die voorafgegaan waren door congruente trials, en niet zo zeer als incongruente trials voorafgegaan waren door andere incongruente trials. De betrokkenheid van de ACC in deze 'trial-tot-trial' aanpassingen in cognitieve controle werd gezien als één van de belangrijkste ondersteuningen van de 'conflict monitoring' theorie. Deze theorie zegt dat de ACC evalueert of er response conflict is en vervolgens in het geval van response

conflict een sein geeft aan andere frontale gebieden om controleaanpassingen uit te voeren. Het is echter gebleken dat instructies voorafgaande aan iedere stimulus, cues genoemd, ook aanpassingen in cognitieve controle teweeg kunnen brengen. Deze cues zijn zelf niet incongruent en hoeven ook niet per se een opkomend response conflict te signaleren.

Instructiecues

In hoofdstuk 2 en 3 heb ik onderzocht of de ACC betrokken is bij dit soort cues die aangeven of de komende Stroop stimulus incongruent of congruent is, zonder nog de exacte response (links of rechts drukken) te voorspellen. Uit de resultaten blijkt dat de ACC al actief is tijdens controle aanpassingen voorafgaand aan de Stroop stimuli, dus tijdens de cues. Belangrijk is dat de ACC niet actiever was voor cues die een incongruente stimulus voorspelden vergeleken met cues die congruente stimuli voorspelden. Dit geeft aan dat de ACC actief kan zijn onafhankelijk van response conflict (al tijdens abstracte cues), maar ook onafhankelijk van *komend* response conflict. Als de controle aanpassingen op basis van de cues zijn gedaan, is de ACC zelfs niet meer actief voor response conflict op de Stroop stimuli. Alleen als de cues niet kloppen (in 25% van de gevallen in het experiment in hoofdstuk 3) wordt de ACC actief; vooral als een congruente Stroop stimulus voorspeld wordt door een congruentie-voorspellende cue, maar de stimulus in plaats daarvan toch incongruent is. Aangezien de ACC op congruentie-voorspellende cues evenveel of zelfs meer actief was dan op incongruentie-voorspellende cues, lijkt het er niet op dat er na een congruentie-voorspellende cue geen controle aanpassingen zijn gedaan. Deze resultaten laten eerder zien dat de controle aanpassingen voor opkomende congruente en incongruente stimuli strategisch zijn en dat het hierbij gaat om 2 verschillende strategieën, waarbij de strategie voor opkomende congruente stimuli niet optimaal is voor incongruente stimuli.

Taakwisselingen

Een andere situatie die vaak gebruikt wordt om doelgericht gedrag te onderzoeken, vraagt proefpersonen snel te wisselen tussen twee taken. Op trials waarbij de taak wisselt ten opzichte van de vorige trials (wissel of ‘switch’ trial) moeten proefpersonen de verleiding

weerstaan de vorige taak te herhalen en zijn ze dus langzamer dan wanneer de taak niet wisselt (herhaal of 'repeat' trial). Deze taaksituatie meet controle processen op het niveau van taken, los van het niveau van de specifieke response. In hoofdstuk 4 en 5 heb ik proefpersonen laten wisselen tussen reageren op het woord van de pijl-woord Stroop stimuli (de woordtaak) en reageren op de pijl van deze stimuli (de pijltaak). Hieruit bleek dat de ACC regio die betrokken is bij controle aanpassingen op het niveau van responses, ook betrokken is bij controle op het niveau van taken.

Beloning

Doelgericht gedrag is vaak gericht op het verkrijgen van beloning of het vermijden van straf. Bovendien is de ACC (net als iedere andere regio) niet een geïsoleerde regio in het brein, maar een onderdeel van hersencircuits die corticale frontale gebieden met sub-corticale striatale gebieden verbinden; de fronto-striatale circuits. Van het (ventrale) striatum is bekend dat deze betrokken is bij motivatie en beloning. Er zijn dan ook verschillende theorieën die voorspellen dat de ACC controle aanpast op basis van motivationele informatie, zoals beloning en straf, predictie of detectie van fouten, en inspanning. Daarom heb ik in hoofdstuk 5 tevens gekeken naar het effect van motivationele processen op aanpassingen in controle. Voorafgaand aan iedere switch of repeat trial kregen proefpersonen in dit experiment te zien of ze veel of weinig beloning (geld) konden verdienen met een correcte en snelle response (anticipatie van beloning). Vervolgens kregen ze na hun response te zien of deze goed, fout of te laat was en of ze dus inderdaad de beloning verdienden of niet (ontvangst van beloning). Omdat bekend is dat activiteit in de fronto-striatale circuits gemoduleerd wordt door dopamine, keken we daarbij naar hersenactiviteit in proefpersonen met verschillende varianten van een gen dat geassocieerd is met dopamine in het striatum. Zodoende kon ik taakgerelateerde hersenactiviteit in een groep met veel dopamine in het striatum vergelijken met een groep met minder dopamine in het striatum. De resultaten laten zien dat in het ventrale striatum dopamine voornamelijk betrokken is bij de anticipatie op beloning in plaats van ontvangst van beloning. Bovendien werd het snel wisselen tussen taken beïnvloedt door de dopamine-gemoduleerde anticipatie van beloning. Deze interactie tussen motivationele en cognitieve controle processen vond onder andere plaats in een regio van

de ACC. Dit bevestigt de theorie dat de ACC niet alleen informatie kan halen uit abstracte cues in een cognitieve taaksituatie, maar ook op basis van motivationele informatie aanpassingen kan maken in cognitieve controle. Deze motivationele informatie was positief van aard. Dat wil zeggen dat de cues beloning beloofden in plaats van straf of inspanning. Dit versterkt onze theorie dat de ACC niet per se alleen betrokken is bij de anticipatie van negatieve gebeurtenissen zoals conflict of fouten.

Toepassing

Het feit dat deze controle processen plaatsvinden onder invloed van dopamine is zeer relevant voor neuro-psychiatrische stoornissen zoals attention deficit hyperactivity disorder (ADHD) en de ziekte van Parkinson. In deze stoornissen is namelijk de dopamine-balans in de fronto-striatale circuits verstoord wat leidt tot zowel motivationele als cognitieve problemen die al dan niet verbeterd worden door dopaminerge medicatie. De resultaten uit hoofdstuk 5 kunnen gebruikt worden om meer inzicht te verkrijgen in de vaak paradoxale effecten van dopaminerge medicatie in ADHD en de ziekte van Parkinson, hierbij gebruikmakend van individuele genetische verschillen in dopamine niveaus in de fronto-striatale circuits.

Conclusies

Concluderend kan ik zeggen dat de ACC betrokken is bij het weerstaan van verleidingen; een situatie die is nagebootst in het lab met Stroop stimuli of taakwisselingen. Als de kans wordt gegeven om de Stroop stimuli voor te bereiden door middel van instructiecues, maakt de ACC al controle aanpassingen op deze cues. De ACC is echter niet alleen betrokken bij voorbereiding op het weerstaan van verleiding (bijvoorbeeld bij response conflict tijdens incongruente stimuli), maar ook als verleiding of afleiding geen rol speelt (bijvoorbeeld bij congruente stimuli); en bovendien niet alleen op responseniveau maar ook op taakniveau. Dit geeft aan dat de rol van de ACC in controle aanpassingen strategisch kan zijn, onafhankelijk van (komend) response conflict of de moeilijkheid of inspanning die een cue signaleert. Daarnaast is uit mijn onderzoek gebleken dat anticipatie van een beloning kan helpen om de verleiding te weerstaan en

dat deze processen zich afspelen in de ACC onder invloed van de neuromodulator dopamine.

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List of Publications

Journal Publications

Aarts, E, Roelofs, A, & Van Turennout, M (2009). Attentional Control of Task and Response in Lateral and Medial Frontal Cortex: Brain Activity and Reaction Time Distributions. *Neuropsychologia*, in press.

Helmich, RC, **Aarts, E**, De Lange, F, Bloem, B, Toni, I (2009). Increased dependence of action selection on recent motor history in Parkinson's disease. *Journal of Neuroscience*, in press.

Aarts, E, Roelofs, A, & Van Turennout, M (2008). Anticipatory activity in anterior cingulate cortex can be independent of conflict and error likelihood. *Journal of Neuroscience* 28(18): 4671– 4678.

Aarts, E & Roelofs, A. Attentional control adjustments in anterior cingulate cortex based on probabilistic cueing. Submitted for publication.

Aarts, E, Roelofs, A, Helmich, RC, Franke, B, Rijpkema, M, Fernandez, G, Cools, R. Parsing the role of dopamine in human reward and its cognitive consequences using genetic imaging. Manuscript in preparation.

Conference Publications

Aarts, E, Roelofs, A, Helmich, RC, Franke, B, Rijpkema, M, Fernandez, G, Cools, R (2009). Parsing the role of dopamine in human reward and its cognitive consequences using genetic imaging [oral presentation + poster]. *Human Brain Mapping meeting*, San Francisco, USA.

Aarts, E, Roelofs, A, Helmich, RC, Franke, B, Rijpkema, M, Fernandez, G, Cools, R (2009). Parsing the role of dopamine in human reward and its cognitive consequences using genetic imaging [oral presentation]. *Endo-Neuro-Psycho meeting*, Doorwerth, The Netherlands.

Aarts, E & Roelofs, A (2008). Adjustments in attentional control by congruent information in anterior cingulate cortex [poster]. *Cognitive Neuroscience Society meeting*, San Francisco, USA.

Aarts, E & Roelofs, A (2007). Adjustments in attentional control by congruent information in anterior cingulate cortex [oral presentation]. *Dutch Psychonomics Society winter conference*, Egmond aan Zee, The Netherlands.

Aarts, E, Roelofs, A, & Van Turennout, M (2007). Symbolically driven preparatory adjustments in cognitive control by anterior cingulate cortex [poster]. *Cognitive Neuroscience Society meeting*, New York, USA.

Aarts, E, Roelofs, A, & Van Turennout, M (2007). Symbolically driven preparatory adjustments in cognitive control by anterior cingulate cortex [poster]. *Endo-Neuro-Psycho meeting*, Doorwerth, The Netherlands.

Aarts, E, Roelofs, A, & Van Turennout, M (2006). Role of medial frontal cortex in endogenous and exogenous control in task switching [poster]. *Medial Frontal Cortex workshop: Errors, Conflicts, and Rewards*, Amsterdam, The Netherlands.

Aarts, E, Roelofs, A, & Van Turennout, M (2006). Neural correlates of endogenous and exogenous control in task switching [poster]. *Cognitive Neuroscience Society meeting*, San Francisco, USA.

Aarts, E, Roelofs, A, & Van Turennout, M (2005). Response and task conflicts in medial and lateral prefrontal areas [oral presentation]. *Dutch Psychonomics Society winter conference*, Egmond aan Zee, The Netherlands.

Aarts, E, Lamers, M, Verhoef, K, Roelofs, A (2005). The reverse Stroop effect in switching between color naming and word reading [poster]. *European Society for Cognitive Psychology conference*, Leiden, The Netherlands.

Curriculum Vitae

Esther Aarts was born on the 10th of December 1980 in Eindhoven, the Netherlands. She attended secondary education (VWO) at the Jeroen Bosch College in 's-Hertogenbosch. From 1999 to 2004 she studied (medical) biology at the Radboud University in Nijmegen. She graduated cum laude after completing her master thesis on a functional magnetic resonance imaging (fMRI) study about cross-modal naming, under supervision of Dr. Miranda van Turennout at the Donders Institute for Brain, Cognition and Behaviour, Centre for Cognitive Neuroimaging.

From 2004 to 2008 she did her PhD research under supervision of Dr. Ardi Roelofs (Centre for Cognition) and Dr. Miranda van Turennout (Centre for Cognitive Neuroimaging). Her fMRI research focused on the role of the frontal cortex - anterior cingulate cortex in particular - in cue-based adjustments in cognitive control. In the last year of her PhD project, she started to work with Dr. Roshan Cools (Centre for Cognitive Neuroimaging), studying the modulation by dopamine of cognitive and motivational control processes. The results of her PhD research are described in this thesis.

Esther Aarts is currently working as a postdoctoral researcher at the Centre for Cognitive Neuroimaging and the Centre for Neuroscience (Psychiatry department) at the Radboud University Nijmegen Medical Centre. Here, she continues to work with Dr. Roshan Cools, studying the dopaminergic modulation of cognitive and motivational control processes in patient populations - attention deficit hyperactivity disorder (ADHD) and Parkinson's disease - as a function of genetic variations and dopaminergic medication.

In 2008, she was awarded a Niels Stensen stipend to investigate the role of catecholamines in attentional control at the University of California at Berkeley, USA in the lab of Mark D'Esposito.

Series Donders Institute for Brain, Cognition and Behaviour

1. van Aalderen-Smeets, S.I. (2007). *Neural dynamics of visual selection.* Maastricht University, Maastricht, The Netherlands.
2. Schoffelen, J.M. (2007). *Neuronal communication through coherence in the human motor system.* Radboud University Nijmegen, Nijmegen, The Netherlands.
3. de Lange, F.P. (2008). *Neural mechanisms of motor imagery.* Radboud University Nijmegen, Nijmegen, The Netherlands.
4. Grol, M.J. (2008). *Parieto-frontal circuitry in visuomotor control.* University Utrecht, Utrecht, The Netherlands.
5. Bauer, M. (2008). *Functional roles of rhythmic neuronal activity in the human visual and somatosensory system.* Radboud University Nijmegen, Nijmegen, The Netherlands.
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11. Lommertzen, J. (2009). *Visuomotor coupling at different levels of complexity.* Radboud University Nijmegen, Nijmegen, The Netherlands.
12. Poljac, E. (2009). *Dynamics of cognitive control in task switching: Looking beyond the switch cost.* Radboud University Nijmegen, Nijmegen, The Netherlands.
13. Poser, B.A. (2009) *Techniques for BOLD and blood volume weighted fMRI.* Radboud University Nijmegen, Nijmegen, The Netherlands.
14. Baggio, G. (2009). *Semantics and the electrophysiology of meaning. Tense, aspect, event structure*. Radboud University Nijmegen, Nijmegen, The Netherlands.
15. van Wingen, G.A. (2009). *Biological determinants of amygdala functioning*. Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.
16. Bakker, M. (2009). *Supraspinal control of walking: lessons from motor imagery.* Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.
17. Aarts, E. (2009). *Resisting temptation: the role of the anterior cingulate cortex in adjusting cognitive control.* Radboud University Nijmegen, Nijmegen, The Netherlands.