# Neural mechanisms of proactive and reactive inhibitory control

Studies in healthy volunteers and schizophrenia patients

**Bram B. Zandbelt**

*The studies described in this thesis were performed at the Rudolf Magnus Institute of Neuroscience, Department of Psychiatry, University Medical Center Utrecht, the Netherlands.*

*Research in this thesis was supported by a Veni grant from the Netherlands Organization for Scientific Research to Dr. M. Vink.*

*Publication of this thesis was financially supported by the Rudolf Magnus Institute of Neuroscience and the Jurriaanse stichting.*

*ISBN: 9789039356074*

*Cover illustration: Bram B. Zandbelt*
*Lay-out: Daan Zandbelt, Eva Cheung*

*Printed in Delft, the Netherlands by Drukkerij NIVO*

# Neural mechanisms of proactive and reactive inhibitory control

Studies in healthy volunteers and schizophrenia patients

## Neurale mechanismen van proactieve en reactieve inhibitie

Studies in gezonde vrijwilligers en schizofrenie patiënten

(met een samenvatting in het Nederlands)

***Proefschrift***

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op donderdag 8 september 2011 des ochtends te 10.30 uur

door

Bram Bastiaan Zandbelt

geboren op 1 november 1982 te Hengelo

**Promotor:** Prof. dr. R.S. Kahn

**Co-promotor:** Dr. M. Vink

Voor Jorien

Voor papa en mama

## Table of contents

1

# Introduction

## General introduction

The other day, I had to catch a train. I left home later than planned, so I had to rush. On my way to the station, I almost bumped into a man leaving his house. Further on, the sidewalk was so crowded with shoppers that I had to slow down my pace. Then, just when I was about to cross the street in front of the train station, I had to stop for a red light. When the traffic light changed green, I held my steps for a short moment to check if I could safely cross to catch my train, as taxi drivers and cyclists often run a red light here.

This example illustrates the importance of being able to restrain and stop actions, a concept referred to as inhibitory control. Inhibitory control can be classified into two categories: proactive inhibition and reactive inhibition (Braver et al., 2007; Aron, 2010).

Proactive inhibition is a top-down form of control that is activated before the occurrence of an event that makes us stop. It is triggered by predictive cues in our environment (e.g. a crowded sidewalk) or by internal signals (e.g. remembering that taxi drivers and cyclists often run a red light at a particular crossing) and results in enhanced motor control and the restraint of actions (e.g. slowing down or holding your steps for a moment). Thus, proactive inhibition is used when actions have to be restrained in anticipation of stopping.

Reactive inhibition is a bottom-up form of control. It is triggered after a salient external event occurred (e.g. somebody crossing your way or a red light) and interrupts actions completely. So, reactive inhibition is used when actions need to be stopped outright.

Inhibitory control is impaired in several neurological and psychiatric

disorders (Verbruggen and Logan, 2008a; Aron, 2010) and poor inhibitory control has been used to explain a variety of clinical symptoms, including inattention and impulsivity in attention deficit hyperactivity disorder (Barkley, 1997), problems with tic suppression in Tourette's syndrome (Peterson et al., 1998), 'washing' and 'checking' in obsessive-compulsive disorder (Chamberlain et al., 2005), repetitive hair-pulling in trichotillomania (Chamberlain and Sahakian, 2007), and perseveration in schizophrenia (Crider, 1997).

This thesis is about the neural mechanisms underlying proactive and reactive inhibition. We investigated these mechanisms in the healthy brain as well as how inhibitory control and its neural underpinnings are impacted by schizophrenia. The present chapter provides an introduction to this topic. First, we will discuss how proactive and reactive inhibition can be studied in an experimental setting. Second, we will provide an overview of what is currently known and unknown about the neural mechanisms underlying proactive and reactive inhibition. Third, background will be given on schizophrenia. Fourth, a brief overview is given of the experimental techniques that were used in this thesis to investigate the neural mechanisms underlying inhibitory control. The chapter will be concluded with an outline of this thesis.

## Experimental paradigms of inhibitory control

The concept of inhibition is widespread in neuroscience. In cellular neuroscience (or neurobiology), inhibition refers to 'the action of one neuron on another tending to prevent it from an impulse' (Lawrence, 2000). It is a readily observable process and therefore a widely accepted concept. In cognitive neuroscience (or psychology), inhibition refers to 'the blocking of one [cognitive] process by another' (Corsini, 2002). Here, the concept of inhibition is much less accepted. The main reason is that many cognitive forms of inhibition probably do not involve inhibitory processes (MacLeod et al., 2003). That is, they refer to interference effects that are explained in terms of inhibition, but that can also be explained in terms of non-inhibitory processes. One notable exception is the inhibition of voluntary movements, for which there is substantial evidence that cognitive inhibition reflects neuronal inhibition (Hanes et al., 1998; Paré and Hanes, 2003; Boucher et al., 2007; Lo et al., 2009). Therefore, the research presented in this thesis will focus on inhibitory control of voluntary movements.

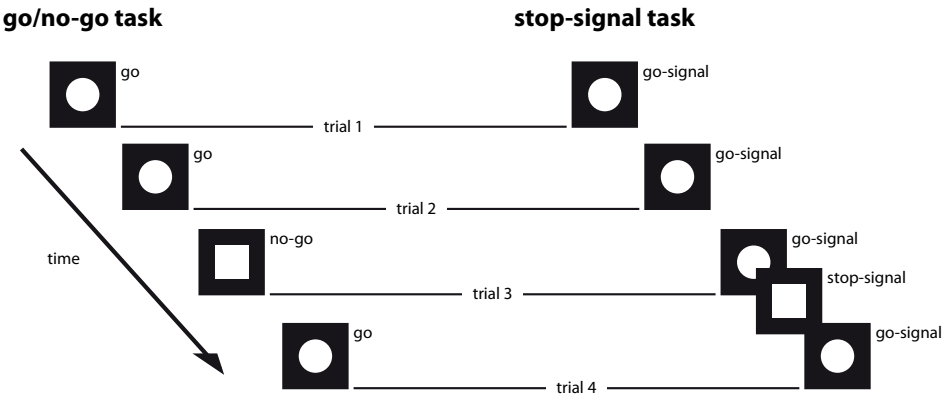



**Figure 1.** Graphic representation of a few trials in the go/no-go task (left) and the stop-signal task (right). The go/no-go task (left) consists of go trials (circles) and no-go trials (squares). The stop-signal task (right) consists of go-signal trials (circles) and stop-signal trials (circle followed by a square). In both tasks, a minority of trials (typically 20%-33%) are no-go or stop-signal trials.

Inhibitory control of voluntary movements has been investigated with a variety of experimental paradigms. The paradigms most frequently used are the go/no-go task (Donders, 1868) and the stop-signal task (Lappin and Eriksen, 1966; Verbruggen and Logan, 2008a) (Figure 1). In both tasks, participants are instructed to make speeded responses to go-signals (e.g. circles), but to refrain from responding to no-go or stop-signals (e.g. squares). The main difference between these tasks is that in the go/no-go task the instruction to inhibit a response occurs before an action is prompted, whereas in the stop-signal task it is given after an action is prompted. So, in the go/no-go task there is always only one stimulus per trial, whereas in the stop-signal task there may be two stimuli (Figure 1). Another difference between these tasks concerns the measurement of reactive inhibition: in the go/no-go task, the index of reactive inhibition is the number of responses to no-go signals (i.e. commission errors), whereas in the stop-signal task, the main index is the latency of the inhibition process, referred to as the stop-signal reaction time.

The stop-signal paradigm has some advantages over the go/no-go task. First, the stop-signal reaction time is relatively insensitive to variation in response speed (e.g. due to strategy or illness-related factors) (Logan and Cowan, 1984), whereas the inhibitory control index of the go/no-go task is not (i.e. slower responding results in a smaller number of no-go

commission errors, but it hardly influences the stop-signal reaction time). Second, the stop-signal task has been suggested to measure a controlled form of inhibition, whereas inhibition in the go/no-go task appears to be more automatic (Verbruggen and Logan, 2008b). For these reasons, we used the stop-signal paradigm to measure inhibitory control in the research presented in this thesis. Below, we will describe how proactive and reactive inhibition can be measured with the stop-signal paradigm.

*Measuring reactive inhibition in the stop-signal paradigm*

The stop-signal reaction time (SSRT) is the main index of reactive inhibition in the stop-signal paradigm and it reflects the latency of the inhibition process. Inhibition latency is defined as the interval between the presentation of a stop-signal and the actual inhibition of a response. However, the length of this interval cannot be measured directly, because, when a response is inhibited, there is no overt response that can be registered. Instead, inhibition latency can be estimated from the task performance data, using a theoretical model of reactive inhibition, called the race model (Logan and Cowan, 1984; Verbruggen and Logan, 2009a) (Figure 2A).

The race model was developed on the basis of two typical observations in the stop-signal paradigm. First, the probability of responding on a stop-signal trial, referred to as the response rate, depends on the delay between the go-signal and the stop-signal, known as the stop-signal delay (SSD). The relationship between the response rate and the SSD is depicted by the inhibition function (Figure 2B): the response rate is low when the SSD is short, but it increases progressively as the SSD becomes longer. In other words, stopping is easy when the stop-signal is presented shortly after the go-signal, but it becomes more difficult as the stop-signal is presented closer to the moment that a response is made. Second, responses on trials in which reactive inhibition fails are, on average, faster than responses on go-signal trials.

These observations have led to the idea that reactive inhibition performance in the stop-signal task can be understood in terms of a race between a 'go' process that facilitates the execution of response and a 'stop' process that inhibits the execution of a response. Whether or not a response can be inhibited is determined by the relative finishing times of these processes (Figure 2A): if the stop process finishes before the go process (i.e. go-signal response time > SSD + SSRT), inhibition is success-

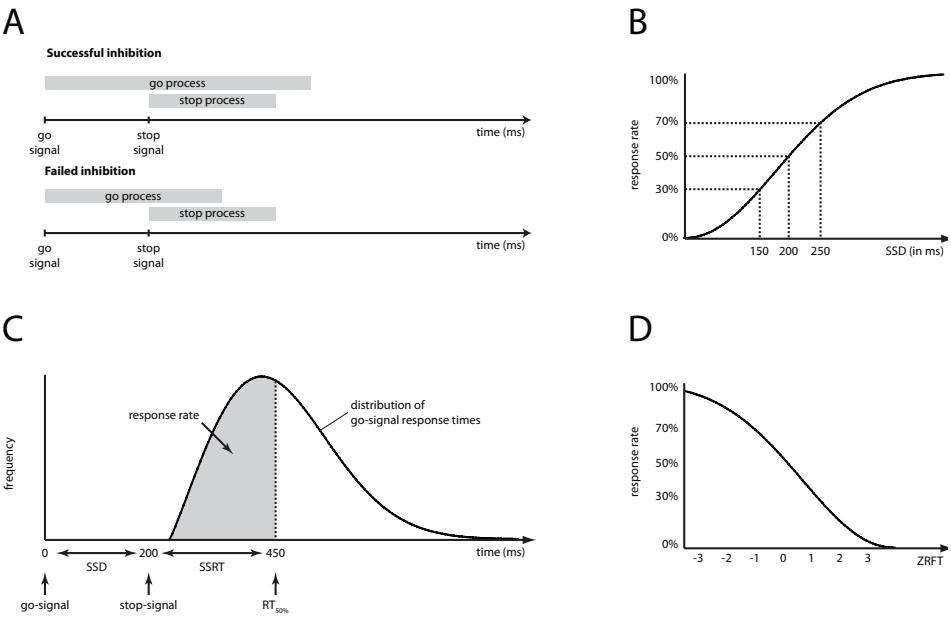



**Figure 2.** The race model of the stop-signal task. **(A)** Schematic of the race model idea. Inhibition is successful (top row) if the process that inhibits a response (stop process) is completed before the process that generates a response (go process). Inhibition fails (bottom row) if the process that inhibits a response (stop process) is completed after the process that generates a response (go process). **(B)** Inhibition function. The inhibition function plots the response rate (the probability of responding on a stop-signal trial) as a function of the stop-signal delay (SSD, the interval between presentation of the go-signal and stop-signal). It shows that inhibiting a response becomes more difficult as the stop-signal is presented closer to the moment that a response is made. **(C)** Graphic representation of the assumptions of the race model, showing how the response rate depends on the distribution of go-signal reaction times (solid graph), the stop-signal delay (SSD) and the stop-signal reaction time (SSRT). **(D)** Normalized inhibition function. The normalized inhibition function plots the response rate as a function of the Z-transformed stop-signal delays, which expresses them in Z-transformed relative finishing times (ZRFT). Positive ZRFT values represent early stop-signal onset, negative ZRFT values indicate late stop-signal onset.

ful and the response is suppressed; if the go process finishes before the stop process (i.e. go-signal response time < SSD + SSRT), inhibition fails and a response is executed.

To determine the SSRT, an estimate of the finishing time of the stop process is needed. The race model postulates that this finishing time can be estimated from the distribution of go-signal reaction times and the response rate on stop-signal trials by making two assumptions: 1) the go processes on go-signal trials and stop-signal trials are equal and 2) the SSRT is a constant. Under these assumptions, the SSRT can be estimated

by integrating the go-signal response time distribution and finding the point where the integral equals the response rate. This is illustrated in Figure 2C: if the response rate was 50% at a SSD of 200 ms, then the inhibition processes must have finished at the go-signal response time corresponding to the 50$^{th}$ percentile of the distribution of go-signal response times ($RT_{50\%}$), which is in this case 450 ms. So, in this example, the SSRT is equal to $RT_{50\%}$ - SSD = 450 - 200 ms = 250 ms.

Besides the SSRT, the race model provides another index of reactive inhibition, called the ZRFT slope. This index captures the variability in the stop process and can be estimated from the slope of the inhibition function. However, the slope of the standard inhibition function (Figure 2B) reflects variability in the go and stop processes together (Logan, 1994). To isolate variability associated with the stop process, the inhibition function has to be corrected (i.e. normalized) for variability related to the go process. To this aim, a Z-transformation is applied to the SSDs, which expresses them in terms of the relative finishing times (RFTs) of the go and stop processes, standardized with respect to variability in go-signal response time:

$$ZRFT = \frac{RT_{go-signal} - SSD - SSRT}{SD(RT_{go-signal})}$$

, where $RT_{go\text{-}signal}$ is the mean response time on go-signal trials, *SSD* is the stop-signal delay, *SSRT* is the stop-signal reaction time, and $SD(RT_{go\text{-}signal})$ is the standard deviation of response times on go-signal trials (Logan, 1994). This normalized inhibition function describes the response rate as a function of the relative finishing time (RFT) of the go and stop processes, expressed as a Z score (Figure 2D). The slope of this normalized inhibition function, called the ZRFT slope, is related to the variability in the stop process.

In Chapter 3 and 5, we will use these two indices to compare reactive inhibition between treatment conditions and demographic groups (i.e. schizophrenia patients, siblings, and healthy controls), respectively. Reduced (or enhanced) reactive inhibition is evidenced by a slower (or faster) SSRT or a flatter (or steeper) ZRFT slope relative to the control condition or group.

*Measuring proactive inhibition with the stop-signal task*

The standard stop-signal task (Lappin and Eriksen, 1966; Verbruggen and Logan, 2008a) described above is useful for investigating reactive inhibition, but is not suitable for the investigation of proactive inhibition. Proactive inhibition may be investigated with modified versions of this standard stop-signal task. In these tasks, anticipation of stopping is manipulated through variation of the probability that a stop-signal occurs (Vink et al., 2005b; Vink et al., 2006; Chikazoe et al., 2009; Verbruggen and Logan, 2009b; Jahfari et al., 2010). Proactive inhibition can be examined in terms of the effect of stop-signal probability on go-signal response time. Typically, the higher the stop-signal probability the longer participants wait with responding. However, the modified stop-signal tasks that have been used so far are not optimal for investigating the neural mechanisms of proactive inhibition.

First, in some studies, stop-signal probability was either 0% or 20% (Chikazoe et al., 2009; Jahfari et al., 2010). This is a problem, because these conditions not only differ in stop-signal probability but also in other aspects, for instance, the number of task goals that have to maintained (Verbruggen and Logan, 2009b). That is, the 20% condition involves two task goals (responding and stopping), whereas the 0% condition involves only one task goal (responding). This problem can be overcome by parametric modulation of stop-signal probability across several levels.

Second, some studies varied stop-signal probability across blocks of trials rather than from trial-to-trial (Logan and Burkell, 1986; Verbruggen and Logan, 2009b). Although this does not influence the degree of proactive slowing (Verbruggen and Logan, 2009b), such task designs limit the study of inhibitory control with functional MRI (Dale and Buckner, 1997; Liddle et al., 2001; Rubia et al., 2003; Culham, 2006), the method we used for mapping the neural mechanisms of proactive and reactive inhibition in this thesis.

Third, another set of studies varied stop-signal probability implicitly (Vink et al., 2005b; Vink et al., 2006), by manipulating the number of go-signal trials between two consecutive stop-signal trials. The disadvantages of this setup are that some participants may not be aware of this variation in stop-signal probability and that stop-signal probability always increased monotonously across trials. This issue may be resolved by cueing stop-signal probability explicitly and varying it randomly across trials.

Fourth, all studies of proactive inhibition to date have used standard (i.e. Lappin-Eriksen) stop-signal tasks. In these tasks, participants are instructed to respond as fast as possible to go-signals. However, it is well known that they tend to wait for the stop-signal (i.e. do not respond as fast as possible) to increase stopping success. These waiting strategies may confound SSRT estimation (Sylwan, 2004; Leotti and Wager, 2010) and the shape of the inhibition function (Tannock et al., 1989). This problem can be reduced with a Slater-Hammel version of the stop-signal paradigm (Slater-Hammel, 1960), in which a response has to be made at a certain point in time, rather than as quickly after the go-signal as possible.

Considering these issues, we developed a new variant of the stop-signal task, with which both proactive and reactive inhibition can be studied. This task, called the stop-signal anticipation task, is a Slater-Hammel version of the stop-signal task. In the stop-signal anticipation task, stop-signal probability is explicitly cued and is varied between trials in three or five steps. The stop-signal anticipation task will be described in detail in Chapters 2 and 4.

In Chapters 3 and 5, we compared proactive inhibition across treatment conditions and demographic groups, respectively. Reduced (or enhanced) proactive inhibition was defined as a decreased (or increased) effect of stop-signal probability on go-signal response time compared to the control condition or group.

### *Neural mechanisms of inhibitory control*

If we would like to understand the neural mechanisms underlying the inhibition of a voluntary movement, it is useful to consider the neural mechanisms involved in the generation of such a voluntary movement first. A voluntary movement is the result of a joint effort of a network of brain regions (Figure 3). This effort is organized hierarchically, that is, from an abstract plan to a concrete movement.

To illustrate this hierarchical organization of movement control, consider the classic textbook example of a baseball pitcher preparing to pitch to a batter (Bear et al., 2002). The pitcher's goal is to throw a pitch in the strike zone that the batter cannot hit. The prefrontal cortex is concerned with the representation of goals and the means to achieve them (Miller and Cohen, 2001). To achieve his goal, the pitcher can select from several options (e.g. curveball, knuckleball, screwball), of which he will select the

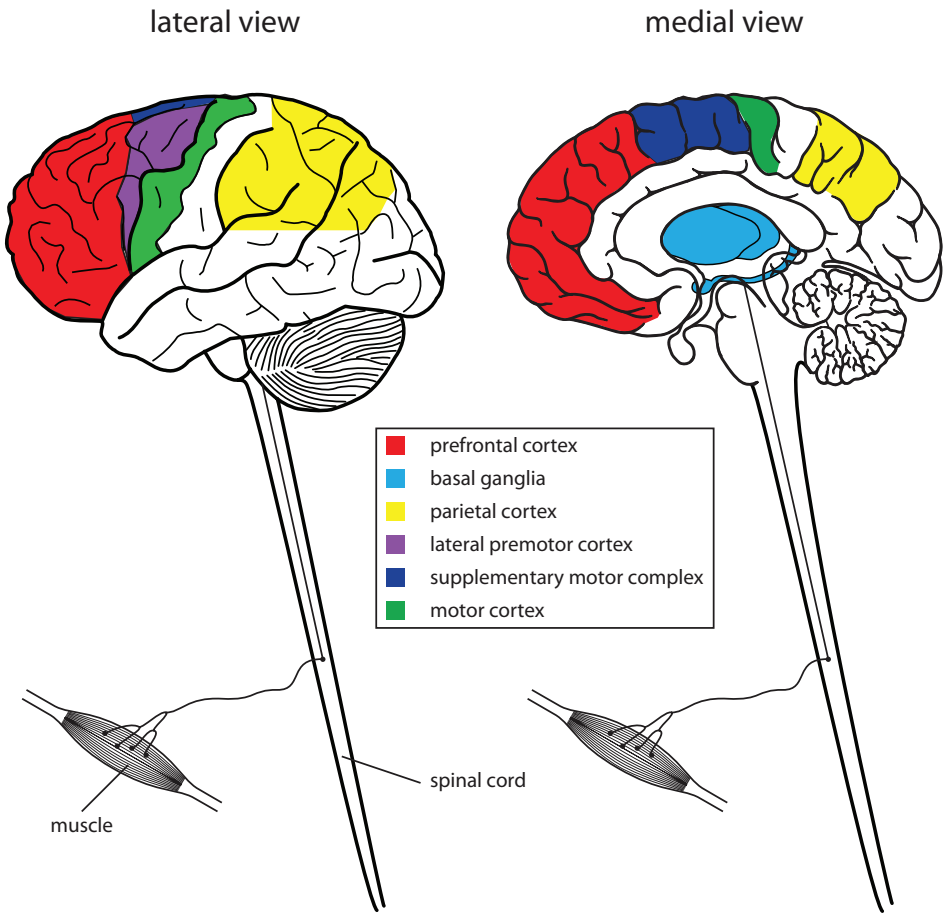



**Figure 3.** Graphic representation of brain regions involved in the generation and inhibition of voluntary movements, shown from a lateral view (left) and medial view (right).

one that most likely results in a positive outcome. The basal ganglia are concerned with the selection between alternative actions based on experience (Graybiel, 2005; Cohen and Frank, 2009). For a successful pitch, the pitcher should also have information about the position of his body in space relative to the position of the batter in terms of orientation and distance. Such a spatial representation is generated in the parietal cortex, based on information from visual, auditory and somatosensory areas of the brain (Colby and Goldberg, 1999). The desired action (e.g. curveball) should be translated into a detailed sequence of movements (e.g. stepping to the left, pivoting in, pitching). The lateral premotor cortex and

supplementary motor complex translate this action plan into a detailed sequence of movements (Hoshi and Tanji, 2007; Nachev et al., 2008). This information is sent to the primary motor cortex (M1) that produces the commands to generate each voluntary movement (Scott, 2003). The primary motor cortex issues commands via the brainstem to motor neurons in the spinal cord that innervate skeletal muscle fibers.

Thus, at the highest level of motor control are regions concerned with strategy (i.e. high-level planning), including the prefrontal cortex, the basal ganglia, and the parietal cortex. At an intermediate level of movement control are regions involved with tactics (i.e. low-level planning), consisting of the lateral premotor, the supplementary motor, and primary motor cortex. At the lowest level of movement control are structures involved with the execution of a voluntary movement, including the lower motor neurons in the spinal cord.

Like the generation of a voluntary movement, the inhibition of a voluntary movement is organized hierarchically and involves more or less the same brain regions. In the following, we will discuss what is known and unknown about the neural mechanisms of both reactive and proactive inhibition.

### *Neural mechanisms of reactive inhibition*

Converging lines of evidence suggest that M1 is the target of reactive inhibition and that a fronto-basal ganglia network is the source (Chambers et al., 2009; Stinear et al., 2009; Aron, 2010). This fronto-basal ganglia network includes the right inferior frontal cortex (rIFC) (Sasaki et al., 1989; Konishi et al., 1998; Aron et al., 2003; Swann et al., 2009; Verbruggen et al., 2010), the supplementary motor complex (SMC) (Floden and Stuss, 2006; Stuphorn and Schall, 2006; Chen et al., 2009; Chen et al., 2010; Sharp et al., 2010), and basal ganglia regions, such as the striatum (Eagle and Robbins, 2003; Rieger et al., 2003; Vink et al., 2005b; Chao et al., 2009; Watanabe and Munoz, 2010) and the subthalamic nucleus (STN) (Aron and Poldrack, 2006; van den Wildenberg et al., 2006; Eagle et al., 2008; Isoda and Hikosaka, 2008; Ballanger et al., 2009).

The precise role of these regions during reactive inhibition is not completely understood. The right IFC appears to be involved in the detection of the stop-signal (i.e. stimulus-driven attention) and replacing the action plan for responding by the action plan for stopping (i.e. action up-

dating) (Mars et al., 2007; Hampshire et al., 2010; Verbruggen et al., 2010). The SMC has also been implicated in updating (Shima et al., 1996) and seems further concerned with the modulation of activity in M1 (Chen et al., 2009; Chen et al., 2010), and the monitoring of response conflict (Ridderinkhof et al., 2004; Isoda and Hikosaka, 2007; Sharp et al., 2010) that is created by the co-activation of the opposing motor plans to respond and to inhibit a response. This response conflict might be resolved in conjunction with the basal ganglia. The basal ganglia, which include the striatum and the STN, are thought to be involved in selection between alternative actions (Cohen and Frank, 2009), such as responding and inhibition of responding. Moreover, the striatum and the STN have been implicated in the implementation of reactive inhibition, because as these structures can supress basal ganglia output, resulting in downstream inhibitory effects on the primary motor cortex (Vink et al., 2005b; Aron and Poldrack, 2006; Chambers et al., 2009). However, some studies suggest that reactive inhibition is implemented by the STN and that the striatum has no role in reactive inhibition (Aron and Poldrack, 2005; Aron and Poldrack, 2006). This issue will be investigated in Chapter 2.

Furthermore, how the regions of this fronto-basal ganglia network interact during reactive inhibition over M1 is a much debated, yet completely unresolved issue. There are at least three controversies about the functional organization of the network subserving reactive inhibition. First, the position of the right IFC and SMC with respect to one another is unclear. For example, there is evidence suggesting that right IFC influences M1 via the SMC (Duann et al., 2009; Hwang et al., 2010), but also for the idea that SMC influences M1 via the right IFC (Aron et al., 2007; Neubert et al., 2010). Second, within the basal ganglia, it is unclear whether reactive inhibition acts via the striatum (via the indirect pathway (Mink, 1996)), via the STN (via the hyperdirect pathway (Nambu et al., 2002)), or involves both basal ganglia structures. In principle, either pathway could mediate reactive inhibition (Chambers et al., 2009), but most studies have focused entirely on the reactive inhibition acting via the STN (Aron and Poldrack, 2006; Aron et al., 2007; Isoda and Hikosaka, 2008). Third, the necessary involvement of the basal ganglia in reactive inhibition has been questioned, given that several studies show that right IFC and SMC are capable to exert control over M1 directly, bypassing the basal ganglia (Mars et al., 2009; Buch et al., 2010). These controversies will be addressed in Chapter 3.

*Neural mechanisms of proactive inhibition*

Research on the neural network of proactive inhibition is still in its infancy. The few studies that have been conducted suggest that the regions involved in reactive inhibition also play a role in proactive inhibition. That is, M1 appears to be the target of proactive inhibition (Jahfari et al., 2010) and a network including the rIFC, the SMC, and the striatum seems to be the source (Vink et al., 2005b; Chikazoe et al., 2009; Jahfari et al., 2010).

The precise role of the rIFC, SMC, and the striatum in proactive inhibition remains to be explored. It has been suggested that these regions have identical roles during proactive and reactive inhibition and that the whole network underlying reactive inhibition is primed in anticipation of stopping (Chikazoe et al., 2009; Aron, 2010). This may indeed be true for the SMC and the striatum, as their roles during reactive inhibition (i.e. conflict monitoring and action selection) seem relevant during proactive inhibition, as well. However, it seems less likely that the rIFC is engaged in proactive inhibition, because the primary role of the rIFC in reactive inhibition appears to be the detection of the stop-signal and the initiation of the inhibition process (Verbruggen et al., 2010). Yet, proactive inhibition refers to situations in which inhibitory control is exerted in absence of a stop-signal. Nevertheless, previous studies reported rIFC activation during proactive inhibition (Chikazoe et al., 2009; Jahfari et al., 2010). It is important to note that these studies measured proactive inhibition as the effect of stop-signal probability on activation during go-signal trials, that is, during trials in which no stop-signals occur. Therefore, this activation may not only reflect expectation of a stop-signal (i.e. proactive inhibition) but also violation of that expectation because no stop-signal occurred. Indeed, the rIFC has been implicated in processes associated with violations of expectations (Arrington et al., 2000; Vossel et al., 2006; Shulman et al., 2009; Asplund et al., 2010). In Chapter 4, we will attempt to distinguish between these processes in order to isolate the proactive inhibition network.

## Schizophrenia

Schizophrenia is a severe and chronic brain disorder. It affects about 1% of the world's population (McGrath et al., 2008) and belongs to the most disabling and costly illnesses worldwide (Rössler et al., 2005). Schizophrenia is characterized by distortions of thought and perception, as well as

by social and occupational dysfunction. There is great diversity in clinical symptoms, course of the illness, and response to treatment, which has led to the view that schizophrenia is probably a mixture of disorders. The life expectancy of patients with schizophrenia is 12 to 15 years less than average (van Os and Kapur, 2009), primarily because of poor physical health (e.g. obesity, smoking), but also due to a higher suicide rate (Saha et al., 2007).

Schizophrenia has no single cause: both genetic and environmental factors contribute, probably in interaction with each other (van Os et al., 2008). Genetic factors contribute to about 80% of the vulnerability to schizophrenia. Multiple genes seem involved, each accounting for only a small increase in risk. Environmental factors associated with increased risk of developing schizophrenia include, among others, maternal infection, personal or family history of migration, and cannabis use (Tandon et al., 2008).

Schizophrenia has its clinical onset typically during late adolescence or early adulthood. Its clinical onset is marked by psychotic symptoms, such as hallucinations (false perceptions), delusions (persistent bizarre or irrational beliefs), and disorganized thought. These psychotic symptoms appear to be caused by hyperactivity of midbrain dopaminergic neurons (van Rossum, 1966; Davis et al., 1991; Howes and Kapur, 2009) and can be treated effectively in the majority of patients with antipsychotic medication. This medication blocks dopaminergic activity in one of the main projection areas of the midbrain dopaminergic system, the striatum (Creese et al., 1976; Seeman et al., 1976; Laruelle et al., 1996).

Besides the psychotic symptoms, schizophrenia is characterized by a general reduction in drive and volition, as evidenced by loss of motivation, lack of initiative, apathy and social withdrawal. These symptoms are largely treatment-resistant and become increasingly dominant over the course of the illness. It is thought that these symptoms originate from dysfunction of the prefrontal cortex (Andreasen et al., 1986; Weinberger, 1987; Goldman-Rakic and Selemon, 1997).

In addition to these clinical symptoms, schizophrenia is associated with impairments in numerous cognitive functions (Mohamed et al., 1999), including inhibitory control (Kiehl et al., 2000; Raemaekers et al., 2002; Vink et al., 2005a; Enticott et al., 2008). The central role of cognitive impairments in schizophrenia has been increasingly accepted (Elvevåg

and Goldberg, 2000; Nuechterlein et al., 2010), because cognitive impairments are relatively stable over time and clinical state (Rund, 1998; Hoff et al., 1999; Heaton et al., 2001) and also occur in relatives of patients (Sitskoorn et al., 2004; Snitz et al., 2006). Further, they are a critical determinant of quality of life (Green et al., 2000). Finally, cognitive impairments have been identified as potential targets for treatment of schizophrenia (Gold, 2004), and inhibitory control tasks have been recommended for the evaluation of treatment effects on cognition (Barch et al., 2009).

However, compared to deficits in other cognitive functions (e.g. working memory), the nature of inhibitory control impairments in schizophrenia is far from clear. First, not all studies have reported impaired inhibitory control in patients (e.g. Rubia et al., 2001; Badcock et al., 2002; Bellgrove et al., 2006; Kaladjian et al., 2007; Nishimura et al., 2011). Since studies have used a variety of inhibitory control tasks that differ in the type of inhibition they measure (Aron, 2007), it could be that some forms of inhibitory control are affected in schizophrenia, whereas others are not. No study to date, however, has compared proactive and reactive inhibition directly in schizophrenia. Second, the majority of inhibitory control studies in schizophrenia measured task performance only, meaning that the neural mechanisms underlying inhibitory control impairments in schizophrenia are largely unknown. There is some evidence implicating the striatum in proactive inhibitory control impairments in schizophrenia (Raemaekers et al., 2002; Raemaekers et al., 2006; Vink et al., 2006). Studies using go/no-go tasks suggest that prefrontal dysfunction may also be involved (Kiehl et al., 2000; Weisbrod et al., 2000), yet this dysfunction is often observed in association with normal behavioral inhibitory control (Rubia et al., 2001; Kaladjian et al., 2007; Nishimura et al., 2011). Third, very few studies included relatives of patients, although inclusion of this group could indicate whether inhibitory control deficits in schizophrenia are associated with the illness itself or with the risk for the illness. Fourth, impaired inhibitory control may reflect a more general deficit in executive functioning, possibly related to deficits in other domains, such as working memory (Roberts Jr. et al., 1994) or processing of contextual information (Servan-Schreiber et al., 1996). These issues will be addressed in Chapter 5.

## Methods

To study the neural mechanisms underlying proactive and reactive inhibition, we used functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS). The nuts and bolts of these techniques will be explained below.

### *Functional magnetic resonance imaging (fMRI)*

Functional MRI is a technique for mapping human brain function. Currently, it is the dominant measurement technique in the field of cognitive neuroscience (Friston, 2009). Compared to other measurement techniques in this field, the advantages of fMRI include its non-invasiveness (enabling application in humans), relatively high spatiotemporal resolution, whole-brain coverage (enabling to image the entire network of brain regions engaged in a cognitive task), and the wide availability of MRI scanners.

### *Equipment*

An MRI scanner consists of three main components: an electromagnet, a transmitter-receiver coil, and a set of gradient coils.

The electromagnet of an MRI scanner generates a strong, static magnetic field, typically 1.5 or 3 Tesla. The magnetic field must be strong to obtain sufficient signal from the body. This signal is obtained from hydrogen nuclei, which are abundant in our body. These hydrogen nuclei align with the magnetic field of the MRI scanner, just like a compass needle aligns with the earth's magnetic field. However, the strong magnetic field itself does not produce a signal that can be measured. For this, a transmitter-receiver coil is needed.

A transmitter-receiver coil consists of two electromagnetic coils: a transmitter coil and a receiver coil. When the transmitter coil is switched on, it generates electromagnetic waves. The energy of these waves is absorbed by the hydrogen nuclei in our body. As soon as the transmitter coil is switched off, the hydrogen nuclei release the absorbed energy, also in the form of electromagnetic waves. These electromagnetic waves are detected by the receiver coil and represent the magnetic resonance (MR) signal that is measured with MRI. Thus, the combination of a static magnetic field and a device to transmit and receive electromagnetic waves provides a means to obtain an MR signal. However, since the static magnetic field is uniform, the MR signal does not contain spatial information,

meaning that the source of the MR signal cannot be determined.

Gradient coils inside the MRI scanner provide a means by which the MR signal becomes spatially dependent, enabling localization. By applying a series of changing magnetic gradients (with the gradient coils) and oscillating electromagnetic waves (with the transmitter-receiver coil), the MR signal can be obtained from multiple locations to create an image of the object inside the scanner.

*How fMRI measures neural activity*

With fMRI, a series of brain images are taken while the participant performs a cognitive task inside the MRI scanner. The neural activity elicited by this task is measured indirectly with fMRI as changes in the level of blood-oxygen. That is, active brain regions have increased oxygen demands. The vasculature surrounding active brain regions responds to this increased oxygen demand by increasing the inflow of oxygen-rich blood. Oxygen in the blood is transported by hemoglobin. Importantly, whereas hemoglobin saturated with oxygen (oxyhemoglobin) has no influence on the magnetic field and the MR signal, the form of hemoglobin without oxygen (deoxyhemoglobin) disturbs the magnetic field and therefore decreases the MR signal. Thus, the inflow of oxygen-rich blood decreases the concentration of deoxyhemoglobin, which, in turn, increases in the MR signal. This increase in the MR signal is referred to as the blood-oxygen level-dependent (BOLD) or hemodynamic response. The hemodynamic response is sluggish and delayed, limiting the temporal resolution of fMRI (i.e. the ability to distinguish two brain responses in time) to the order of seconds (Menon and Kim, 1999). Furthermore, there is a mismatch between oxygen extraction (focal) and oxygen supply (regional), limiting the spatial resolution of fMRI (i.e. the ability to distinguish brain responses between different locations) to the order of millimeters (Malonek and Grinvald, 1996; Sirotin et al., 2009).

By comparing images taken during the performance of a certain cognitive function (e.g. successfully inhibiting a response) with images taken during a control condition in which this cognitive function was not performed (e.g. executing a response, or failing to inhibit a response), fMRI enables the mapping of brain regions that activate (or deactivate) concomitantly with a specific cognitive function.

### *Transcranial magnetic stimulation*

Although fMRI is an excellent technique for mapping human brain function, it cannot establish whether the contribution of a brain region to a cognitive function is crucial or more subsidiary (Robertson et al., 2003). This issue can be elucidated with transcranial magnetic stimulation (TMS). With TMS, neural activity can be perturbed and the effect of this perturbation can be measured on performance or brain activation (e.g. with fMRI). If a brain region is crucial for a certain cognitive function, then perturbation of activity in this region should affect that cognitive function. The advantages of TMS relative to other perturbation techniques include its noninvasiveness, the reversibility of the stimulation effect, and its excellent spatial and temporal resolution.

### *Equipment*

A TMS machine consists of two main components: a capacitor and a stimulation coil. The capacitor charged to a high voltage can be discharged, generating a large current in the connected stimulation coil. This pulse of current flowing through the stimulation coil generates a changing magnetic field (i.e. Faraday's principle of electromagnetic induction). The changing magnetic field induces an opposing current in any nearby conductor parallel to the stimulation coil. When held over the head, the stimulation coil generates an electric current in the brain.

### *How TMS perturbs neural activity*

The electrical current that TMS induces modifies neuronal activity in an area of about 4 by 3 cm at a depth of 2 cm under the stimulation coil (Walsh and Pascual-Leone, 2003). How this electrical current perturbs cognitive functioning is still unknown (Hoogendam et al., 2010). The most influential hypothesis is that the electrical current induced by TMS randomly excites neurons, adding noise into the neural processes of the stimulated area (Walsh and Cowey, 2000). The effect of stimulation on cognitive function (e.g. facilitation vs. disruption) appears to depend on a number of factors, including intensity, frequency, and duration of stimulation, as well as coil orientation, the brain region stimulated, and state of this brain region (Robertson et al., 2003; Sandrini et al., 2011). Since these factors interact in a complex manner that is not well understood, it is not possible to predict whether TMS will facilitate or disrupt a cognitive function.

In the research presented in this thesis, we used a TMS variant called repetitive TMS (rTMS) (Robertson et al., 2003). With rTMS, a brain region is stimulated with a series of pulses, typically for a period of 30 s to 30 min. Compared to single-pulse TMS, the effect of rTMS is more powerful and lasts longer, even beyond the period of stimulation (Iyer et al., 2003; Robertson et al., 2003). This latter feature enables the measurement of effects on brain activation with fMRI after rTMS (e.g. Lee et al., 2003; O'Shea et al., 2007).

## Outline of this thesis

The goal of this thesis is to increase the understanding of the neural mechanisms underlying proactive and reactive inhibition and how these mechanisms are affected in schizophrenia.

In Chapter 2, we focus on the role of the striatum in proactive and reactive inhibition. Several studies implicate the striatum in inhibitory control, whereas others have suggested that it is not involved. We employed fMRI activation and functional connectivity analyses to test hypotheses regarding the meaning of striatal activation during inhibitory control.

In Chapter 3, we concentrate on two other key components of the inhibitory control network, the rIFC and the SMC. We combined rTMS and fMRI to address two questions about the functional organization of the neural network underlying inhibitory control: the relative position of the rIFC and the SMC with respect to each other as well as the route through which rIFC and SMC exert control over M1.

In Chapter 4, we take a closer look at the neural mechanisms of proactive inhibition. Previous fMRI studies have suggested that the whole network activated during reactive inhibition is already activated in anticipation of stopping. However, no study measured proactive inhibition in isolation. In an attempt to delineate the neural network of proactive inhibition more precisely, we adjusted our stop-signal task so that we could investigate the effect of stop-signal probability on preparatory activation only, using fMRI.

In Chapter 5, we investigate proactive and reactive inhibition in schizophrenia. The nature of inhibitory control deficits in schizophrenia remains controversial; it is unclear to what extent proactive and reactive inhibition are affected, what the underlying neural mechanisms are, whether these deficits are related to the illness itself or to risk for the illness, and whether there is a relation with impairments in other executive functions. To this end, we used fMRI to compare proactive and reactive inhibition between schizophrenia patients, unaffected siblings of patients, and healthy controls. To compare inhibitory control performance with performance on other executive functions, we correlated indices of inhibitory control and working memory.

In Chapter 6, we summarize the main findings of the research presented in this thesis. Further, we discuss what these findings tell us about the neural mechanisms underlying proactive and reactive inhibition in health and how these mechanisms may be affected in schizophrenia. In addition, limitations of our studies are described and suggestions for future research are given.

## References

Andreasen N, Nasrallah HA, Dunn V, Olson SC, Grove WM, Ehrhardt JC, Coffman JA, Crossett JH (1986) Structural abnormalities in the frontal system in schizophrenia. A magnetic resonance imaging study. Arch Gen Psychiatry 43:136-144.

Aron AR (2007) The neural basis of inhibition in cognitive control. Neuroscientist 13:214-228.

Aron AR (2010) From Reactive to Proactive and Selective Control: Developing a Richer Model for Stopping Inappropriate Responses. Biol Psychiatry.

Aron AR, Poldrack RA (2005) The cognitive neuroscience of response inhibition: relevance for genetic research in attention-deficit/hyperactivity disorder. Biol Psychiatry 57:1285-1292.

Aron AR, Poldrack RA (2006) Cortical and subcortical contributions to stop signal response inhibition: role of the subthalamic nucleus. J Neurosci 26:2424-2433.

Aron AR, Fletcher PC, Bullmore ET, Sahakian BJ, Robbins TW (2003) Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. Nat Neurosci 6:115-116.

Aron AR, Behrens TE, Smith S, Frank MJ, Poldrack RA (2007) Triangulating a cognitive control network using diffusion-weighted magnetic resonance imaging (MRI) and functional MRI. J Neurosci 27:3743-3752.

Arrington CM, Carr TH, Mayer AR, Rao SM (2000) Neural mechanisms of visual attention: object-based selection of a region in space. J Cogn Neurosci 12 Suppl 2:106-117.

Asplund CL, Todd JJ, Snyder AP, Marois R (2010) A central role for the lateral prefrontal cortex in goal-directed and stimulus-driven attention. Nat Neurosci 13:507-512.

Badcock JC, Michie PT, Johnson L, Combrinck J (2002) Acts of control in schizophrenia: dissociating the components of inhibition. Psychol Med 32:287-297.

Ballanger B, van Eimeren T, Moro E, Lozano AM, Hamani C, Boulinguez P, Pellecchia G, Houle S, Poon YY, Lang AE, Strafella AP (2009) Stimulation of the subthalamic nucleus and impulsivity: release your horses. Ann Neurol 66:817-824.

Barch DM, Braver TS, Carter CS, Poldrack RA, Robbins TW (2009) CNTRICS final task selection: executive control. Schizophr Bull 35:115-135.

Barkley RA (1997) Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychol Bull 121:65-94.

Bear MF, Connors BW, Paradiso MA (2002) Brain control of movement. In: Neuroscience - Exploring the brain, 2nd Edition (Bear MF, Connors BW, Paradiso MA, eds). Philadelphia PA: Lippincott, Williams & Wilkins.

Bellgrove MA, Chambers CD, Vance A, Hall N, Karamitsios M, Bradshaw JL (2006) Lateralized deficit of response inhibition in early-onset schizophrenia. Psychol Med 36:495-505.

Boucher L, Palmeri TJ, Logan GD, Schall JD (2007) Inhibitory control in mind and brain: an interactive race model of countermanding saccades. Psychol Rev 114:376-397.

Braver TS, Gray JR, Burgess GC (2007) Explaning the many varieties of working memory variation: dual mechanisms of cognitive control. In: Variation in Working Memory (Conway A, Jarrold C, Kane M, Miyake A, Towse K, eds), pp 76-106. Oxford: Oxford University Press.

Buch ER, Mars RB, Boorman ED, Rushworth MFS (2010) A network centered on ventral premotor cortex exerts both facilitatory and inhibitory control over primary motor cortex

during action reprogramming. J Neurosci 30:1395-1401.
Chamberlain SR, Sahakian BJ (2007) The neuropsychiatry of impulsivity. Curr Opin Psychiatry 20:255-261.
Chamberlain SR, Blackwell AD, Fineberg NA, Robbins TW, Sahakian BJ (2005) The neuropsychology of obsessive compulsive disorder: the importance of failures in cognitive and behavioural inhibition as candidate endophenotypic markers. Neurosci Biobehav Rev 29:399-419.
Chambers CD, Garavan H, Bellgrove MA (2009) Insights into the neural basis of response inhibition from cognitive and clinical neuroscience. Neurosci Biobehav Rev 33:631-646.
Chao HHA, Luo X, Chang JLK, Li C-SR (2009) Activation of the pre-supplementary motor area but not inferior prefrontal cortex in association with short stop signal reaction time - an intra-subject analysis. BMC Neurosci 10:75.
Chen C-Y, Muggleton NG, Tzeng OJL, Hung DL, Juan C-H (2009) Control of prepotent responses by the superior medial frontal cortex. Neuroimage 44:537-545.
Chen X, Scangos K, Stuphorn V (2010) Supplementary Motor Area Exerts Proactive and Reactive Control of Arm Movements. J Neurosci 30:14657-14675.
Chikazoe J, Jimura K, Hirose S, Yamashita K-i, Miyashita Y, Konishi S (2009) Preparation to inhibit a response complements response inhibition during performance of a stop-signal task. J Neurosci 29:15870-15877.
Cohen MX, Frank MJ (2009) Neurocomputational models of basal ganglia function in learning, memory and choice. Behav Brain Res 199:141-156.
Colby CL, Goldberg ME (1999) Space and attention in parietal cortex. Annu Rev Neurosci 22:319-349.
Corsini RJ (2002) The dictionary of psychology. Psychology Press.
Creese I, Burt DR, Snyder SH (1976) Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. Science 192:481-483.
Crider A (1997) Perseveration in schizophrenia. Schizophr Bull 23:63-74.
Culham JC (2006) Functional neuroimaging: experimental design and analysis. In: Handbook of functional neuroimaging of cognition, 2nd Edition (Cabeza R, Kingstone A, eds), pp 53-82: MIT Press.
Dale AM, Buckner RL (1997) Selective averaging of rapidly presented individual trials using fMRI. Hum Brain Mapp.
Davis KL, Kahn RS, Ko G, Davidson M (1991) Dopamine in schizophrenia: a review and reconceptualization. Am J Psychiatry 148:1474-1486.
Donders FC (1868) Over de snelheid van psychische processen. In: Onderzoekingen gedaan in het Physiologisch Laboratorium der Utrechtse Hoogeschool, pp 92-120.
Duann J-R, Ide JS, Luo X, Li C-sR (2009) Functional connectivity delineates distinct roles of the inferior frontal cortex and presupplementary motor area in stop signal inhibition. J Neurosci 29:10171-10179.
Eagle DM, Robbins TW (2003) Inhibitory control in rats performing a stop-signal reaction-time task: effects of lesions of the medial striatum and d-amphetamine. Behav Neurosci 117:1302-1317.
Eagle DM, Baunez C, Hutcheson DM, Lehmann O, Shah AP, Robbins TW (2008) Stop-signal reaction-time task performance: role of prefrontal cortex and subthalamic nucleus.

Cereb Cortex 18:178-188.
Elvevåg B, Goldberg TE (2000) Cognitive impairment in schizophrenia is the core of the disorder. Crit Rev Neurobiol 14:1-21.
Enticott PG, Ogloff JR, Bradshaw JL (2008) Response inhibition and impulsivity in schizophrenia. Psychiatry Res 157:251-254.
Floden D, Stuss DT (2006) Inhibitory Control is Slowed in Patients with Right Superior Medial Frontal Damage. J Cogn Neurosci.
Friston KJ (2009) Modalities, modes, and models in functional neuroimaging. Science 326:399-403.
Gold JM (2004) Cognitive deficits as treatment targets in schizophrenia. Schizophr Res 72:21-28.
Goldman-Rakic PS, Selemon LD (1997) Functional and anatomical aspects of prefrontal pathology in schizophrenia. Schizophr Bull 23:437-458.
Graybiel AM (2005) The basal ganglia: learning new tricks and loving it. Curr Opin Neurobiol 15:638-644.
Green MF, Kern RS, Braff DL, Mintz J (2000) Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? Schizophr Bull 26:119-136.
Hampshire A, Chamberlain SR, Monti MM, Duncan J, Owen AM (2010) The role of the right inferior frontal gyrus: inhibition and attentional control. Neuroimage 50:1313-1319.
Hanes DP, Patterson WF, Schall JD (1998) Role of frontal eye fields in countermanding saccades: visual, movement, and fixation activity. J Neurophysiol 79:817-834.
Heaton RK, Gladsjo JA, Palmer BW, Kuck J, Marcotte TD, Jeste DV (2001) Stability and course of neuropsychological deficits in schizophrenia. Arch Gen Psychiatry 58:24-32.
Hoff AL, Sakuma M, Wieneke M, Horon R, Kushner M, DeLisi LE (1999) Longitudinal neuropsychological follow-up study of patients with first-episode schizophrenia. The American journal of psychiatry 156:1336-1341.
Hoogendam JM, Ramakers GMJ, Di Lazzaro V (2010) Physiology of repetitive transcranial magnetic stimulation of the human brain. Brain Stimulation 3:95-118.
Hoshi E, Tanji J (2007) Distinctions between dorsal and ventral premotor areas: anatomical connectivity and functional properties. Curr Opin Neurobiol 17:234-242.
Howes OD, Kapur S (2009) The dopamine hypothesis of schizophrenia: version III - the final common pathway. Schizophr Bull 35:549-562.
Hwang K, Velanova K, Luna B (2010) Strengthening of top-down frontal cognitive control networks underlying the development of inhibitory control: a functional magnetic resonance imaging effective connectivity study. J Neurosci 30:15535-15545.
Isoda M, Hikosaka O (2007) Switching from automatic to controlled action by monkey medial frontal cortex. Nat Neurosci 10:240-248.
Isoda M, Hikosaka O (2008) Role for subthalamic nucleus neurons in switching from automatic to controlled eye movement. J Neurosci 28:7209-7218.
Iyer MB, Schleper N, Wassermann EM (2003) Priming stimulation enhances the depressant effect of low-frequency repetitive transcranial magnetic stimulation. J Neurosci 23:10867-10872.
Jahfari S, Stinear C, Claffey M, Verbruggen F, Aron A (2010) Responding with restraint: what are the neurocognitive mechanisms? J Cogn Neurosci 22:1479-1492.
Kaladjian A, Jeanningros R, Azorin J-M, Grimault S, Anton J-L, Mazzola-Pomietto P (2007) Blunted activation in right ventrolateral prefrontal cortex during motor response inhi-

bition in schizophrenia. Schizophr Res 97:184-193.
Kiehl KA, Smith AM, Hare RD, Liddle PF (2000) An event-related potential investigation of response inhibition in schizophrenia and psychopathy. Biol Psychiatry 48:210-221.
Konishi S, Nakajima K, Uchida I, Sekihara K, Miyashita Y (1998) No-go dominant brain activity in human inferior prefrontal cortex revealed by functional magnetic resonance imaging. Eur J Neurosci 10:1209-1213.
Lappin JS, Eriksen CW (1966) Use of a delayed signal to stop a visual reaction-time response. J Exp Psychol 72:805-811.
Laruelle M, Abi-Dargham A, van Dyck CH, Gil R, D'Souza CD, Erdos J, McCance E, Rosenblatt W, Fingado C, Zoghbi SS, Baldwin RM, Seibyl JP, Krystal JH, Charney DS, Innis RB (1996) Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug-free schizophrenic subjects. Proc Natl Acad Sci USA 93:9235-9240.
Lawrence E (2000) Henderon's dictionary of biological terms, 12th Edition: Prentice Hall.
Lee L, Siebner HR, Rowe JB, Rizzo V, Rothwell JC, Frackowiak RS, Friston KJ (2003) Acute remapping within the motor system induced by low-frequency repetitive transcranial magnetic stimulation. J Neurosci 23:5308-5318.
Leotti LA, Wager TD (2010) Motivational influences on response inhibition measures. Journal of experimental psychology Human perception and performance 36:430-447.
Liddle PF, Kiehl KA, Smith AB (2001) Event-related fMRI study of response inhibition. Hum Brain Mapp.
Lo CC, Boucher L, Paré M, Schall JD, Wang XJ (2009) Proactive inhibitory control and attractor dynamics in countermanding action: a spiking neural circuit model. J Neurosci 29:9059-9071.
Logan G (1994) On the ability to inhibit though and action - a user's guide to the stop-signal paradigm. In: Inhibitory processes in attention, memory, and language (Dagenbach D, Carr TH, eds), pp 189-239. San Diego: Academic Press.
Logan GD, Cowan WB (1984) On the ability to inhibit thought and action: A theory of an act of control. Psychol Rev 91:291-327.
Logan GD, Burkell J (1986) Dependence and independence in responding to double stimulation. A comparison of stop, change, and dual-task paradigms. J Exp Psychol Hum Percept Perform 12:549-563.
MacLeod CM, Dodd MD, Sheard ED, Wilson DE, Bibi U (2003) In Opposition to Inhibition. In: The psychology of learning and motivation (Ross BH, ed), pp 163-214. San Diego: Elsevier Science.
Malonek D, Grinvald A (1996) Interactions between electrical activity and cortical microcirculation revealed by imaging spectroscopy: implications for functional brain mapping. Science 272:551-554.
Mars RB, Piekema C, Coles MGH, Hulstijn W, Toni I (2007) On the programming and reprogramming of actions. Cereb Cortex 17:2972-2979.
Mars RB, Klein MC, Neubert F-X, Olivier E, Buch ER, Boorman ED, Rushworth MFS (2009) Short-latency influence of medial frontal cortex on primary motor cortex during action selection under conflict. J Neurosci 29:6926-6931.
McGrath J, Saha S, Chant D, Welham J (2008) Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev 30:67-76.
Menon R, Kim S (1999) Spatial and temporal limits in cognitive neuroimaging with fMRI.

Trends Cogn Sci (Regul Ed) 3:207-216.

Miller EK, Cohen JD (2001) An integrative theory of prefrontal cortex function. Annu Rev Neurosci.

Mink JW (1996) The basal ganglia: focused selection and inhibition of competing motor programs. Prog Neurobiol 50:381-425.

Mohamed S, Paulsen J, O'leary D, Arndt S, Andreasen N (1999) Generalized Cognitive Deficits in Schizophrenia: A Study of First-Episode Patients. Arch Gen Psychiatry 56:749.

Nachev P, Kennard C, Husain M (2008) Functional role of the supplementary and pre-supplementary motor areas. Nature Reviews Neuroscience 9:856-869.

Nambu A, Tokuno H, Takada M (2002) Functional significance of the cortico-subthalamopallidal 'hyperdirect'pathway. Neurosci Res 43:111-117.

Neubert FX, Mars RB, Buch ER, Olivier E, Rushworth MF (2010) Cortical and subcortical interactions during action reprogramming and their related white matter pathways. Proc Natl Acad Sci U S A 107:13240-13245.

Nishimura Y, Takizawa R, Muroi M, Marumo K, Kinou M, Kasai K (2011) Prefrontal cortex activity during response inhibition associated with excitement symptoms in schizophrenia. Brain Res 1370:194-203.

Nuechterlein K, Green M, Kern R (2010) Schizophrenia as a Cognitive Disorder: Recent Approaches to Identifying its Core Cognitive Components to Aid Treatment Development. Advances in Schizophrenia ....

O'Shea J, Johansen-Berg H, Trief D, Göbel S, Rushworth MFS (2007) Functionally specific reorganization in human premotor cortex. Neuron 54:479-490.

Paré M, Hanes DP (2003) Controlled movement processing: superior colliculus activity associated with countermanded saccades. J Neurosci 23:6480-6489.

Peterson BS, Skudlarski P, Anderson AW, Zhang H, Gatenby JC, Lacadie CM, Leckman JF, Gore JC (1998) A functional magnetic resonance imaging study of tic suppression in Tourette syndrome. Arch Gen Psychiatry 55:326-333.

Raemaekers M, Ramsey NF, Vink M, al. e (2006) Brain Activation During Antisaccades in Unaffected Relatives of Schizophrenic Patients. Biol Psychiatry.

Raemaekers M, Jansma JM, Cahn W, Van der Geest JN, van der Linden JA, Kahn RS, Ramsey NF (2002) Neuronal substrate of the saccadic inhibition deficit in schizophrenia investigated with 3-dimensional event-related functional magnetic resonance imaging. Arch Gen Psychiatry 59:313-320.

Ridderinkhof K, Ullsperger M, Crone E, Nieuwenhuis S (2004) The Role of the Medial Frontal Cortex in Cognitive Control. Science 306:443.

Rieger M, Gauggel S, Burmeister K (2003) Inhibition of ongoing responses following frontal, nonfrontal, and basal ganglia lesions. Neuropsychology 17:272-282.

Roberts Jr. RJ, Hager LD, Heron C (1994) Prefrontal cognitive processes: working memory and inhibition in the antisaccade task. J Exp Psychol Gen 123:374-393.

Robertson EM, Théoret H, Pascual-Leone A (2003) Studies in cognition: the problems solved and created by transcranial magnetic stimulation. J Cogn Neurosci 15:948-960.

Rössler W, Joachim Salize H, van Os J, al. e (2005) Size of burden of schizophrenia and psychotic disorders. Eur Neuropsychopharmacol.

Rubia K, Smith AB, Brammer MJ, Taylor E (2003) Right inferior prefrontal cortex mediates response inhibition while mesial prefrontal cortex is responsible for error detection. Neuroimage 20:351-358.

Rubia K, Russell T, Bullmore ET, Soni W, Brammer MJ, Simmons A, Taylor E, Andrew C, Giampietro V, Sharma T (2001) An fMRI study of reduced left prefrontal activation in schizophrenia during normal inhibitory function. Schizophr Res 52:47-55.

Rund BR (1998) A review of longitudinal studies of cognitive functions in schizophrenia patients. Schizophr Bull 24:425-435.

Saha S, Chant D, McGrath J (2007) A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? Arch Gen Psychiatry 64:1123-1131.

Sandrini M, Umiltà C, Rusconi E (2011) The use of transcranial magnetic stimulation in cognitive neuroscience: a new synthesis of methodological issues. Neurosci Biobehav Rev 35:516-536.

Sasaki K, Gemba H, Tsujimoto T (1989) Suppression of visually initiated hand movement by stimulation of the prefrontal cortex in the monkey. Brain Res 495:100-107.

Scott SH (2003) The role of primary motor cortex in goal-directed movements: insights from neurophysiological studies on non-human primates. Curr Opin Neurobiol 13:671-677.

Seeman P, Lee TM, Chau-Wong M, Wong K (1976) Antipsychotic drug doses and neuroleptic/dopamine receptors. Nature.

Servan-Schreiber D, Cohen JD, Steingard S (1996) Schizophrenic deficits in the processing of context. A test of a theoretical model. Arch Gen Psychiatry 53:1105-1112.

Sharp DJ, Bonnelle V, De Boissezon X, Beckmann CF, James SG, Patel MC, Mehta MA (2010) Distinct frontal systems for response inhibition, attentional capture, and error processing. Proc Natl Acad Sci U S A 107:6106-6111.

Shima K, Mushiake H, Saito N, Tanji J (1996) Role for cells in the presupplementary motor area in updating motor plans. Proc Natl Acad Sci USA 93:8694-8698.

Shulman G, Astafiev S, Franke D, Pope D, Snyder A, Mcavoy M, Corbetta M (2009) Interaction of Stimulus-Driven Reorienting and Expectation in Ventral and Dorsal Frontoparietal and Basal Ganglia-Cortical Networks. J Neurosci 29:4392.

Sirotin YB, Hillman EMC, Bordier C, Das A (2009) Spatiotemporal precision and hemodynamic mechanism of optical point spreads in alert primates. Proc Natl Acad Sci USA 106:18390-18395.

Sitskoorn MM, Aleman A, Ebisch SJH, Appels MCM, Kahn RS (2004) Cognitive deficits in relatives of patients with schizophrenia: a meta-analysis. Schizophr Res 71:285-295.

Slater-Hammel AT (1960) Reliability, accuracy, and refractoriness of a transit reaction. Res Q 31:217-228.

Snitz BE, MacDonald AW, Carter CS (2006) Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: a meta-analytic review of putative endophenotypes. Schizophr Bull 32:179-194.

Stinear CM, Coxon JP, Byblow WD (2009) Primary motor cortex and movement prevention: Where Stop meets Go. Neurosci Biobehav Rev 33:662-673.

Stuphorn V, Schall JD (2006) Executive control of countermanding saccades by the supplementary eye field. Nat Neurosci 9:925-931.

Swann N, Tandon N, Canolty R, Ellmore TM, McEvoy LK, Dreyer S, DiSano M, Aron AR (2009) Intracranial EEG reveals a time- and frequency-specific role for the right inferior frontal gyrus and primary motor cortex in stopping initiated responses. J Neurosci 29:12675-12685.

Sylwan RP (2004) The control of deliberate waiting strategies in a stop-signal task. Braz J

Med Biol Res 37:853-862.

Tandon R, Keshavan MS, Nasrallah HA (2008) Schizophrenia, "just the facts" what we know in 2008. 2. Epidemiology and etiology. Schizophr Res 102:1-18.

Tannock R, Schachar RJ, Carr RP, Chajczyk D, Logan GD (1989) Effects of methylphenidate on inhibitory control in hyperactive children. J Abnorm Child Psychol 17:473-491.

van den Wildenberg WPM, van Boxtel GJM, van der Molen MW, Bosch DA, Speelman JD, Brunia CHM (2006) Stimulation of the subthalamic region facilitates the selection and inhibition of motor responses in Parkinson's disease. J Cogn Neurosci 18:626-636.

van Os J, Kapur S (2009) Schizophrenia. Lancet 374:635-645.

van Os J, Rutten BP, Poulton R (2008) Gene-environment interactions in schizophrenia: review of epidemiological findings and future directions. Schizophr Bull 34:1066-1082.

van Rossum JM (1966) The significance of dopamine-receptor blockade for the action of neuroleptic drugs. In: Neuro-psycho-pharmacology (H. B, ed), pp 321-329. Amsterdam: Excerpta Medica Foundation.

Verbruggen F, Logan GD (2008a) Response inhibition in the stop-signal paradigm. Trends Cogn Sci 12:418-424.

Verbruggen F, Logan GD (2008b) Automatic and controlled response inhibition: associative learning in the go/no-go and stop-signal paradigms. Journal of experimental psychology General 137:649-672.

Verbruggen F, Logan GD (2009a) Models of response inhibition in the stop-signal and stop-change paradigms. Neurosci Biobehav Rev 33:647-661.

Verbruggen F, Logan GD (2009b) Proactive adjustments of response strategies in the stop-signal paradigm. Journal of experimental psychology Human perception and performance 35:835-854.

Verbruggen F, Aron AR, Stevens MA, Chambers CD (2010) Theta burst stimulation dissociates attention and action updating in human inferior frontal cortex. Proc Natl Acad Sci USA 107:13966-13971.

Vink M, Ramsey NF, Raemaekers M, Kahn RS (2005a) Negative priming in schizophrenia revisited. Schizophr Res 79:211-216.

Vink M, Ramsey NF, Raemaekers M, Kahn RS (2006) Striatal dysfunction in schizophrenia and unaffected relatives. Biol Psychiatry 60:32-39.

Vink M, Kahn RS, Raemaekers M, van den Heuvel M, Boersma M, Ramsey NF (2005b) Function of striatum beyond inhibition and execution of motor responses. Hum Brain Mapp 25:336-344.

Vossel S, Thiel CM, Fink GR (2006) Cue validity modulates the neural correlates of covert endogenous orienting of attention in parietal and frontal cortex. Neuroimage 32:1257-1264.

Walsh V, Cowey A (2000) Transcranial magnetic stimulation and cognitive neuroscience. Nature Reviews Neuroscience 1:73-79.

Walsh V, Pascual-Leone A (2003) The nuts and bolts of TMS. In: Transcranial magnetic stimulation - a neurochronometrics of mind (Walsh V, Pascual-Leone A, eds), pp 39-64. Cambridge, MA: MIT Press.

Watanabe M, Munoz D (2010) Saccade Suppression by Electrical Microstimulation in Monkey Caudate Nucleus. J Neurosci 30:2700.

Weinberger DR (1987) Implications of normal brain development for the pathogenesis of schizophrenia. Arch Gen Psychiatry 44:660-669.

Weisbrod M, Kiefer M, Marzinzik F, Spitzer M (2000) Executive control is disturbed in schizophrenia: evidence from event-related potentials in a Go/NoGo task. Biol Psychiatry 47:51-60.

# On the role of the striatum in response inhibition

2

Bram B. Zandbelt, Matthijs Vink

*PLoS ONE 2010*

Stopping a manual response requires suppression of the primary motor cortex (M1) and has been linked to activation of the striatum. Here, we test three hypotheses regarding the role of the striatum in stopping: striatum activation during successful stopping may reflect suppression of M1, anticipation of a stop-signal occurring, or a slower response build-up. Twenty-four healthy volunteers underwent functional magnetic resonance imaging (fMRI) while performing a stop-signal paradigm, in which anticipation of stopping was manipulated using a visual cue indicating stop-signal probability, with their right hand. We observed activation of the striatum and deactivation of left M1 during successful versus unsuccessful stopping. In addition, striatum activation was proportional to the degree of left M1 deactivation during successful stopping, implicating the striatum in response suppression. Furthermore, striatum activation increased as a function of stop-signal probability and was to linked to activation in the supplementary motor complex (SMC) and right inferior frontal cortex (rIFC) during successful stopping, suggesting a role in anticipation of stopping. Finally, trial-to-trial variations in response time did not affect striatum activation. The results identify the striatum as a critical node in the neural network associated with stopping motor responses. As striatum activation was related to both suppression of M1 and anticipation of a stop-signal occurring, these findings suggest that the striatum is involved in proactive inhibitory control over M1, most likely in interaction with SMC and rIFC.

*We would like to thank Mariët van Buuren, Thomas Gladwin, Janna Marie Hoogendam and René Kahn for helpful comments on previous versions of the manuscript.*

## Introduction

The ability to stop a response is crucial in everyday life. The stop-signal paradigm (Logan and Cowan, 1984) provides a framework for investigating the processes underlying stopping. In this paradigm, go-signals requiring a response are infrequently followed by a stop-signal, indicating that the planned response should be stopped. Stopping performance depends on the outcome of an interactive race between a Go process (activated by the go-signal) building up to response threshold and a Stop process (activated by the stop-signal) that can inhibit the Go process (Boucher et al., 2007). The neural correlates of these Go and Stop processes have been found in the higher motor centers for eye movements (Hanes et al., 1998; Paré and Hanes, 2003), and such Go and Stop units are thought to be present in the primary motor cortex (M1) as well (Stinear et al., 2009).

Converging lines of evidence suggest that a fronto-basal ganglia network is involved in controlling such Go and Stop units (for review, see Chambers et al., 2009). The striatum, the main input station of the basal ganglia, is considered an important region for stopping. Specifically, functional neuroimaging studies observe increased striatum activation during successful versus unsuccessful stopping (Rubia et al., 2005; Vink et al., 2005; Aron and Poldrack, 2006; Boehler et al., 2010; Padmala and Pessoa, 2010), when comparing short to long stop-signal reaction times (Chao et al., 2009), and with a parametric increase in stop-signal probability (Vink et al., 2005; Vink et al., 2006). Meta-analyses of functional neuroimaging studies of response inhibition confirm that the striatum is commonly recruited during stopping (Aron and Poldrack, 2005; Chikazoe et al., 2007; Simmonds et al., 2008). Clinical populations characterized by striatum dysfunction have stopping impairments (Rubia et al., 1999; Gauggel et al., 2004; Menon et al., 2004; Vink et al., 2006; Woolley et al., 2008). Finally, striatum lesions cause stopping impairments in rats (Eagle and Robbins, 2003).

Three hypotheses have been put forward regarding the meaning of stopping-related activation of the striatum. First, it may reflect suppression of response-related M1 activation, as striatum activation and M1 deactivation co-occur with successful stopping (Vink et al., 2005; Aron and Poldrack, 2006). Second, it may indicate anticipation of a stop-signal occurring, given that striatum activation and response delaying in order to improve stopping performance co-occur with increasing stop-signal prob-

ability (Vink et al., 2005). Third, it may reflect a slower build-up of the Go process to response threshold, which would allow the Stop process sufficient time to cancel the response (Aron and Poldrack, 2006). We refer to these concepts as the response suppression, stop-signal anticipation, and response build-up hypotheses, respectively.

Here, we investigate the role of the striatum in stopping, testing the hypotheses outlined above with a novel stop-signal paradigm (Fig. 1), in which stop-signal probability was manipulated using a visual cue. This enabled the measurement of response strategy adjustments in anticipation of stop-signals. Furthermore, to constrain waiting strategies that may limit the validity of the stop-signal paradigm (Leotti and Wager, 2010), subjects were required to make timed rather than speeded responses (Slater-Hammel, 1960). We tested the hypotheses outlined above, using fMRI subtraction and psychophysiological interaction (PPI) analyses (Table 1). Specifically, we predict that if the striatum suppresses M1, striatum activation levels during successful stopping may be proportional to the amount of M1 deactivation. If the striatum is involved in stop-signal anticipation, then activation should increase as a function of stop-signal probability. It may very well be that the striatum signals the current context (i.e. stop-signal probability) to the cortex to guide behavior, for example, to enhance stop-signal monitoring by the right inferior frontal cortex (rIFC) and right temporoparietal junction (rTPJ) (Corbetta and Shulman, 2002) or to delay responding via the rIFC or the supplementary motor complex (SMC), as stimulation of these areas improves stopping performance by delaying responses (Sasaki et al., 1989; Stuphorn and Schall, 2006). We therefore predict that if the striatum is involved in stop-signal anticipation, striatum activation during successful stopping may be associated with activation in SMC, rIFC, and rTPJ. Finally, if striatum activation reflects response build-up speed, it should be proportional to response time on Go trials.

## Methods

### *Ethics statement*

This study was approved by the University Medical Center Utrecht ethics committee. All participants gave written informed consent according to procedures approved by this committee.

*Table 1. Hypotheses*

| | Stop-related activation of the striatum | Go-related activation of the striatum | Functional connectivity |
|---|---|---|---|
| Response suppression hypothesis | StopSuccess > StopFailure | - | Negative PPI of striatum with M1 for StopSuccess > StopFailure |
| Stop-signal anticipation hypothesis | StopSuccess > StopFailure | Parametric effect of stop-signal probability | Positive PPI of striatum with SMC, rIFC and rTPJ for StopSuccess > StopFailure |
| Response build-up hypothesis | StopSuccess > StopFailure | Parametric effect of response time | - |

M1, primary motor cortex; PPI, psychophysiological interaction; rIFC, right inferior frontal gyrus; SMC, supplementary motor complex;

### *Participants*

24 healthy volunteers (mean age 22.2 years, range 19 - 26; 18 females) participated in this study. All participants were right-handed, had normal or corrected-to-normal vision, and did report no history of neurological or psychiatric illness.

### *Stop-signal anticipation task*

Participants peformed the stop-signal anticipation task (Fig. 1), a paradigm based on the stop-signal task (Logan and Cowan, 1984; Vink et al., 2005) and Slater-Hammel task (Slater-Hammel, 1960; Coxon et al., 2007). Three horizontal lines displayed one above the other, the middle line located 4/5 of the distance from the lower to the upper line, formed the background that was displayed continuously throughout the task. On each trial, a bar moved at a constant speed from the lower line towards the upper line, reaching the middle line in 800 ms. The main task was to stop the bar as close to the middle line as possible, by pressing a button with the right thumb (i.e. Go trial). Thus, the target response time was

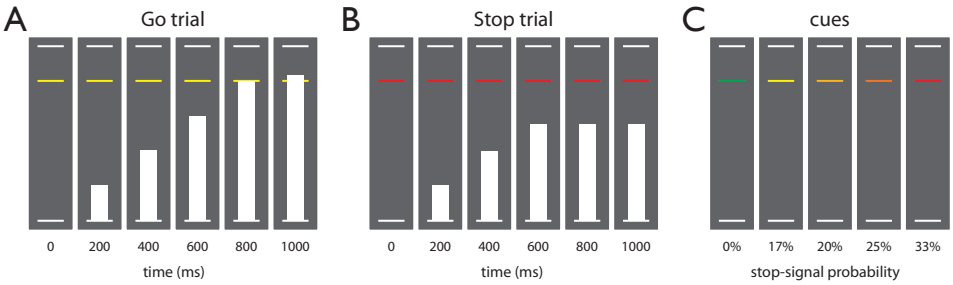



**Figure 1**. Schematic of the stop-signal anticipation task. Three horizontal lines formed the background displayed continuously during the task. **(A)** In each trial, a bar moved at constant speed from the bottom up, reaching the middle line in 800 ms. The main task was to stop the bar as close to the middle line as possible by pressing a button with the right thumb. These trials are referred to as Go trials. **(B)** In a minority of trials, the bar stopped moving automatically before reaching the middle line, indicating that a response had to be stopped. These trials are referred to as Stop trials. Stop-signal onset was adjusted in steps of 25 ms based on stopping performance, according to a 1-up-1-down staircase procedure (see Methods section). **(C)** The probability that a stop-signal would occur was manipulated across trials and was indicated by the color of the target response line. There were five stop-signal probability levels: 0% (green), 17% (yellow), 20% (amber), 25% (orange), and 33% (red).

800 ms. Stop trials were identical to Go trials, except that the bar stopped moving automatically before reaching the middle line, indicating that a response had to be suppressed (i.e. stop-signal). The probability that such a stop-signal would appear was manipulated across trials and could be anticipated on the basis of the color of the middle line (green, 0%; yellow, 17%; amber, 20%; orange, 25%; red, 33%).

The stop-signal onset time was initially set to 550 ms (i.e. 250 ms before the target response time) for all stop-signal probability levels. During the experiment, stop-signal onset time was adjusted (in steps of 25 ms) depending on stopping performance and for each stop-signal probability level separately. Specifically, if stopping was successful on the previous Stop trial, then stopping was made more difficult by shifting the stop-signal onset time 25 ms towards the target response time. The process was reversed when stopping failed. This ensures roughly equal numbers of successful and unsuccessful Stop trials.

Trials were presented in baseline and experimental blocks consisting of 12 to 15 trials, with an intertrial interval of 1000 ms. Baseline

blocks consisted of Go trials with stop-signal probability of 0%, indicated to the subject by green stop-signal probability cues. Experimental blocks contained Go trials with stop-signal probability > 0% (non-green cues) and Stop trials (non-green cues). Specifically, Stop trials were pseudorandomly interspersed between Go trials and stop-signal probability was manipulated across trials. We ran simulations prior to the experiment to determine the optimal trial order, such that correlations between the different model regressors was sufficiently low to allow for reliable estimation of parameter estimates. In total, 234 Go trials with stop-signal probability of 0%, 180 Go trials with stop-signal probability > 0% (yellow, n = 30; amber, n = 48; orange, n = 54; red, n = 48), and 60 Stop trials (yellow, n = 6; amber, n = 12; orange, n = 18; red, n = 24) were presented. Two rest blocks of 24 s each, displaying the background only, were implemented at one-third and two-thirds of the task, respectively. The total task duration was 16 m 36 s.

Participants were trained on the stop-signal anticipation task before the fMRI experiment. We instructed participants that the Go task and Stop task were equally important and that it would not always be possible to suppress a response when a stop-signal occurred. We informed participants that stop-signals would never appear on trials with a green cue and that stop-signals could occur on trials with non-green cues. Participants were told that stop-signals were least likely in the context of a yellow cue and most likely in the context of a red cue, with the amber and orange cues coding intermediate stop-signal probabilities.

*Image acquisition*

The experiment was performed on a 3.0 T Philips Achieva MRI scanner (Philips Medical Systems, Best, the Netherlands) at the University Medical Center Utrecht. Head motion was restricted using a vacuum cushion and foam wedges. Images were acquired using an eight-channel sensitivity-encoding (SENSE) parallel-imaging head coil. Whole-brain T2*-weighted echo planar images (EPI) with blood-oxygen level-dependent (BOLD) contrast (622 volumes; 30 slices per volume; interleaved acquisition; repetition time, 1600 ms; echo time, 23.5 ms; field of view: 256 x 208 mm; flip angle = 72.5˚; 64 x 51 matrix; 4 x 4 mm in-plane resolution; 4 mm slice thickness; SENSE-factor, 2.4 (anterior-posterior)) oriented in a transverse plane tilted 20˚ over the left-right axis were acquired in a single run.

The first six images were discarded to allow for T1 equilibration effects. A whole-brain three-dimensional fast field echo T1-weighted scan (150 slices; repetition time = 8.4 ms; echo time = 3.8 ms; flip angle = 8°; field of view, 288 x 252 x 185 mm; voxel size: 1mm isotropic) was acquired for within-subject registration purposes.

*Data analysis*

Behavioral data were analyzed using custom written software in Matlab 7 (Mathworks Inc., Natick, MA, USA). Response times (for Go) and accuracy were calculated for each stop-signal probability level separately. The stop-signal reaction time (SSRT) was calculated across all stop-signal probability conditions using the integration method (Verbruggen and Logan, 2009a). We also computed inhibition functions for each subject, depicting the proportion of Stop trials in which stopping succeeded for each stop-signal onset time (collapsed across stop-signal probability levels). Go trials with response times of more than 1.5 times the interquartile range away from the 25$^{th}$ and 75$^{th}$ percentiles of the response time distribution of each stop-signal probability level were defined as outliers.

Image data were preprocessed and analyzed using Statistical Parametric Mapping 5 (SPM5) software (http://www.fil.ion.ucl.ac.uk/spm/software/spm5/) running in Matlab 7 (Mathworks Inc., Natick, MA, USA). Images were converted from PAR/REC to NifTI-1 format. Functional images were corrected for differences in acquisition times across slices, resampling all slices in time relative to the fifteenth slice using Fourier interpolation. To adjust for head motion, functional images were registered to the mean image using 4th-degree B-spline interpolation (Friston et al., 1995). Estimated motion parameters were inspected to ensure that absolute motion over the course of the experiment did not exceed 4 mm and that the maximum image-to-image motion was never more than 1 mm. The anatomical image was co-registered to the mean functional image using the mutual information criteria method and segmented and normalized to the International Consortium for Brain Mapping template using linear and non-linear deformations (Ashburner and Friston, 1999, 2005). The normalization parameters were applied to the functional and anatomical images. Functional images were spatially smoothed using an 6-mm full-width at half-maximum Gaussian kernel. The T1-weighted images were skull-stripped using an automated brain extraction method (Smith, 2002).

Statistical analysis was performed within the framework of the general linear model and followed a two-level procedure. First-level statistical analysis involved modeling of StopSuccess, StopFailure, and Go trials with stop-signal probability > 0% (conditions of interest), as well as rest and outlier trials (conditions of no interest) for each subject. We also included two parametric regressors modeling response time and stop-signal probability level of Go trials. Post-hoc analyses revealed that the correlation between the parametric regressors was sufficiently low to enable reliable estimation of parameter estimates. Go trials with stop-signal probability of 0% were not explicitly modeled and therefore constituted an implicit baseline. Regressors were created by convolving delta functions coding for response time (or target response time for StopSuccess trials) with a canonical hemodynamic response function. We accounted for residual head motion effects by including the motion parameters from the realignment procedure into the statistical model. Time series statistical analysis was performed using restricted maximum likelihood. Low frequency drifts were controlled using a discrete cosine transform with cutoff of 128 s. Serial correlations in the fMRI signal were estimated using restricted maximum likelihood estimates of variance components using a first-order autoregressive model. The resulting non-sphericity was used to form maximum-likelihood estimates of the activations. Contrast images were generated for the comparisons (1) StopSuccess versus StopFailure, (2) StopSuccess verusus Go, (3) parametric effect of stop-signal probability on Go, and (4) parametric effect of response time on Go.

First-level contrast images were analyzed in a second-level random-effects analysis, using one-sample t-tests. Group statistical parametric maps were tested for significance using cluster-level inference (cluster-defining threshold, $P < 0.001$; cluster probability of $P < 0.05$, family wise error-corrected for multiple comparisons). Reported local maxima correspond to Montreal Neurological Institute space. Activations were localized according to anatomical landmarks identified from the mean T1-weighted structural image of all participants with the aid of a human brain atlas (Duvernoy, 1999) and a probabilistic atlas of human brain structures (Shattuck et al., 2008).

In an additional statistical analysis, we classified Go trials into eight different regressors according to stop-signal probability (17%, 20%, 25%, 33%) and response time bin (slow and fast). This analysis was conducted

to confirm the results from the parametric analysis of stop-signal probability and response time, as parametric modulators may have reduced statistical power (Grinband et al., 2008). First-level model construction and estimation was performed as described above. Contrast images were generated for each combination of stop-signal probability level and response time bin. They were entered into a second-level random effects full factorial analysis, to test the main effects of stop-signal probability and response time bin, as well as the interaction between these factors. In addition, we performed a region-of-interest analysis by extracting mean parameter estimates from four striatal regions (see Results) for all the contrast images. For each ROI, we performed a repeated-measures analysis of variance with stop-signal probability and reaction time bin as factors.

We investigated effective connectivity of the striatum in a psychophysiological interaction (PPI) analysis (Friston et al., 1997; Gitelman et al., 2003), testing for condition-specific (StopSuccess versus StopFailure) changes in coupling between the striatum and the rest of the brain that occurred over and above any main effects of context and striatal functional connectivity. A significant PPI entails a change in the slope of the regression of activity in a 'sink' region (e.g. left M1) onto activity in a 'seed' region (e.g. left striatum) from one condition (e.g. StopSuccess) to another (e.g. StopFailure). In the present analysis, a positive PPI indicates that the slope of the regression line is more positive in the StopSuccess condition as compared to the StopFailure condition, whereas a negative PPI indicates that this slope is more negative in the StopSuccess condition relative to the StopFailure condition. We performed PPI analyses using seed regions in the striatum, based on the local maxima from the one-sample t-test testing the contrast StopSuccess versus StopFailure (see Results section). For each subject and seed region, we extracted the first eigenvariate of the fMRI signal (adjusted for head motion) from a sphere with 8-mm radius centered around the local maximum. We obtained estimates of neural activity in this region by hemodynamic deconvolution using parametric empirical Bayes (physiological vector). The psychological vector was a delta function coding for onset times of StopSuccess (1) and StopFailure (-1) trials. We computed the PPI by taking the product of the physiological and psychological vectors at each point in time. The physiological, psychological and PPI vectors were then convolved with the

canonical hemodynamic response function and entered as regressors in a first-level general linear model. Similar to the standard first-level general linear model, correlations between the three regressors were low, enabling reliable estimation of parameter estimates. Time series statistical analysis was identical to that described above. A contrast image was created for the PPI. The contrast images of all participants were tested at the second level in a one-sample t-test to identify regions showing a positive PPI or negative PPI, again using cluster-level inference.

## Results

### *Behavior*

Response times on baseline Go trials (stop-signal probability of 0%) were close to the target response time of 800 ms (806 ms, 801 - 812 ms; mean, 95% C.I.), indicating that participants were able to perform the response task accurately. Response times on Go trials in which stop-signals could occur (829 ms, 821 - 837 ms; mean, 95% C.I.) were significantly higher than response times on baseline Go trials (paired t-test, $t(23) = 9.13$, $P < 0.001$). Moreover, response times increased linearly as a function of stop-signal probability (Fig. 2A; linear contrast, $F(1,23) = 29.07$, $P < 0.001$), suggesting that participants slowed responding according to the degree to which they anticipated stop-signals. This interpretation was confirmed by the finding that accuracy on Stop trials also increased linearly as a function of stop-signal probability (Fig. 2B; linear contrast, $F(1,23) = 44.86$, $P < 0.001$).

The SSRT was longer than usually reported (326 ms, 320 - 333 ms; mean, 95% C.I.). Nevertheless, the data were in agreement with assumptions of the race model (Logan and Cowan, 1984). First, stop rate decreased with later stop-signal onset (Fig 2C). Second, response times on StopFailure trials were faster than on Go trials in which stop-signals could occur (Fig. 2D; paired t-test, $t(23) = 7.43$, $P < 0.001$).

### *Functional MRI*

#### *Successful stopping versus failing to stop*

We first identified brain regions showing stopping-related activation by contrasting fMRI signals from StopSuccess and StopFailure trials (Table 1). Successful stopping significantly activated clusters in the left and right striatum (Fig. 3A) and both clusters were restricted to the putamen. The

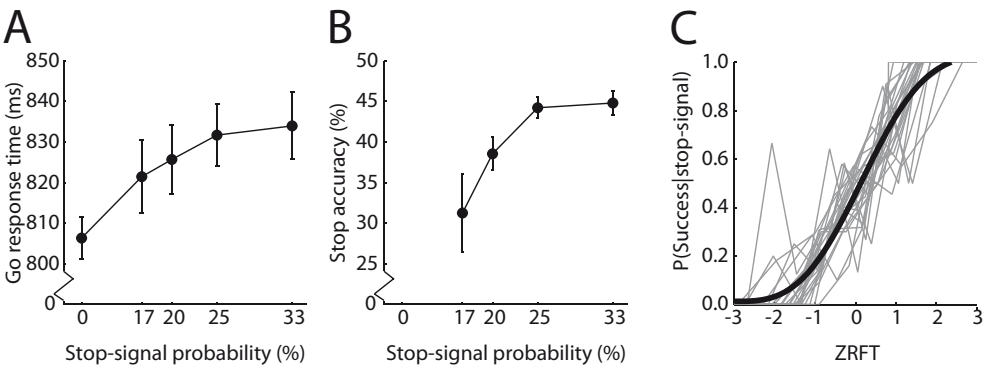



**Figure 2.** Stop-signal anticipation task performance. Stop-signal probability effects on **(A)** Go trial response time and **(B)** Stop trial accuracy. **(C)** Individual (grey) and group mean (black) normalized inhibition functions. The normalized inhibition function plots the proportion of successfully stopped responses as a function of the relative finishing times (RFT) of the stop and response processes, expressed as a Z-score (ZRFT). ZRFT was calculated as described in [1], collapsed across stop-signal probability levels. Positive ZRFT values represent early stop-signal onset, negative ZRFT values indicate late stop-signal onset. A cumulative Weibull function was fit to the group mean standardized inhibition function. **(D)** Mean response time on StopFailure trials and Go trials with stop-signal probability > 0%. Error bars indicate 95% confidence intervals.

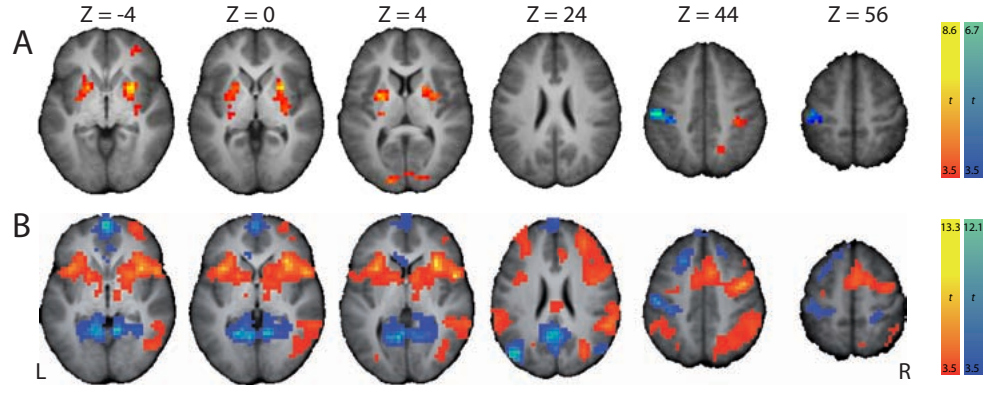



**Figure 3.** Brain regions with significant BOLD signal changes when contrasting **(A)** StopSuccess with StopFailure and **(B)** StopSuccess with Go trials with stop-signal probability of 0%. Warm colors represent activation during StopSuccess trials, cool colors represent deactivation during StopSuccess trials. Significant clusters of activation ($P < .05$, FWE-corrected) are displayed on the normalized and skull-stripped group-average brain (neurological orientation). L, left; R, right.

left and right striatum were also activated when contrasting StopSuccess trials and Go trials with stop-signal probability of 0% (Fig. 3B). Importantly, these findings support the notion that the striatum is involved in stopping a planned response. Other regions that were activated included occipital areas, the right supramarginal gyrus, and the right orbitofrontal cortex (StopSuccess > StopFailure), as well as the supplementary motor complex, right inferior frontal cortex, and bilateral temporoparietal junction (StopSuccess > Go stop-signal probability of 0%). The left sensorimotor cortex, including M1, was deactived during successful stopping, consistent with suppression of a right-hand response.

To further examine the role of the striatum in stopping, we analyzed condition-specific changes (StopSuccess > StopFailure and StopSuccess < StopFailure) in cortico-striatal effective connectivity and the influence of stop-signal anticipation and response speed on striatum activation during Go trials (Table 1). Stopping outcome-dependent changes in cortico-striatal effective connectivity were investigated in four psychophysiological interaction (PPI) analyses. The striatal seeds for these PPI analyses were based on the previous analysis testing for stopping-related activation (i.e. StopSuccess > StopFailure). Specifically, we selected the two most significant local maxima in the left striatum (-20 8 -4, left ventral putamen; -28 0 8, left dorsal putamen) and right striatum (28 8 -4, right ventral putamen; 20 4 12, right dorsal putamen).

*Response suppression hypothesis*

The co-occurrence of left M1 deactivation and bilateral activation of the striatum during successful versus unsuccessful stopping (Fig. 3A) does not necessarily mean that activation of the striatum is linked to deactivation of M1. We therefore performed a PPI analysis and found that activation of the left ventral putamen (-20 8 -4) during successful stopping was proportional to the level of deactivation in left M1 (Fig. 4A). Figure 5A shows this negative PPI in a representative subject. This result indicates that stronger activation of the left ventral putamen during successful stopping was associated with stronger deactivation of left M1. The other PPI analyses, seeded in the left dorsal and right ventral and dorsal putamen, did not show significant negative PPIs with left M1 (Fig. 4B-D). However, lowering the threshold (height, $P < .01$, uncorrected; extent, 5 voxels) revealed negative PPIs with left M1 for the left dorsal putamen and right

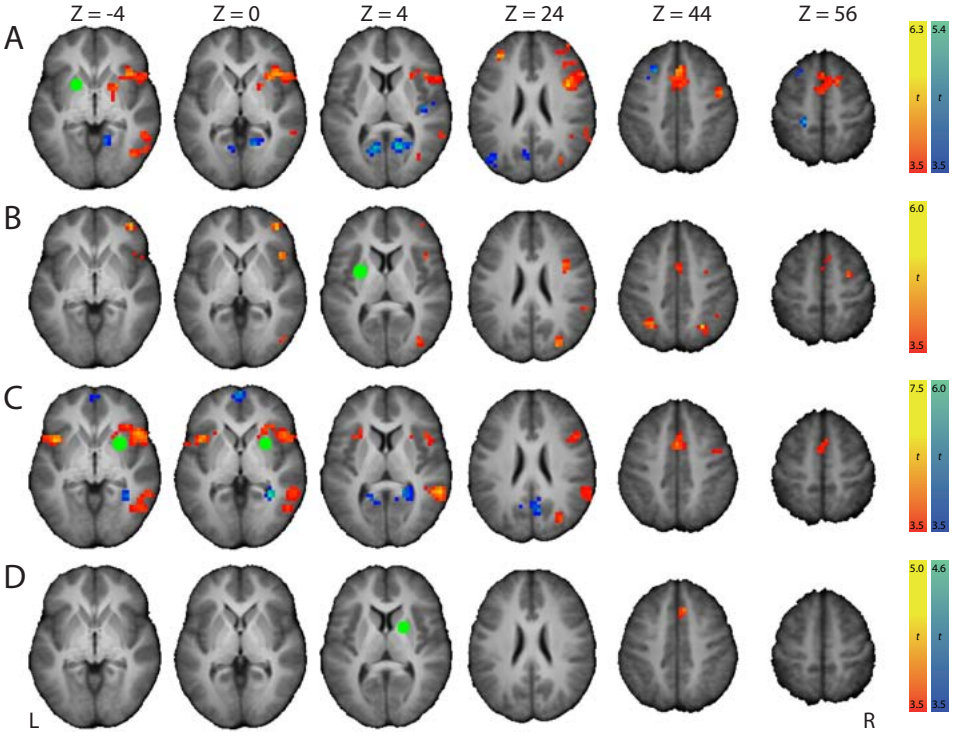



**Figure 4.** Brain regions with significant differences in coupling with the striatum as a function of Stop trial outcome (StopSuccess vs StopFailure). The statistical parametric maps shown are the result from four psychophysiological interaction (PPI) analyses, each for a different seed region in the striatum (shown as a green dot), defined as 8-mm spheres around the two most significant local maxima of the left and right striatum clusters of the StopSuccess vs StopFailure contrast, being **(A)** -20 8 -4, **(B)** -28 0 8, **(C)** 28 8 -4, and **(D)** 20 4 12. Warm colors indicate a positive PPI, cool colors indicate a negative PPI. Significant clusters of activation ($P < .05$, FWE-corrected) are displayed on the normalized and skull-stripped group-average brain (neurological orientation). L, left; R, right.

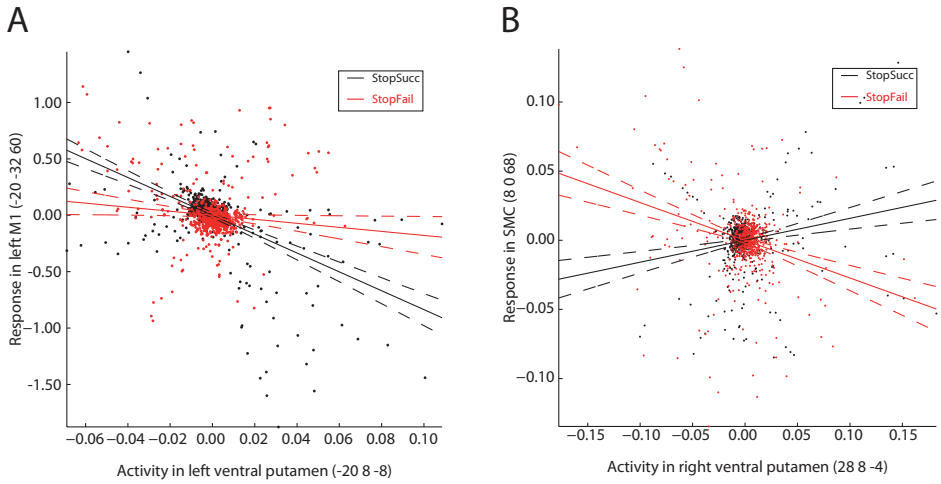



**Figure 5.** Example psychophysiological interaction (PPI) plots. **(A)** Example of a negative PPI between left ventral putamen and left primary motor cortex (M1) in one of the participants. **(B)** Example of a positive PPI between right ventral putamen and supplementary motor complex (SMC) in one of the participants. StopSucc, successful Stop trials. StopFail, unsuccessful Stop trials.

ventral putamen. These data provide indirect support for a role for the striatum in suppressing left M1 during successful stopping.

*Stop-signal anticipation hypothesis*

As indicated by the behavioral results, participants improved stopping performance through response slowing (i.e. anticipation). If the striatum is implicated in stop-signal anticipation, then we expect its activation to increase with stop-signal probability. This response slowing may be induced by modulation of activity in SMC and rIFC, as stimulation of these areas improved stopping performance by delaying responses (Sasaki et al., 1989; Stuphorn and Schall, 2006). If true, then striatum activation should show a stronger coupling with activation of SMC and rIFC during successful stopping (i.e. positive PPI), in which anticipation is at its maximum (Table 1).

Similar to the reaction time effect, we found a parametric effect of stop-signal probability on activation of a right anterior striatum cluster during Go trials, suggesting that right striatum activation reflects stop-signal anticipation (Fig. 6A). We did not observe a significant effect of stop-signal probability in the left striatum at the cluster level, but we did at a more liberal threshold (height, $P < .01$, uncorrected; extent, 5 voxels).

Interestingly, activation increased parametrically with stop-signal probability also in the rIFC and SMC, extending into the cingulate motor area and bilateral parietal regions. Given that the statistical model included a parametric regressor coding for Go response time (that had a low correlation with the stop-signal probability regressor, see Methods), these stop-signal anticipation-related activations were not confounded by trial-to-trial variations in response speed.

The PPI analyses showed that there was a significant positive coupling between striatum activation and activation of SMC, rIFC and a number of other cortical areas during successful stopping (Fig. 4A-D). We found the most pronounced effects for the right ventral striatum seed (Fig. 4C). Remarkably, this seed (28 8 -4) was close to the local maximum of the right striatum cluster (24 16 -4), showing a parametric effect of stop-signal probability on Go trial activation (Fig. 6A). Figure 5B shows the positive PPI between the right ventral putamen and the SMC in a representative subject. In an additional analysis, we tested for reverse PPIs with seeds in the SMC and rIFC. None of these PPI analyses showed a significant coupling with striatum activation during successful stopping. At a more liberal threshold (height, $P < .01$, uncorrected; extent, 5 voxels), however, there was a positive PPI between the SMC and left dorsal caudate and between the rIFC and right dorsal putamen. Together, these data indicate that striatum is involved in stop-signal anticipation.

*Response build-up hypothesis*

We already showed that the increased activation of the right striatum with stop-signal probability is not confounded by response time. However, there may be an effect of response time on left striatum activation. We therefore tested the response build-up hypothesis by assessing whether striatum activation on Go trials increases linearly with response time, while at the same time controlling for any effects of stop-signal anticipation (Table 1).

There were no significant effects of Go response time on striatum activation. In contrast, activation in left M1 and the left and right superior parietal lobule increased, whereas activation in anterior cingulate and right insula decreased as a function of response time (Fig. 6B). Even at a lower threshold (height, $P < .01$, uncorrected; extent, 5 voxels) there were no significantly activated clusters in the striatum.

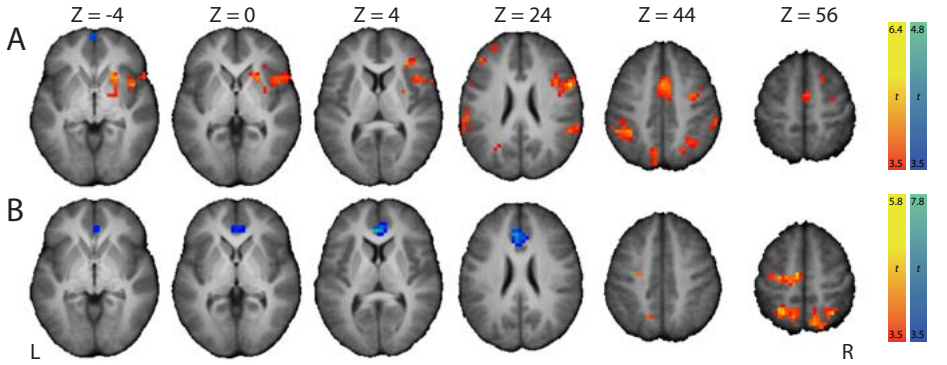



**Figure 6.** Brain regions with significant parametric effects of **(A)** stop-signal probability and **(B)** response time on the BOLD signal during Go trials. Significant clusters of activation (P < .05, FWE-corrected) are displayed on the normalized and skull-stripped group-average brain (neurological orientation). L, left; R, right.

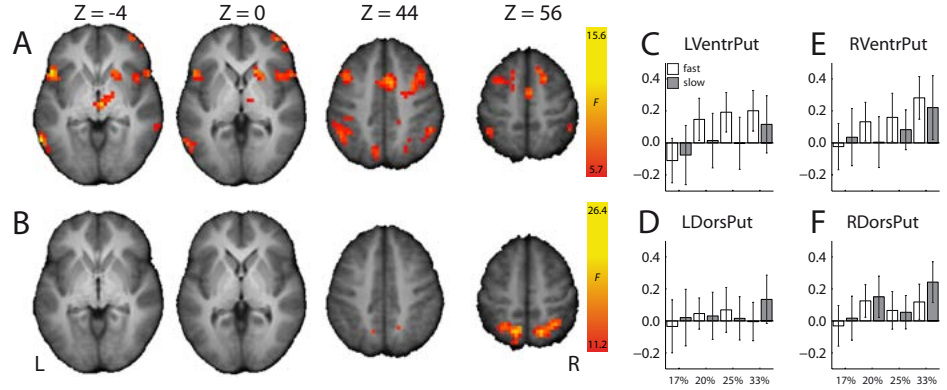



**Figure 7.** Results from the repeated-measures analysis of variance testing effects of stop-signal probability and response time bin on BOLD signal changes during Go trials. **(A)** Brain regions showing a significant main effect of stop-signal probability (17%, 20%, 25%, 33%) on BOLD signal changes during Go trials. **(B)** Brain regions showing a significant main effect of response time bin (fast, slow) on BOLD signal changes during Go trials. Significant clusters of activation (P < .05, FWE-corrected) are displayed on the normalized and skull-stripped group-average brain (neurological orientation). L, left; R, right. **(C-F)** Effects of stop-signal probability (horizontal axis) and response time bin (white, fast response times; grey, slow response times) on BOLD signal changes (vertical axis, arbitrary units) during Go trials in **(C)** left ventral putamen, **(D)** left dorsal putamen, **(E)** right ventral putamen, and **(F)** right dorsal putamen.

To address the possibility that this null finding reflects a lack of statistical power associated with parametric modulators (Grinband et al., 2008), we performed an additional analysis. In this analysis, Go trials were classified according to stop-signal probability (17%, 20%, 25%, 33%) and response time bin (slow and fast). We investigated the main effects of stop-signal probability and response time bin and the interaction between the two in a whole-brain voxel-wise analysis and in a region-of-interest (ROI) analysis. The ROIs were the four spheres that were used as seeds in the PPI analyses. The whole-brain voxel-wise analyses revealed significant main effects of stop-signal probability (Fig. 7A) and response time (Fig. 7B). The network activated for each of these main effects was strikingly similar to the network activated in the parametric analyses testing for stop-signal probability and response time (Fig. 6). Again, there were no striatal clusters showing a significant effect of response time. Note that the left M1 cluster that reached significance in the parametric analysis, did not reach significance in the additional repeated-measures analysis ($P = .065$). There were also no clusters showing a stop-signal probability by response time interaction effect on activation. The ROI analyses (Fig. 7C-F) revealed that none of the striatum clusters showed a main or interaction effect of response time (all $P > .12$). However, there was a significant effect of stop-signal probability on activation in the left ventral putamen ($F(2.9,67.2) = 3.52$, $P = .02$) and the right ventral and dorsal putamen ($F(2.6,59.6) = 3.60$, $P = .02$ and $F(2.3,53.5) = 3.37$, $P = .04$). These findings replicate those from the parametric effect of stop-signal probability and extend them by showing also an effect in the left ventral striatum. Collectively, these findings indicate that striatum activation during successful stopping unlikely reflects a difference in response build-up speed between successful and unsuccessful stopping.

## Discussion

This study examined the role of the striatum in stopping using functional MRI. Based on previous findings, we hypothesized that striatum activation during successful stopping could reflect either suppression of the primary motor cortex (M1), anticipation of a stop-signal occurring, or a slower response build-up (Table 1). We used a stop-signal paradigm, in which stop-signal anticipation was manipulated using a visual cue indicating stop-signal probability. As expected, Go response time increased

as a function of stop-signal probability (Fig. 2), confirming earlier findings (Ramautar et al., 2004; Vink et al., 2005; Vink et al., 2006; Verbruggen and Logan, 2009b).

The present findings provide support for the response suppression hypothesis. We observed bilateral activation of the striatum and deactivation of left M1 during successful versus unsuccessful stopping (Fig. 3A), in line with previous reports (Rubia et al., 2005; Vink et al., 2005; Aron and Poldrack, 2006; Boehler et al., 2010; Padmala and Pessoa, 2010). Moreover, the degree of left M1 deactivation during successful stopping was proportional to activation of the left striatum (Fig. 4A). Note that the rIFC and SMC were not activated in this contrast, corroborating others (Vink et al., 2005; Aron and Poldrack, 2006; Cai and Leung, 2009; Padmala and Pessoa, 2010). Perhaps, timing of activity rather than activation level dissociates successful from unsuccessful stopping in these regions.

The stop-signal anticipation hypothesis was also confirmed by our findings. Our finding of striatal activation during successful stopping (Fig. 3) is in accordance with results from studies using a standard stop-signal task, but in which stop-signal occurrence was nonetheless predictable. For example, striatal activation during successful stopping was observed by Aron & Poldrack (2006), who presented a stop-signal once in every four trials, and by Vink et al. (2005; 2006), who manipulated the number of Go trials between two consecutive Stop trials. Furthermore, activation of the right striatum increased with the probability of having to stop (Fig. 6A), in line with our previous findings (Vink et al., 2005; Vink et al., 2006). We extended these initial observations by showing that not only the striatum was activated as a function of stop-signal probability, but almost the complete network associated with stopping (Garavan et al., 1999; Aron and Poldrack, 2006), including the supplementary motor complex (SMC), right inferior frontal cortex (rIFC), anterior cingulate cortex, and bilateral parietal regions. Furthermore, a recent study investigating preparation of inhibition, by comparing activation related to “uncertain” go signals (i.e. those infrequently followed by a stop-signal) with “certain” go signals, also found activation of the SMC and rIFC (Chikazoe et al., 2009). These findings suggest that regions commonly associated with outright stopping are in fact also activated during preparation for stopping. In addition, our psychophysiological interaction (PPI) analyses showed that ac-

tivation of the striatum during successful versus unsuccessful stopping was positively coupled with activation in SMC and rIFC (among other regions) (Fig. 4), providing indirect evidence suggesting that the striatum induces response slowing for improved stopping performance. The reverse PPI, testing whether SMC and rIFC activation during successful stopping was positively coupled with the striatum, was not significant, in line with PPI findings from Duann et al. (2009). Note that the absence of a change in coupling in the reverse PPI is not necessarily odd, because PPIs are not symmetrical (i.e. regression of the interaction between activity in area 1 and context A onto the time series of area 2 is not equal to regression of the interaction between activity in area 2 and context A onto the time series of area 1) (Stephan, 2004).

Our results are not consistent with the response build-up hypothesis, proposed by Aron and Poldrack (2006). They argue that striatum activation during successful versus unsuccessful stopping reflects a faster Go response build-up during unsuccessful Stop trials, making it more difficult to inhibit a response. As there is no overt response during successful Stop trials, a direct comparison between successful and unsuccessful Stop trials based on response build-up speed is not possible. Therefore, they tested this hypothesis indirectly by contrasting unsuccessful Stop trials with Go trials with matched response times. They found no striatum activation and interpreted this as showing that response build up is faster during unsuccessful than successful Stop trials. However, in doing so they may also have matched for low stop-signal anticipation (see Fig. 2A). That is, a lack of anticipation probably results in failing to stop. Here, we tested the response build-up hypothesis directly by assessing the parametric effect of Go response time on neural activation. Striatum activation did not increase as a function of response time, but activation of left M1 and left and right superior parietal lobe did (Fig. 6B). This is in line with findings from a study showing that anticipatory response slowing is more likely to be explained by active braking of M1 corticospinal neurons than a slower response build-up (Jahfari et al., 2010). We therefore conclude that striatum activation unlikely reflects an index of response slowing.

Taken together, the present findings indicate that the striatum is a critical node in the neural network associated with stopping planned

responses: the data support a role for the striatum in suppression of M1 and anticipation of a stop-signal occurring. Suppression of M1 corticospinal neurons not only occurs after a stop-signal is presented (i.e. reactive inhibitory control) (Coxon et al., 2006; van den Wildenberg et al., 2010), but also before presentation of a stop-signal (i.e. proactive inhibitory control) (Lo et al., 2009; Jahfari et al., 2010). Such a distinction between reactive and proactive mechanisms not only holds for inhibitory control. In fact, a recent influential theory (Braver et al., 2007), termed the dual mechanisms of control (DMC) account, postulates that cognitive control in general varies along a reactive-proactive continuum. Specifically, proactive control serves an early selection mechanism that can be activated by predictive contextual cues as well as by endogenous signals. It involves anticipation and prevention of interference before it occurs. On the other hand, reactive control can be thought of as a late correction mechanism, triggered by interfering stimuli (e.g. a stop-signal). It relies on stimulus detection and interference resolution. In the following, we will discuss how the striatum may play a role in reactive and proactive inhibitory control.

It is generally agreed that the basal ganglia are important for reactive inhibitory control, but most studies link this function to the subthalamic nucleus rather than the striatum. Foremost, cortical signals conducted via the STN (i.e. via the hyperdirect pathway) reach the basal ganglia output nuclei faster than signals conducted via the striatum (i.e. via the direct and indirect pathways) (Nambu et al., 2002), making the hyperdirect pathway through the STN a stronger candidate for reactive inhibitory control (Aron and Poldrack, 2006). Other findings implicating the STN in reactive inhibitory control include a relation between shorter stop-signal reaction times (SSRT, a measure of reactive inhibitory control) and stronger STN activation in functional neuroimaging studies (Aron and Poldrack, 2006; Aron et al., 2007), longer SSRTs after lesioning the STN in rodents (Eagle et al., 2008), and shorter SSRTs during deep-brain stimulation of the STN in Parkinson's disease patients (van den Wildenberg et al., 2006). Finally, STN activity associated with reactive inhibitory control occurs early enough to influence movements (Isoda and Hikosaka, 2008). However, the advantage of signal conduction via the STN over signal conduction via the striatum in terms of time (~ 22 ms) is small relative to the SSRT (which

is typically 200-250 ms) (Chambers et al., 2009). Furthermore, striatum activation has also been associated with short SSRTs (Chao et al., 2009). Also, as Robbins (2007) points out, lesions of the striatum impact SSRT performance more selectively than STN lesions do (Eagle and Robbins, 2003; Eagle et al., 2008). Finally, functional neuroimaging studies observe striatum activation, but no STN activation, during successful versus unsuccessful stopping (Vink et al., 2005; Aron and Poldrack, 2006). If inhibition of M1 acts via the striatum, it probably depends upon the indirect pathway that competes with the direct pathway in a push-pull fashion to adjust the amount of inhibitory activity in the basal ganglia output nuclei to brake or facilitate cortically initiated actions, respectively (Alexander and Crutcher, 1990; Graybiel, 2000; Frank, 2005). Although these results implicate the striatum in reactive inhibitory control, the evidence is at best indirect. More direct evidence, showing that activity in the striatum during successful Stop trials modulates before SSRT (De Jong et al., 1990; Hanes et al., 1998; Paré and Hanes, 2003) is lacking.

The role of the striatum in inhibitory control may be much more proactive. Indeed, neurophysiological findings in monkeys implicate striatal neurons in prospective coding of future events, possibly reflecting outcome-oriented behavioral modulation (Blazquez et al., 2002; Lauwereyns et al., 2002; Yamada et al., 2007). This is consistent with data from our previous studies, showing that striatum activation was associated with proactive adjustments of response strategies, such as response slowing to improve stopping performance (Vink et al., 2005; Vink et al., 2006). The striatum exerts its proactive control possibly by modulating the response threshold in M1 (Lo and Wang, 2006; Forstmann et al., 2008; Jahfari et al., 2010). Based on our data, we suggest that this modulation may occur via SMC or rIFC, or both. First, in addition to a coupling between left striatum activation and left M1 deactivation, we found a positive coupling between the striatum and the SMC, and between the striatum and the rIFC. Second, the most significant local maxima in the striatum during stop-signal anticipation and successful stopping (which were used as seeds in the PPI analysis) were located in the anterior putamen. This part of the striatum mediates the cortico-basal ganglia loops through SMC and rIFC. In contrast, we did not find an effect of stop-signal probability in the the posterior part of the putamen that conveys cortico-basal ganglia loops through the primary and premotor cortices (Lehéricy et al., 2004a; Lehéricy et al.,

2004b; Leh et al., 2007; Draganski et al., 2008). Third, the striatum modulating activity in M1 via SMC or rIFC, rather than SMC or rIFC modulating activity in M1 via the striatum would also be consistent with two recent paired-pulse TMS studies, showing that SMC and rIFC can exert inhibitory control over M1 directly (Mars et al., 2009; Buch et al., 2010). We speculate that the striatum signals the current context to the cortex to guide behavior, for example, to enhance monitoring of the stop-signal by the rIFC and rTPJ (Corbetta and Shulman, 2002) or to induce response time adjustments via the rIFC and SMC, given that stimulation of these areas improves stopping performance by response slowing (Sasaki et al., 1989; Stuphorn and Schall, 2006). Note that the striatum may signal the cortex not only through cortico-basal ganglia loops. Since the striatum harbors the main input to the midbrain dopamine neurons (Haber et al., 2000), it may also modulate the dopaminergic projections to the cortex. In sum, our data together with the studies discussed above suggest that the striatum is involved in proactive inhibitory control and possibly modulates activity in M1 via SMC and rIFC.

A potential caveat of this study is that PPI analyses are limited in drawing conclusions about the interactions between brain regions in complex neural networks (Friston et al., 1997; Stephan, 2004). For instance, it is impossible to determine whether the contribution of one area (e.g. left striatum) onto another (e.g. left M1) is direct, whether the contribution acts via a third structure (e.g. SMC), or whether a third structure (e.g. right orbitofrontal cortex) provides condition-specific input to the two areas (e.g. left striatum and left M1) implicated in the PPI. The present results, therefore, do not allow strong conclusions about the precise pathway via which the striatum contributes to suppression of M1 corticospinal neurons. On the positive side, the results from the present study provide several testable models of how inhibitory control is implemented in the brain. These models can be tested in future studies with more sophisticated effective connectivity analyses, such as dynamic causal modeling and Granger causality analysis.

Another issue that invites further investigation is that our SSRT estimates are longer than usual. Although the SSRT in the standard manual stop-signal paradigm are typically between 200 and 250 ms, there seems to be no strong theoretical reason to expect SSRT to fall within this range.

We speculate that our longer SSRT estimates may be characteristic of our particular version of the stop-signal paradigm. The stop-signal anticipation task involves manipulation of stop-signal probability, which varies from trial-to-trial and is made explicit with a visual cue. Stopping in the stop-signal anticipation task may therefore be harder than in the standard stop-signal paradigm. Indeed, there is a tendency for SSRT to increase with task complexity (van Gaal et al., 2009) and information load (Ridderinkhof et al., 1999). It is also possible that the stop-signal used in this study (i.e. the bar stopping automatically) was less intense than the stop-signal usually used (e.g. a loud auditory tone), given that previous studies have shown that SSRT increases with a reduction in stop-signal salience (Van Der Schoot et al., 2005; Morein-Zamir and Kingstone, 2006).

In sum, this study demonstrates that the striatum plays a crucial role in stopping planned responses. We propose that this role entails proactive inhibitory control over response-related activity in M1, most likely achieved in interaction with SMC and rIFC, in order to induce behavioral adjustments that improve stopping performance.

## References

Alexander GE, Crutcher MD (1990) Functional architecture of basal ganglia circuits: neural substrates of parallel processing. Trends Neurosci.

Aron AR, Poldrack RA (2005) The cognitive neuroscience of response inhibition: relevance for genetic research in attention-deficit/hyperactivity disorder. Biol Psychiatry 57:1285-1292.

Aron AR, Poldrack RA (2006) Cortical and subcortical contributions to stop signal response inhibition: role of the subthalamic nucleus. J Neurosci 26:2424-2433.

Aron AR, Behrens TE, Smith S, Frank MJ, Poldrack RA (2007) Triangulating a cognitive control network using diffusion-weighted magnetic resonance imaging (MRI) and functional MRI. J Neurosci 27:3743-3752.

Ashburner J, Friston KJ (1999) Nonlinear spatial normalization using basis functions. Hum Brain Mapp 7:254-266.

Ashburner J, Friston KJ (2005) Unified segmentation. Neuroimage 26:839-851.

Blazquez PM, Fujii N, Kojima J, Graybiel AM (2002) A network representation of response probability in the striatum. Neuron 33:973-982.

Boehler CN, Appelbaum LG, Krebs RM, Hopf JM, Woldorff MG (2010) Pinning down response inhibition in the brain - conjunction analyses of the Stop-signal task. Neuroimage.

Boucher L, Palmeri TJ, Logan GD, Schall JD (2007) Inhibitory control in mind and brain: an interactive race model of countermanding saccades. Psychol Rev 114:376-397.

Braver TS, Gray JR, Burgess GC (2007) Explaning the many varieties of working memory variation: dual mechanisms of cognitive control. In: Variation in Working Memory (Conway A, Jarrold C, Kane M, Miyake A, Towse K, eds), pp 76-106. Oxford: Oxford University Press.

Buch ER, Mars RB, Boorman ED, Rushworth MFS (2010) A network centered on ventral premotor cortex exerts both facilitatory and inhibitory control over primary motor cortex during action reprogramming. J Neurosci 30:1395-1401.

Cai W, Leung H-C (2009) Cortical activity during manual response inhibition guided by color and orientation cues. Brain Res 1261:20-28.

Chambers CD, Garavan H, Bellgrove MA (2009) Insights into the neural basis of response inhibition from cognitive and clinical neuroscience. Neurosci Biobehav Rev 33:631-646.

Chao HHA, Luo X, Chang JLK, Li C-SR (2009) Activation of the pre-supplementary motor area but not inferior prefrontal cortex in association with short stop signal reaction time - an intra-subject analysis. BMC Neurosci 10:75.

Chikazoe J, Konishi S, Asari T, Jimura K, Miyashita Y (2007) Activation of right inferior frontal gyrus during response inhibition across response modalities. J Cogn Neurosci 19:69-80.

Chikazoe J, Jimura K, Hirose S, Yamashita K-i, Miyashita Y, Konishi S (2009) Preparation to inhibit a response complements response inhibition during performance of a stop-signal task. J Neurosci 29:15870-15877.

Corbetta M, Shulman GL (2002) Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 3:201-215.

Coxon JP, Stinear CM, Byblow WD (2006) Intracortical inhibition during volitional inhibition of prepared action. J Neurophysiol 95:3371-3383.

Coxon JP, Stinear CM, Byblow WD (2007) Selective inhibition of movement. J Neurophysiol

97:2480-2489.
De Jong R, Coles MGH, Logan GD, Gratton G (1990) In search of the point of no return: the control of response processes. Journal of experimental psychology Human perception and performance 16:164-182.
Draganski B, Kherif F, Kloppel S, Cook PA, Alexander DC, Parker GJM, Deichmann R, Ashburner J, Frackowiak RSJ (2008) Evidence for Segregated and Integrative Connectivity Patterns in the Human Basal Ganglia. J Neurosci 28:7143-7152.
Duann J-R, Ide JS, Luo X, Li C-sR (2009) Functional connectivity delineates distinct roles of the inferior frontal cortex and presupplementary motor area in stop signal inhibition. J Neurosci 29:10171-10179.
Duvernoy HM (1999) The Human Brain: Surface, Three-Dimensional Sectional Anatomy with MRI, and Blood Supply, 2nd Edition. New York: Springer-Verlag.
Eagle DM, Robbins TW (2003) Inhibitory control in rats performing a stop-signal reaction-time task: effects of lesions of the medial striatum and d-amphetamine. Behav Neurosci 117:1302-1317.
Eagle DM, Baunez C, Hutcheson DM, Lehmann O, Shah AP, Robbins TW (2008) Stop-signal reaction-time task performance: role of prefrontal cortex and subthalamic nucleus. Cereb Cortex 18:178-188.
Forstmann BU, Dutilh G, Brown S, Neumann J, von Cramon DY, Ridderinkhof KR, Wagenmakers EJ (2008) Striatum and pre-SMA facilitate decision-making under time pressure. Proc Natl Acad Sci USA 105:17538-17542.
Frank MJ (2005) Dynamic dopamine modulation in the basal ganglia: a neurocomputational account of cognitive deficits in medicated and nonmedicated Parkinsonism. J Cogn Neurosci 17:51-72.
Friston K, Ashburner J, Frith C, Poline J, Heather J, Frackowiak R (1995) Spatial registration and normalization of images. Hum Brain Mapp 3:165-189.
Friston KJ, Buechel C, Fink GR, Morris J, Rolls E, Dolan RJ (1997) Psychophysiological and modulatory interactions in neuroimaging. Neuroimage 6:218-229.
Garavan H, Ross TJ, Stein EA (1999) Right hemispheric dominance of inhibitory control: an event-related functional MRI study. Proc Natl Acad Sci USA 96:8301-8306.
Gauggel S, Rieger M, Feghoff TA (2004) Inhibition of ongoing responses in patients with Parkinson's disease. J Neurol Neurosurg Psychiatr 75:539-544.
Gitelman DR, Penny WD, Ashburner J, Friston KJ (2003) Modeling regional and psychophysiologic interactions in fMRI: the importance of hemodynamic deconvolution. Neuroimage 19:200-207.
Graybiel AM (2000) The basal ganglia. Curr Biol 10:R509-511.
Grinband J, Wager TD, Lindquist M, Ferrera VP, Hirsch J (2008) Detection of time-varying signals in event-related fMRI designs. Neuroimage 43:509-520.
Haber S, Fudge J, Mcfarland N (2000) Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. J Neurosci 20:2369.
Hanes DP, Patterson WF, Schall JD (1998) Role of frontal eye fields in countermanding saccades: visual, movement, and fixation activity. J Neurophysiol 79:817-834.
Isoda M, Hikosaka O (2008) Role for subthalamic nucleus neurons in switching from automatic to controlled eye movement. J Neurosci 28:7209-7218.
Jahfari S, Stinear C, Claffey M, Verbruggen F, Aron A (2010) Responding with restraint: what are the neurocognitive mechanisms? J Cogn Neurosci 22:1479-1492.

Lauwereyns J, Watanabe K, Coe B, Hikosaka O (2002) A neural correlate of response bias in monkey caudate nucleus. Nature 418:413-417.

Leh SE, Ptito A, Chakravarty MM, Strafella AP (2007) Fronto-striatal connections in the human brain: A probabilistic diffusion tractography study. Neurosci Lett 419:113-118.

Lehéricy S, Ducros M, Krainik A, Francois C, al. e (2004a) 3-D Diffusion Tensor Axonal Tracking shows Distinct SMA and Pre-SMA Projections to the Human Striatum. Cereb Cortex 14:1302-1309.

Lehéricy S, Ducros M, Van de Moortele PF, Francois C, Thivard L, Poupon C, Swindale N, Ugurbil K, Kim DS (2004b) Diffusion tensor fiber tracking shows distinct corticostriatal circuits in humans. Ann Neurol 55:522-529.

Leotti LA, Wager TD (2010) Motivational influences on response inhibition measures. Journal of experimental psychology Human perception and performance 36:430-447.

Lo C, Wang X (2006) Cortico-basal ganglia circuit mechanism for a decision threshold in reaction time tasks. Nat Neurosci 9:956-963.

Lo C, Boucher L, Paré M, Schall JD, Wang X (2009) Proactive inhibitory control and attractor dynamics in countermanding action: a spiking neural circuit model. J Neurosci 29:9059-9071.

Logan GD, Cowan WB (1984) On the ability to inhibit thought and action: A theory of an act of control. Psychol Rev 91:291-327.

Mars R, Klein M, Neubert F-X, Olivier E, Buch E, Boorman E, Rushworth M (2009) Short-latency influence of medial frontal cortex on primary motor cortex during action selection under conflict. J Neurosci 29:6926-6931.

Menon V, Leroux J, White CD, Reiss AL (2004) Frontostriatal deficits in fragile X syndrome: relation to FMR1 gene expression. Proc Natl Acad Sci USA 101:3615-3620.

Morein-Zamir S, Kingstone A (2006) Fixation offset and stop signal intensity effects on saccadic countermanding: a crossmodal investigation. Experimental brain research Experimentelle Hirnforschung Expérimentation cérébrale 175:453-462.

Nambu A, Tokuno H, Takada M (2002) Functional significance of the cortico-subthalamopallidal 'hyperdirect'pathway. Neurosci Res 43:111-117.

Padmala S, Pessoa L (2010) Interactions between cognition and motivation during response inhibition. Neuropsychologia 48:558-565.

Paré M, Hanes DP (2003) Controlled movement processing: superior colliculus activity associated with countermanded saccades. J Neurosci 23:6480-6489.

Ramautar JR, Kok A, Ridderinkhof KR (2004) Effects of stop-signal probability in the stop-signal paradigm: the N2/P3 complex further validated. Brain Cogn 56:234-252.

Ridderinkhof KR, Band GPH, Logan GD (1999) A study of adaptive behavior: Effects of age and irrelevant information on the ability to inhibit one's actions. Acta Psychol (Amst) 101:315-337.

Robbins TW (2007) Shifting and stopping: fronto-striatal substrates, neurochemical modulation and clinical implications. Philos Trans R Soc Lond, B, Biol Sci 362:917-932.

Rubia K, Smith AB, Brammer MJ, Toone B, Taylor E (2005) Abnormal brain activation during inhibition and error detection in medication-naive adolescents with ADHD. Am J Psychiatry.

Rubia K, Overmeyer S, Taylor E, Brammer MJ, Williams SC, Simmons A, Bullmore ET (1999) Hypofrontality in attention deficit hyperactivity disorder during higher-order motor control: a study with functional MRI. Am J Psychiatry 156:891-896.

Sasaki K, Gemba H, Tsujimoto T (1989) Suppression of visually initiated hand movement by stimulation of the prefrontal cortex in the monkey. Brain Res 495:100-107.
Shattuck D, Mirza M, Adisetiyo V, Hojatkashani C, Salamon G, Narr K, Poldrack RA, Bilder R, Toga A (2008) Construction of a 3D probabilistic atlas of human cortical structures. Neuroimage 39:1064-1080.
Simmonds DJ, Pekar JJ, Mostofsky SH (2008) Meta-analysis of Go/No-go tasks demonstrating that fMRI activation associated with response inhibition is task-dependent. Neuropsychologia 46:224-232.
Slater-Hammel AT (1960) Reliability, accuracy, and refractoriness of a transit reaction. Res Q 31:217-228.
Smith SM (2002) Fast robust automated brain extraction. Hum Brain Mapp 17:143-155.
Stephan KE (2004) On the role of general system theory for functional neuroimaging. J Anat 205:443-470.
Stinear CM, Coxon JP, Byblow WD (2009) Primary motor cortex and movement prevention: Where Stop meets Go. Neurosci Biobehav Rev 33:662-673.
Stuphorn V, Schall JD (2006) Executive control of countermanding saccades by the supplementary eye field. Nat Neurosci 9:925-931.
van den Wildenberg W, Burle B, Vidal F, van der Molen M, Ridderinkhof K, Hasbroucq T (2010) Mechanisms and Dynamics of Cortical Motor Inhibition in the Stop-signal Paradigm: A TMS Study. J Cogn Neurosci 22:225-239.
van den Wildenberg WPM, van Boxtel GJM, al. e (2006) Stimulation of the Subthalamic Region Facilitates the Selection and Inhibition of Motor Responses in Parkinson's Disease. J Cogn Neurosci 18:626-636.
Van Der Schoot M, Licht R, Horsley TM, Sergeant JA (2005) Effects of stop signal modality, stop signal intensity and tracking method on inhibitory performance as determined by use of the stop signal paradigm. Scand J Psychol 46:331-341.
van Gaal S, Ridderinkhof KR, van den Wildenberg WPM, Lamme VAF (2009) Dissociating consciousness from inhibitory control: evidence for unconsciously triggered response inhibition in the stop-signal task. Journal of experimental psychology Human perception and performance 35:1129-1139.
Verbruggen F, Logan GD (2009a) Models of response inhibition in the stop-signal and stop-change paradigms. Neurosci Biobehav Rev 33:647-661.
Verbruggen F, Logan GD (2009b) Proactive adjustments of response strategies in the stop-signal paradigm. J Exp Psychol Hum Percept Perform 35:835-854.
Vink M, Ramsey NF, Raemaekers M, Kahn RS (2006) Striatal dysfunction in schizophrenia and unaffected relatives. Biol Psychiatry 60:32-39.
Vink M, Kahn RS, Raemaekers M, van den Heuvel M, Boersma M, Ramsey NF (2005) Function of striatum beyond inhibition and execution of motor responses. Hum Brain Mapp 25:336-344.
Woolley J, Heyman I, Brammer M, Frampton I, Mcguire P, Rubia K (2008) Brain activation in paediatric obsessive compulsive disorder during tasks of inhibitory control. Br J Psychiatry 192:25-31.
Yamada H, Matsumoto N, Kimura M (2007) History- and current instruction-based coding of forthcoming behavioral outcomes in the striatum. J Neurophysiol 98:3557-3567.

# 3 Transcranial magnetic stimulation and functional neuroimaging reveal cortical and subcortical interactions during stop-signal response inhibition

Bram B. Zandbelt, Mirjam Bloemendaal, Janna Marie Hoogendam, René S. Kahn, Matthijs Vink

*Under review*

Stopping a manual response from being executed requires suppression of the primary motor cortex (M1). Inhibitory control over M1 relies on a network, in which the right inferior frontal cortex (rIFC) and the supplementary motor complex (SMC) have important roles. How these regions exert inhibitory control over M1 is a much debated, yet unresolved issue. Specifically, the relative position of the rIFC and SMC with respect to each other and the routes by which these regions control M1 remain unclear. To address these issues, we combined offline repetitive transcranial magnetic stimulation (rTMS) and functional magnetic resonance imaging (fMRI). 24 healthy volunteers received real rTMS over the rIFC, real rTMS over the SMC, and sham rTMS in a counterbalanced order. After rTMS, participants underwent fMRI while performing a stop-signal task that evokes two forms of inhibitory control: proactive inhibition (anticipation of stopping) and reactive inhibition (outright stopping). Both rIFC and SMC stimulation improved reactive inhibition by shortening the stop-signal reaction time (SSRT) and shorter SSRTs were associated with increased M1 deactivation. Furthermore, rIFC and SMC stimulation increased right striatal activation, implicating cortico-basal ganglia pathways through the right striatum in reactive inhibition. Moreover, rIFC stimulation influenced SMC activation, but SMC stimulation did not influence right IFC activation, suggesting that the rIFC lies upstream from SMC. Finally, proactive inhibition was not altered by rIFC and SMC stimulation. Together, these findings extend our knowledge about the functional organization of inhibitory control, suggesting that rIFC exerts control over M1 via SMC and the striatum.

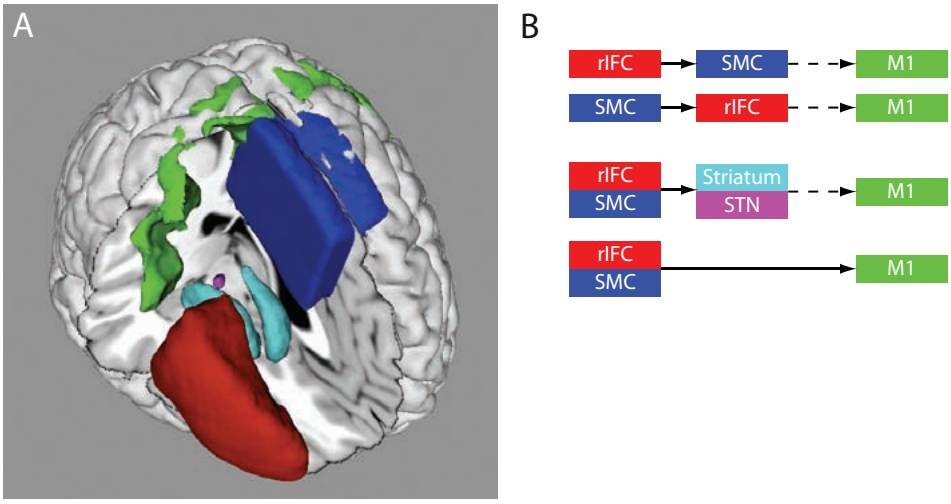



**Figure 1. A,** Key regions in the neural network of inhibitory control, including the right inferior frontal cortex (rIFC, red), supplementary motor complex (SMC, blue), striatum (cyan), and subthalamic nucleus (STN, magenta), and primary motor cortex (M1, green), shown on a three-dimensional reconstruction of a normalized brain. **B,** Hypothetical interactions during inhibitory control over M1. First, the rIFC could modulate M1 via the SMC, or the SMC could modulate M1 via the rIFC. Second, rIFC and SMC could modulate M1 via a cortico-basal ganglia route or via a cortico-cortical pathway. Solid arrows represent direct projections, dashed arrows represent indirect projections.

## Introduction

Stopping a manual response from being executed requires suppression of the primary motor cortex (M1) (Stinear et al., 2009). Converging lines of evidence suggest that M1 is under control of a network in which the right inferior frontal cortex (rIFC) and the supplementary motor complex (SMC) have important roles (Chambers et al., 2009; Aron, 2010). How the regions in this network interact with each other to exert control over M1 is intensely debated, but remains unclear (Figure 1). Whereas it has been suggested that the SMC exerts control over M1 via the rIFC (Aron et al., 2007; Neubert et al., 2010), others suggest that rIFC exerts control over M1 via the SMC (Duann et al., 2009; Hwang et al., 2010). Furthermore, rIFC and SMC may exert control over M1 via cortico-basal ganglia pathways through the striatum or subthalamic nucleus (Aron and Poldrack, 2006; Aron et al., 2007; Zandbelt and Vink, 2010), but also via direct cortico-cortical connections (Mars et al., 2009; Buch et al., 2010).

To address these issues, we combined repetitive transcranial magnetic stimulation (rTMS) and functional magnetic resonance imaging (fMRI).

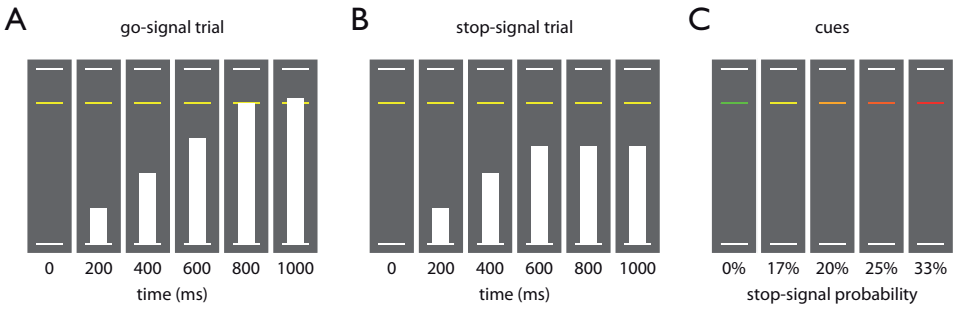



**Figure 2.** Stop-signal anticipation task. Three horizontal lines formed the background displayed continuously during the task. **A,** In each trial, a bar moved at constant speed from the bottom up, reaching the middle line in 800 ms. The main task was to stop the bar as close to the middle line as possible by pressing a button with the right thumb (i.e. the target response time was 800 ms). These trials are referred to as go-signal trials. **B,** In a minority of trials, the bar stopped moving automatically before reaching the middle line (i.e. the stop-signal), indicating that a response had to be stopped. These trials are referred to as stop-signal trials. Stop-signal trials in which a response was successfully inhibited are referred to as successful stop-signal trials, those in which inhibition failed are referred to as failed stop-signal trials. **C,** The probability that a stop-signal would occur was manipulated across trials and was indicated by the color of the target response line (i.e. cue). There were five stop-signal probability levels: 0% (green cue), 17% (yellow cue), 20% (amber cue), 25% (orange cue), and 33% (red cue). For more details on the stop-signal anticipation task, see Zandbelt and Vink (2010).

Each participant underwent three rTMS-fMRI sessions; they received real stimulation over the rIFC, real stimulation over the SMC, and sham stimulation over the right superior parietal lobe in a single-blind counterbalanced crossover design. Immediately after rTMS, we used fMRI to map the impact of this intervention on activation during a task (Zandbelt and Vink, 2010) (Figure 2) that evokes two forms of inhibitory control of motor responses: proactive (i.e. top-down) and reactive (bottom-up) inhibition (Braver et al., 2007; Aron, 2010). This experimental setup allowed us to visualize the interactions between rIFC, the SMC, and the basal ganglia during inhibitory control over M1.

## Methods

### *Participants*

All 24 participants (mean age 24.1 years, range 20 - 38 years; 12 females) were right-handed (Oldfield, 1971), had normal or corrected-to-normal vision, had no signs of present or past neurological or psychiatric illness (Sheehan et al., 1998), had no contraindication to TMS (Keel et al., 2001),

and gave written informed consent. None of the participants reported adverse effects after rTMS and none of them abandoned the study. Data from three participants had to be excluded from the fMRI analysis, due to excessive head motion during fMRI data acquisition.

*TMS procedure*

Each session started with identification of the stimulation site on the head of the participant. The stimulation sites were defined based on group activation peak coordinates of a previous fMRI study using the same stop-signal task (Zandbelt and Vink, 2010). These coordinates were marked on a normalized T1-weighted scan of each participant, which was obtained before the first rTMS-fMRI session. The individual stimulation sites were derived by reversing the normalization procedure of the T1-weighted scan. Using this native T1-weighted scan and a frameless stereotactic neuronavigation system (Neggers et al., 2004) we could identify the site where the TMS coil had to be positioned in order to stimulate the rIFC and SMC. These sites were marked on a tight-fitting Lycra cap, which participants wore during the entire rTMS-fMRI session.

We delivered rTMS with a Double 70-mm Air Film Coil (real rTMS) or a Double 70-mm Air Film Placebo Coil (sham rTMS), connected to a magnetic stimulator (Magstim Rapid2, Magstim, Welwyn Garden City, United Kingdom). Prior to rTMS, the resting motor threshold (RMT) was determined, according to a standardized procedure (Schutter and van Honk, 2006). The rTMS protocol (Iyer et al., 2003) consisted of 20 trains of 30 6-Hz pulses at 90% RMT with an intertrain interval of 25 s, followed by 600 1-Hz pulses at 110% RMT. This protocol produces neural effects persisting for up to 60 min beyond stimulation (Iyer et al., 2003), enabling offline mapping of stimulation effects on brain function (Siebner et al., 2009). During rTMS, participants wore earplugs to protect against TMS noise and were seated in a comfortable chair with their head stabilized by a forehead and chin rest. The stimulation site was marked on the cap with a vitamin E capsule for post-hoc identification on the MRI scan.

*MRI procedure*

Immediately after rTMS, participants were placed in a 3.0 Tesla MRI scanner (Philips Medical System, Best, the Netherlands). We collected 622 whole-brain T2*-weighted echo planar images (EPI) with blood-oxygen

level-dependent (BOLD) contrast while participants performed the stop-signal anticipation task (see below) and a T1-weighted image thereafter, using scan parameters identical to those described before (Zandbelt and Vink, 2010).

*Stop-signal anticipation task*

Participants performed a modified version of the stop-signal paradigm (Verbruggen and Logan, 2008), called the stop-signal anticipation task (Zandbelt and Vink, 2010) (Figure 2). The majority of trials were go-signal trials, in which participants had to make a response. A minority of trials were stop-signal trials, in which participants had to withhold a response. Stop-signal probability was manipulated across trials and was indicated by a cue.

The stop-signal anticipation task evokes two forms of inhibitory control: proactive inhibition and reactive inhibition. Proactive inhibition is a top-down form of control and refers to mechanisms underlying anticipation of stopping. It involves processes such as response selection and response preparation (Braver et al., 2007). In the current task, the degree of proactive inhibition was manipulated using a visual cue indicating stop-signal probability. Reactive inhibition is a bottom-up form of control and refers to mechanisms underlying outright stopping. It involves processes such as stimulus detection and interference resolution (Braver et al., 2007). In the current task, reactive inhibition was triggered by the presentation of stop-signals.

*Data analysis - task performance*

For go-signal trials, we computed mean response times and omission rates, separately for each stop-signal probability level. Furthermore, we calculated the stop-signal probability slope (SSPS), defined as the linear effect of stop-signal probability on go-signal response time. For stop-signal trials, we computed mean response times on failed stop-signal trials, success rates for stop-signal trials, and the stop-signal reaction time (SSRT) (Logan and Cowan, 1984), the latter of which was calculated according to the integration method (Verbruggen and Logan, 2009c). For each of these indices, the effect of stimulation was computed as the difference between real stimulation and sham stimulation (i.e. rIFC vs. sham and SMC vs. sham).

In keeping with previous studies (Vink et al., 2005; Vink et al., 2006; Verbruggen and Logan, 2009b; Zandbelt and Vink, 2010), proactive inhibition was measured as the effect of stop-signal probability on go-signal trial response time, whereas reactive inhibition was studied in terms of the SSRT.

We analyzed the effect of stimulation on go-signal reaction time and go-signal omission rate using two repeated-measures ANOVAs with "stop-signal probability" (0%, 17%, 20%, 25%, 33%) and "stimulation site" (rIFC, SMC) as within-subject factors. A stronger positive (or negative) effect of stop-signal probability after real vs. sham stimulation would indicate an improvement (or decline) of proactive inhibition. We analyzed the effect of stimulation on SSRT, stopping rate, and response times on failed stop-signal trials in three repeated-measures ANOVAs, with "stimulation site" (rIFC, SMC) as within-subject factor. A shorter (or longer) SSRT after real vs. sham stimulation would indicate an improvement (or decline) of reactive inhibition.

*Data analysis - fMRI*

Functional MRI data were analyzed with SPM5 (http://www.fil.ion.ucl.ac.uk/spm/software/spm5/). Pre-processing and first-level statistical analysis was performed as previously described (Zandbelt and Vink, 2010), Pre-processing involved correction for slice timing differences, realignment for head motion correction, spatial normalization to the Montreal Neurological Institute (MNI) template brain, and spatial smoothing to accommodate interindividual differences in neuroanatomy.

For each participant, we constructed a model containing the three rTMS-fMRI sessions. For each session, the following events were included as regressors: successful stop-signal trial, failed stop-signal trial, and go-signal trials with stop-signal probability > 0%. For these go-signal trials, we also included two parametric regressors modeling response time and stop-signal probability level. These regressors were created by convolving delta functions coding for each event's response time (or target response time for successful stop-signal trials) with a canonical haemodynamic response function. The fMRI data were high-pass filtered to remove low-frequency drifts. A first-order autoregressive model was used to model the remaining serial correlations. For each participant, we generated contrast images for proactive inhibition (defined as the parametric effect

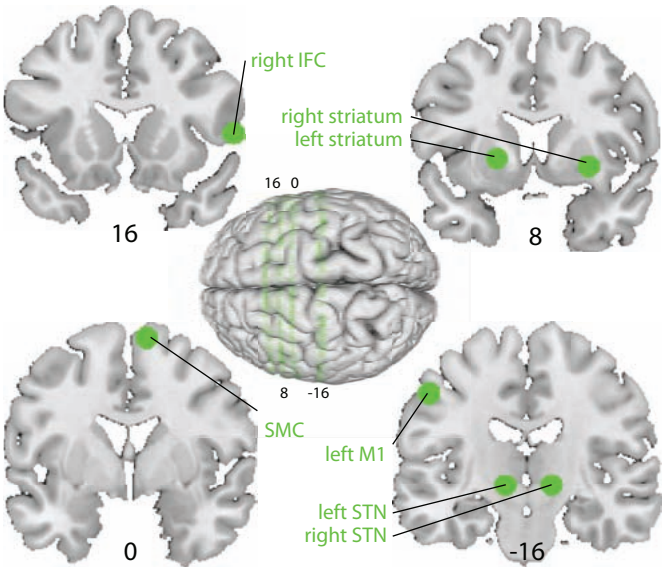



**Figure 3.** Regions-of-interest (ROIs) in the inhibitory control network. Regions were the stimulated right inferior frontal cortex (rIFC, top left) and supplementary motor complex (SMC, bottom left), as well as the left and right striatum (top right) and the left and right subthalamic nucleus (STN, bottom right). Each region was defined as a sphere with 6-mm radius. Numbers indicate the y-coordinates of the coronal slices (in Montreal Neurological Institute space). The center image depicts a top view representation of a normalized brain, showing the location of coronal slices in green.

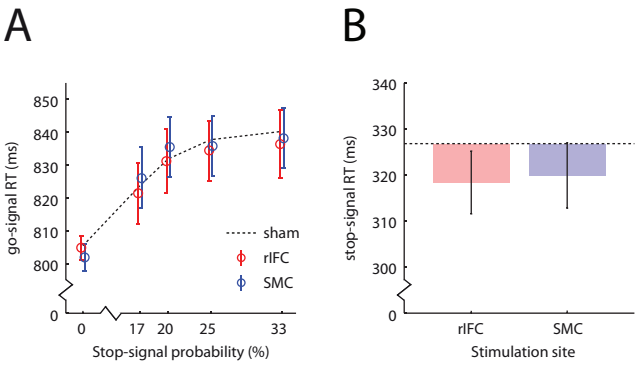



**Figure 4.** Effect of rIFC and SMC stimulation on proactive inhibition and reactive inhibition. **A,** Mean effect of rIFC stimulation (red) and SMC stimulation (blue), relative to sham stimulation (dashed line), on the effect of stop-signal probability on go-signal response time (proactive inhibition). **B,** Mean effect of rIFC stimulation (red) and SMC stimulation (blue), relative to sham stimulation (dashed line) on the stop-signal reaction time (SSRT) (reactive inhibition). Error bars indicate 95% confidence intervals.

of stop-signal probability on go-signal activation) and reactive inhibition (defined as successful stop-signal trials vs. go-signal trials in the 0% stop-signal probability context) for three TMS conditions: sham, rIFC vs. sham, and SMC vs. sham.

We used these contrast images to investigate the effect of frontal stimulation on activation during proactive and reactive inhibition in key regions-of-interest (ROIs) of the inhibitory control network. The ROIs were the stimulated rIFC and SMC, as well as the left and right striatum, the left and right subthalamic nucleus (STN), and the left M1 (Figure 3). The ROIs were defined as 6-mm spheres around local maxima from a previous study (Zandbelt and Vink, 2010), except for the left and right STN that were defined as 6-mm spheres around the coordinate [+/-12, -16, -4], in accordance with a human basal ganglia template (Prodoehl et al., 2008) and a previous study investigating STN activation during inhibitory control (Aron and Poldrack, 2006). From these ROIs, we extracted for each participant the mean effect of stimulation (rIFC - sham, SMC - sham) on proactive and reactive inhibition. These were entered into two ANOVAs testing for effects of stimulation on activation during proactive inhibition and reactive inhibition, respectively. Both ANOVAs contained the within-subject factors "stimulation site" (rIFC, SMC) and "ROI" (rIFC, SMC, left striatum, right striatum, left STN, right STN, left M1). In addition, a between-subjects factor reflecting the effect of stimulation on behavior was included: ΔSSPSreal-sham for proactive inhibition and ΔSSRTreal-sham for reactive inhibition. Greenhouse-Geisser correction was used when the assumption of sphericity was violated.

## Results

*rIFC and SMC stimulation do not alter proactive inhibition*

Figure 4A shows the effect of frontal stimulation on go-signal reaction time as a function of stop-signal probability. In the baseline condition (sham rTMS), go-signal response times increased as a function of stop-signal probability, indicating that participants slowed down proactively in anticipation of a stop-signal, replicating previous observations (Logan and Burkell, 1986; Ramautar et al., 2004; Vink et al., 2005; Ramautar et al., 2006; Vink et al., 2006; Verbruggen and Logan, 2009a; Zandbelt and Vink, 2010). After frontal stimulation, we observed an almost identical response time profile that did neither differ from baseline (intercept, F <

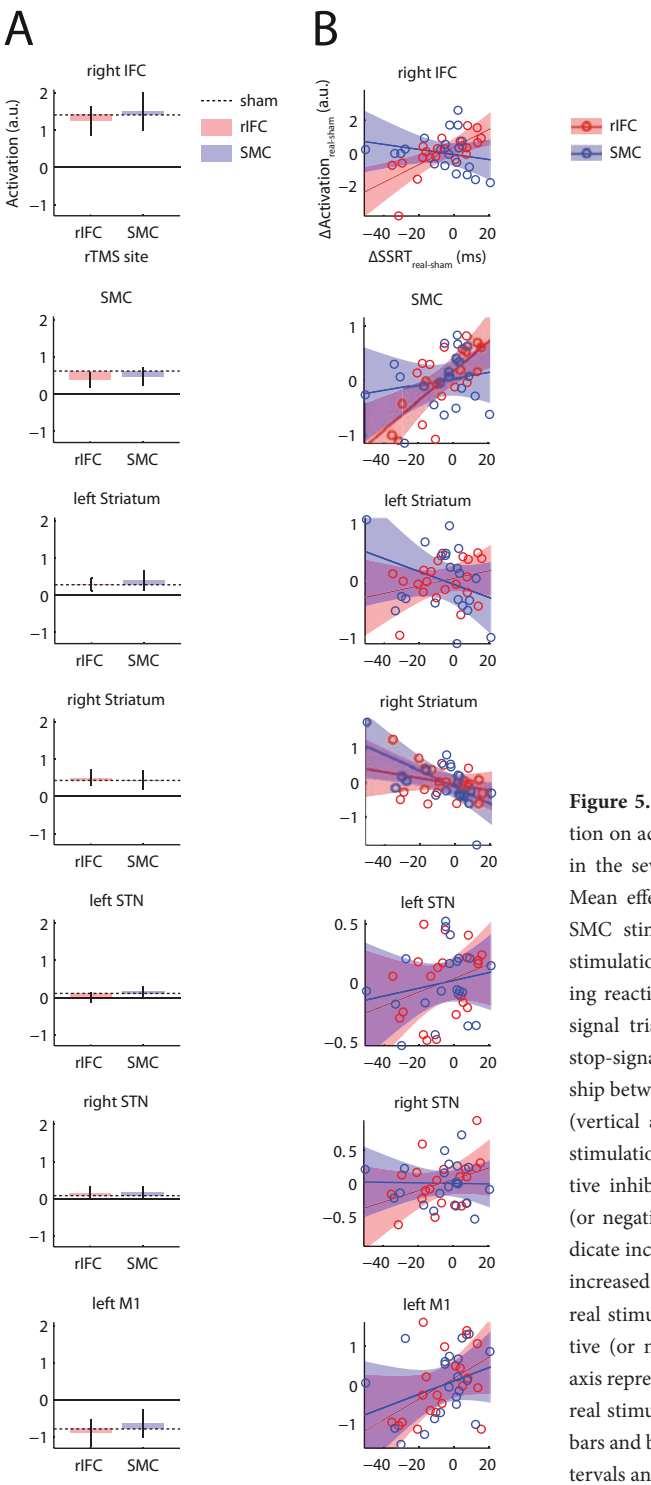



**Figure 5.** Effect of rIFC and SMC stimulation on activation during reactive inhibition in the seven regions-of-interest (ROIs). **A,** Mean effect of rIFC stimulation (red) and SMC stimulation (blue), relative to sham stimulation (dashed line), on activation during reactive inhibition (i.e. successful stop-signal trials vs. go-signal trials in the 0% stop-signal probability context). **B,** Relationship between the neural effect of stimulation (vertical axis) and the behavioral effect of stimulation (horizontal axis) during reactive inhibition across participants. Positive (or negative) values on the vertical axis indicate increased (or decreased) activation or increased (or decreased) deactivation after real stimulation vs. sham stimulation. Positive (or negative) values on the horizontal axis represent longer (or shorter) SSRTs after real stimulation vs. sham stimulation. Error bars and bands represent 95% confidence intervals and bands.

1, P = .76) nor between rIFC and SMC stimulation (stimulation site, F < 1, P = .88; stimulation site x stop-signal probability linear contrast, F < 1, P = .81). In addition, there were no significant effects of frontal stimulation on go-signal omission errors (intercept, F < 1, P = .07; stimulation site, F = 1.93, P = .49; stimulation site x stop-signal probability linear contrast, F < 1, P = .21).

*rIFC and SMC stimulation facilitate reactive inhibition*

Figure 4B shows the effect of frontal stimulation on the stop-signal reaction time (SSRT). In the baseline condition (sham rTMS), the SSRT was on average 327 ms, similar to a previous report of the stop-signal anticipation task (Zandbelt and Vink, 2010). After frontal stimulation, participants were slightly but significantly faster in reactive stopping (intercept, F = 6.66, P = .017) and this effect was similar for rIFC and SMC stimulation (stimulation site, F < 1, P = .63). There were no effects of frontal stimulation on other stop-signal indices, such as stop success rate (intercept, F = 3.46, P = .08; stimulation site, F < 1, P = .99) and stop-failure response time (intercept, F < 1, P = .92; stimulation site, F < 1, P = .68).

*Facilitation of reactive inhibition is accompanied by activation changes in rIFC, SMC, right striatum and left M1*

Figure 5 depicts the effect of rIFC and SMC stimulation on activation during reactive inhibition in key regions-of-interest (ROIs) of the inhibitory control network. In the baseline condition (sham rTMS), all ROIs were activated during reactive inhibition, except for the left M1 that was deactivated (Figure 5A, all P-values < .046, small volume-corrected), validating our selection of ROIs. As depicted in Figure 5A, frontal stimulation did not affect activation in the inhibitory control network as a whole (intercept, F < 1, P = .75) and there was no difference between rIFC and SMC stimulation on overall network activation (stimulation site, F < 1, P = .70) or activation in any of the individual regions (ROI x stimulation site, F < 1, P = .51).

However, as shown in Figure 5B, there was a significant relation between the behavioral and neural effect of stimulation across participants (ΔSSRT x ROI, F = 4.45, P = .006). Post-hoc tests revealed that participants who became faster in reactive inhibition after rIFC or SMC stimulation showed reduced SMC activation (P = .013), enhanced right striatum activation (P < .001), and enhanced left M1 deactivation (P = .041).

Interestingly, there were regions in which the relation between the be-

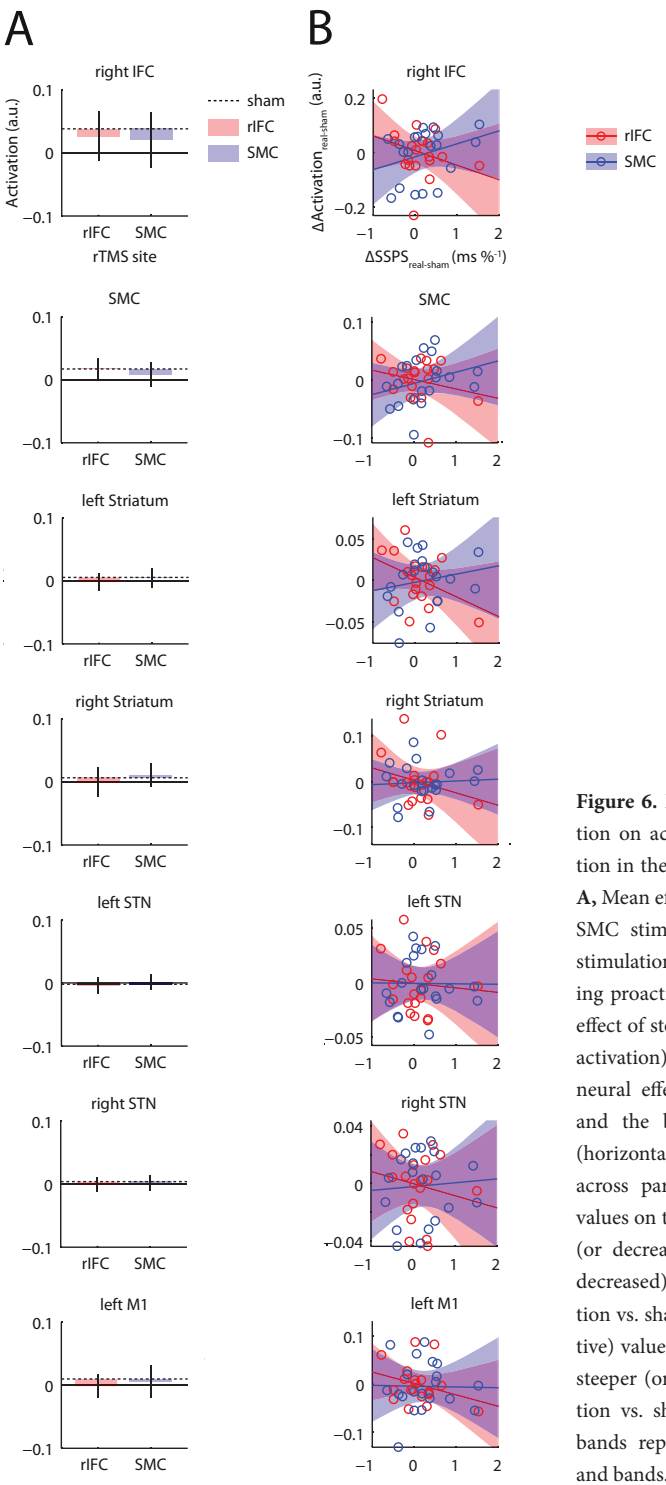



**Figure 6.** Effect of rIFC and SMC stimulation on activation during proactive inhibition in the seven regions-of-interest (ROIs). **A,** Mean effect of rIFC stimulation (red) and SMC stimulation (blue), relative to sham stimulation (dashed line), on activation during proactive inhibition (i.e. the parametric effect of stop-signal probability on go-signal activation). **B,** Relationship between the neural effect of stimulation (vertical axis) and the behavioral effect of stimulation (horizontal axis) during proactive inhibition across participants. Positive (or negative) values on the vertical axis indicate increased (or decreased) activation or increased (or decreased) deactivation after real stimulation vs. sham stimulation. Positive (or negative) values on the horizontal axis represent steeper (or f atter) SSPSs after real stimulation vs. sham stimulation. Error bars and bands represent 95% confidence intervals and bands.

havioral and neural effect of stimulation across participants differed between rIFC and SMC stimulation (ΔSSRT x ROI x stimulation site, F = 3.20, P = .028). Right IFC stimulation compared to SMC stimulation resulted in reduced rIFC activation (P = .015) and slightly reduced SMC activation (P = .053) in participants who became faster in stopping. Thus, in addition to common effects in the SMC, the right striatum, and the left M1, there was a differential effect in the stimulated regions: rIFC stimulation altered SMC activation, but SMC stimulation did not alter rIFC activation.

### *No effect of rIFC and SMC stimulation on activation during proactive inhibition*

Figure 6 shows the effect of rIFC and SMC stimulation on activation during proactive inhibition in key ROIs of the inhibitory control network. In the baseline condition (sham rTMS), activation increased with stop-signal probability in the SMC and the right striatum (Figure 6A, all P-values < .018, small volume-corrected), in agreement with previous reports (Chikazoe et al., 2009; Jahfari et al., 2010; Zandbelt and Vink, 2010). Figure 6A demonstrates that frontal stimulation did not affect activation in the inhibitory control network as a whole (intercept, F < 1, P = .48) and that there was no difference between stimulation sites on overall network activation (site, F < 1, P = .50) or activation in any of the individual regions (ROI x site, F < 1, P = .15). Furthermore, as shown in Figure 6B, there was no effect when the neural effect of stimulation was studied in relation to the behavioral effect: the neural effect of frontal stimulation did not depend on the effect of stimulation on the stop-signal probability slope (ΔSSPS x ROI, F < 1, P = .99) and there were also no differences between rIFC and SMC stimulation (ΔSSSP x ROI x site, F < 1, P = .19).

## Discussion

The functional organization of the neural network of inhibitory control is intensely debated, but remains unclear. We combined offline repetitive transcranial magnetic stimulation (rTMS) and functional magnetic resonance imaging (fMRI) to address two outstanding issues regarding the functional organization of this network: the relative position of the right inferior frontal cortex (rIFC) and the supplementary motor complex (SMC) with respect to each other and the routes by which these structures exert inhibitory control over the primary motor cortex (M1).

Stimulation of the rIFC and the SMC improved reactive inhibition, as evidenced by shorter stop-signal reaction times (SSRTs) as compared with sham stimulation. More importantly, using fMRI we were able to show for the first time that this shortening of SSRTs was associated with increased M1 deactivation. Since the SSRT was the only behavioral parameter affected by rTMS and because reactive inhibition involves suppression of activity in M1 (Coxon et al., 2006, 2007; van den Wildenberg et al., 2010), we take our data to suggest that rIFC and SMC stimulation facilitated reactive inhibition by suppressing activity in M1 faster compared with sham stimulation, resulting in a greater deactivation of M1. Our results extend previous rTMS studies of the stop-signal task (Chambers et al., 2006; Chambers et al., 2007; Chen et al., 2009; Verbruggen et al., 2010) by showing that changes in SSRTs induced by rIFC and SMC stimulation are, as expected, accompanied by altered activity in the primary target region of inhibitory control.

Although both rIFC and SMC stimulation resulted in increased deactivation of M1, rIFC stimulation altered SMC activation, but SMC stimulation did not alter rIFC activation significantly during reactive inhibition. This is in agreement with previous findings suggesting that rIFC lies upstream from SMC (Duann et al., 2009; Hwang et al., 2010) and indicates that rIFC may exert control over M1 via the SMC. Importantly, the effect of rIFC stimulation on SMC activation was proportional to the behavioral effect of stimulation across participants. That is, participants showing the largest improvement in reactive inhibition also showed the greatest change in activation, emphasizing the functional significance of this finding. More generally, the current findings are congruent with models of the functional organization of executive functioning in the frontal lobe, proposing that control is exerted in an anterior-posterior direction, rather than from posterior to anterior (Koechlin and Summerfield, 2007; Badre and D'Esposito, 2009).

This study is the first to investigate the neural network underlying inhibitory control using both TMS and fMRI, hence it is difficult to compare our results directly to other studies. However, there have been some studies investigating the interactions between rIFC, SMC, and M1 using paired-pulse TMS and task switching paradigms (Mars et al., 2009; Neubert et al., 2010). Our findings are in line with those of Neubert et al. (2010), showing that rTMS-induced inactivation of the SMC breaks

down the interaction between the rIFC and M1. This implicates the SMC in mediating rIFC-M1 interactions. However, from their data it is not clear whether rIFC controls M1 via the SMC or whether SMC controls M1 via the rIFC. Support for this latter view comes from Mars et al. (2009) and Neubert et al. (2010) who showed that a facilitatory effect of SMC stimulation on M1 occurs earlier (125 ms after the instruction to switch) than an inhibitory effect of rIFC stimulation on M1 (175 ms after the instruction to switch). However, it is unclear what happens after 175 ms. This is of particular relevance for studies using the stop-signal task, because it has been shown that the response of the rIFC and SMC to the stop-signal occurs around 200 to 250 ms after its presentation (Swann et al., 2009; Chen et al., 2010). In sum, our data support the idea that in the context of stop-signal response inhibition, M1 activation is controlled by the rIFC via the SMC. However, this interpretation should be confirmed in future paired-pulse TMS studies, which are suitable for examining the temporal profile of such interactions.

In addition to providing insight into the relative position of rIFC and SMC with respect to each other, our findings shed light on the pathways through which the rIFC and the SMC exert inhibitory control over M1. We showed that rIFC and SMC stimulation not only increased M1 deactivation, but also increased right striatum activation. We take these results to indicate that reactive inhibition relies on cortico-basal ganglia pathways and, more specifically, involves pathways through the right striatum. Two aspects are noteworthy here. First, we showed effects in the right, rather than the left striatum. This may reflect that reactive inhibition involves processes that depend on the right hemisphere, such as detection of salient stimuli (Corbetta and Shulman, 2002; Corbetta et al., 2008) and updating of action plans (Mars et al., 2007). The rIFC has a prominent role in these processes (Verbruggen et al., 2010), so it may very well be that the right striatum mediates input from the right IFC. Second, we found effects of stimulation in the striatum, rather than in the subthalamic nucleus (STN). This is important, because the dominant view is that reactive inhibition acts via cortico-basal ganglia pathways through the STN (Aron and Poldrack, 2006; Aron et al., 2007; Isoda and Hikosaka, 2008; Neubert et al., 2010). However, it has been recognized that pathways through the striatum are also possible (Chambers et al., 2009; Zandbelt and Vink,

2010), as supported by a tight coupling between striatal activation and M1 deactivation during stopping (Zandbelt and Vink, 2010), stronger striatal activation in individuals with short compared to long SSRTs (Chao et al., 2009), and the finding that stimulation of striatal neurons improves inhibitory control (Watanabe and Munoz, 2010). Although we did find activation in the STN during reactive inhibition, consistent with a previous report (Aron and Poldrack, 2006), we failed to detect an effect of rIFC and SMC stimulation on STN activation. These findings do not necessarily preclude a role for the STN in reactive inhibition. Indeed, the STN may contribute to reactive inhibition either via the hyperdirect pathway (Aron and Poldrack, 2006) or via its position downstream of the striatum in the indirect pathway (Mink, 1996). Future studies are required to establish the relative contribution of the striatum and STN to reactive inhibition.

Despite profound effects on reactive inhibition, there were no significant effects of rIFC and SMC stimulation on proactive inhibition. In view of previous reports, it may not be surprising that rIFC stimulation did not alter proactive inhibition, but it is unexpected that SMC stimulation had no effect on proactive inhibition. First, previous studies have found that proactive inhibition is influenced by SMC stimulation (Stuphorn and Schall, 2006), but not by rIFC stimulation (Verbruggen et al., 2010). Second, the SMC, but not the rIFC, is activated during preparation for an upcoming stop-signal (Vink et al., 2011). Third, dorsal frontal regions, such as the SMC, have been implicated in preparatory, top-down processes (e.g. proactive inhibition), whereas ventrolateral frontal regions, such as the rIFC, are thought to be involved in bottom-up processes (e.g. reactive inhibition) (Corbetta and Shulman, 2002; Corbetta et al., 2008). Indeed, several studies have implicated the SMC in proactive inhibition (Chikazoe et al., 2009; Chen et al., 2010; Stuphorn et al., 2010)

Note, however, that SMC stimulation did alter behavior and activation during reactive inhibition, excluding the possibility that rTMS had no impact on the SMC. We speculate that the discrepancy between our findings and the results from Stuphorn & Schall (2006), who did find altered proactive inhibition after SMC stimulation, may be due to differences in species (human vs. monkey), effector (hand vs. eye), and perturbation technique (rTMS vs. intracortical microstimulation).

To summarize, our results provide insight into the functional organization of the neural network subserving inhibitory control, an important component of executive functioning. We take our findings to indicate that rIFC lies upstream from SMC in this network and that rIFC and SMC modulate M1 via cortico-basal ganglia pathways through the right striatum.

## References

Aron AR (2010) From Reactive to Proactive and Selective Control: Developing a Richer Model for Stopping Inappropriate Responses. Biol Psychiatry.

Aron AR, Poldrack RA (2006) Cortical and subcortical contributions to stop signal response inhibition: role of the subthalamic nucleus. J Neurosci 26:2424-2433.

Aron AR, Behrens TE, Smith S, Frank MJ, Poldrack RA (2007) Triangulating a cognitive control network using diffusion-weighted magnetic resonance imaging (MRI) and functional MRI. J Neurosci 27:3743-3752.

Badre D, D'Esposito M (2009) Is the rostro-caudal axis of the frontal lobe hierarchical? Nature Reviews Neuroscience 10:659-669.

Braver TS, Gray JR, Burgess GC (2007) Explaning the many varieties of working memory variation: dual mechanisms of cognitive control. In: Variation in Working Memory (Conway A, Jarrold C, Kane M, Miyake A, Towse K, eds), pp 76-106. Oxford: Oxford University Press.

Buch ER, Mars RB, Boorman ED, Rushworth MFS (2010) A network centered on ventral premotor cortex exerts both facilitatory and inhibitory control over primary motor cortex during action reprogramming. J Neurosci 30:1395-1401.

Chambers CD, Garavan H, Bellgrove MA (2009) Insights into the neural basis of response inhibition from cognitive and clinical neuroscience. Neurosci Biobehav Rev 33:631-646.

Chambers CD, Bellgrove MA, Stokes MG, Henderson TR, Garavan H, Robertson IH, Morris AP, Mattingley JB (2006) Executive "Brake Failure" following Deactivation of Human Frontal Lobe. J Cogn Neurosci 18:444-455.

Chambers CD, Bellgrove MA, Gould IC, English T, Garavan H, McNaught E, Kamke M, Mattingley JB (2007) Dissociable mechanisms of cognitive control in prefrontal and premotor cortex. J Neurophysiol 98:3638-3647.

Chao HHA, Luo X, Chang JLK, Li C-SR (2009) Activation of the pre-supplementary motor area but not inferior prefrontal cortex in association with short stop signal reaction time - an intra-subject analysis. BMC Neurosci 10:75.

Chen C-Y, Muggleton NG, Tzeng OJL, Hung DL, Juan C-H (2009) Control of prepotent responses by the superior medial frontal cortex. Neuroimage 44:537-545.

Chen X, Scangos K, Stuphorn V (2010) Supplementary Motor Area Exerts Proactive and Reactive Control of Arm Movements. J Neurosci 30:14657-14675.

Chikazoe J, Jimura K, Hirose S, Yamashita K-i, Miyashita Y, Konishi S (2009) Preparation to inhibit a response complements response inhibition during performance of a stop-signal task. J Neurosci 29:15870-15877.

Corbetta M, Shulman GL (2002) Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 3:201-215.

Corbetta M, Patel G, Shulman GL (2008) The reorienting system of the human brain: from environment to theory of mind. Neuron 58:306-324.

Coxon JP, Stinear CM, Byblow WD (2006) Intracortical inhibition during volitional inhibition of prepared action. J Neurophysiol 95:3371-3383.

Coxon JP, Stinear CM, Byblow WD (2007) Selective inhibition of movement. J Neurophysiol 97:2480-2489.

Duann J-R, Ide JS, Luo X, Li C-sR (2009) Functional connectivity delineates distinct roles of

the inferior frontal cortex and presupplementary motor area in stop signal inhibition. J Neurosci 29:10171-10179.

Hwang K, Velanova K, Luna B (2010) Strengthening of top-down frontal cognitive control networks underlying the development of inhibitory control: a functional magnetic resonance imaging effective connectivity study. J Neurosci 30:15535-15545.

Isoda M, Hikosaka O (2008) Role for subthalamic nucleus neurons in switching from automatic to controlled eye movement. J Neurosci 28:7209-7218.

Iyer MB, Schleper N, Wassermann EM (2003) Priming stimulation enhances the depressant effect of low-frequency repetitive transcranial magnetic stimulation. J Neurosci 23:10867-10872.

Jahfari S, Stinear C, Claffey M, Verbruggen F, Aron A (2010) Responding with restraint: what are the neurocognitive mechanisms? J Cogn Neurosci 22:1479-1492.

Keel J, Smith M, Wassermann E (2001) A safety screening questionnaire for transcranial magnetic stimulation. Clin Neurophysiol.

Koechlin E, Summerfield C (2007) An information theoretical approach to prefrontal executive function. Trends Cogn Sci 11:229-235.

Logan GD, Cowan WB (1984) On the ability to inhibit thought and action: A theory of an act of control. Psychol Rev 91:291-327.

Logan GD, Burkell J (1986) Dependence and independence in responding to double stimulation. A comparison of stop, change, and dual-task paradigms. J Exp Psychol Hum Percept Perform 12:549-563.

Mars RB, Piekema C, Coles MGH, Hulstijn W, Toni I (2007) On the programming and reprogramming of actions. Cereb Cortex 17:2972-2979.

Mars RB, Klein MC, Neubert F-X, Olivier E, Buch ER, Boorman ED, Rushworth MFS (2009) Short-latency influence of medial frontal cortex on primary motor cortex during action selection under conflict. J Neurosci 29:6926-6931.

Mink JW (1996) The basal ganglia: focused selection and inhibition of competing motor programs. Prog Neurobiol 50:381-425.

Neggers SF, Langerak TR, Schutter DJ, Mandl RC, Ramsey NF, Lemmens PJ, Postma A (2004) A stereotactic method for image-guided transcranial magnetic stimulation validated with fMRI and motor-evoked potentials. Neuroimage 21:1805-1817.

Neubert FX, Mars RB, Buch ER, Olivier E, Rushworth MF (2010) Cortical and subcortical interactions during action reprogramming and their related white matter pathways. Proc Natl Acad Sci U S A 107:13240-13245.

Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9:97-113.

Prodoehl J, Yu H, Little DM, Abraham I, Vaillancourt DE (2008) Region of interest template for the human basal ganglia: comparing EPI and standardized space approaches. Neuroimage 39:956-965.

Ramautar JR, Kok A, Ridderinkhof KR (2004) Effects of stop-signal probability in the stop-signal paradigm: the N2/P3 complex further validated. Brain Cogn 56:234-252.

Ramautar JR, Slagter HA, Kok A, Ridderinkhof KR (2006) Probability effects in the stop-signal paradigm: the insula and the significance of failed inhibition. Brain Res 1105:143-154.

Schutter D, van Honk J (2006) A Standardized Motor Threshold Estimation Procedure for Transcranial Magnetic Stimulation Research. The Journal of ECT.

Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC (1998) The mini-international neuropsychiatric interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 59 Suppl 20:22-33.

Siebner HR et al. (2009) Consensus paper: combining transcranial stimulation with neuroimaging. Brain Stimulation 2:58-80.

Stinear CM, Coxon JP, Byblow WD (2009) Primary motor cortex and movement prevention: Where Stop meets Go. Neurosci Biobehav Rev 33:662-673.

Stuphorn V, Schall JD (2006) Executive control of countermanding saccades by the supplementary eye field. Nat Neurosci 9:925-931.

Stuphorn V, Brown JW, Schall JD (2010) Role of supplementary eye field in saccade initiation: executive, not direct, control. J Neurophysiol 103:801-816.

Swann N, Tandon N, Canolty R, Ellmore TM, McEvoy LK, Dreyer S, DiSano M, Aron AR (2009) Intracranial EEG reveals a time- and frequency-specific role for the right inferior frontal gyrus and primary motor cortex in stopping initiated responses. J Neurosci 29:12675-12685.

van den Wildenberg W, Burle B, Vidal F, van der Molen M, Ridderinkhof K, Hasbroucq T (2010) Mechanisms and Dynamics of Cortical Motor Inhibition in the Stop-signal Paradigm: A TMS Study. J Cogn Neurosci 22:225-239.

Verbruggen F, Logan GD (2008) Response inhibition in the stop-signal paradigm. Trends Cogn Sci 12:418-424.

Verbruggen F, Logan GD (2009a) Proactive adjustments of response strategies in the stop-signal paradigm. J Exp Psychol Hum Percept Perform 35:835-854.

Verbruggen F, Logan GD (2009b) Proactive adjustments of response strategies in the stop-signal paradigm. Journal of experimental psychology Human perception and performance 35:835-854.

Verbruggen F, Logan GD (2009c) Models of response inhibition in the stop-signal and stop-change paradigms. Neurosci Biobehav Rev 33:647-661.

Verbruggen F, Aron AR, Stevens MA, Chambers CD (2010) Theta burst stimulation dissociates attention and action updating in human inferior frontal cortex. Proc Natl Acad Sci USA 107:13966-13971.

Vink M, Ramsey NF, Raemaekers M, Kahn RS (2006) Striatal dysfunction in schizophrenia and unaffected relatives. Biol Psychiatry 60:32-39.

Vink M, Zandbelt BB, Bloemendaal M, Kahn RS (2011) Neural subprocesses of proactive inhibition. In: 17th Annual Meeting of the Organization for Human Brain Mapping Quebec.

Vink M, Kahn RS, Raemaekers M, van den Heuvel M, Boersma M, Ramsey NF (2005) Function of striatum beyond inhibition and execution of motor responses. Hum Brain Mapp 25:336-344.

Watanabe M, Munoz D (2010) Saccade Suppression by Electrical Microstimulation in Monkey Caudate Nucleus. J Neurosci 30:2700.

Zandbelt BB, Vink M (2010) On the role of the striatum in response inhibition. PLoS ONE 11:e13848.

# Expectations and violations: delineating the neural network of proactive inhibitory control

4

**Bram B. Zandbelt, Mirjam Bloemendaal, Sebastiaan F.W. Neggers, René S. Kahn, Matthijs Vink**

*Under review*

The ability to stop a prepared response (reactive inhibition) depends on the degree to which stopping is expected (proactive inhibition). Functional MRI studies have shown that activation during proactive and reactive inhibition overlaps, suggesting that the whole neural network for reactive inhibition becomes already activated in anticipation of stopping. However, these studies measured proactive inhibition as the effect of stop-signal probability on activation during go-signal trials. Therefore, activation could reflect expectation of a stop-signal (evoked by the stop-signal probability cue), but also violation of this expectation because stop-signals do not occur on go-signal trials. We addressed this problem, using a stop-signal task in which the stop-signal probability cue and the go-signal were separated in time. Hence, we could separate activation during the cue, reflecting expectation of the stop-signal, from activation during the go-signal, reflecting expectation of the stop-signal or violation of that expectation. During the cue, the striatum, the supplementary motor complex (SMC), and the midbrain activated. During the go-signal, the right inferior parietal cortex (IPC) and the right inferior frontal cortex (IFC) activated. These findings suggest that the neural network previously associated with proactive inhibition can be subdivided into two components. One component, including the striatum, the SMC, and the midbrain, activated during the cue, implicating this network in proactive inhibition. Another component, consisting of the right IPC and the right IFC, activated during the go-signal. Rather than being involved in proactive inhibition, this network appears to be involved in processes associated with violation of expectations.

*We thank Mariët van Buuren and Thomas Gladwin for helpful comments on the manuscript.*

## Introduction

The ability to stop a prepared response (i.e. reactive inhibition) depends on the degree to which stopping is expected (i.e. proactive inhibition). This is supported by experimental findings from stop-signal tasks that manipulate stop-signal expectation through variation of stop-signal probability. For example, the higher the stop-signal probability the longer participants wait with responding to go-signals (Logan and Burkell, 1986; Ramautar et al., 2004; Vink et al., 2005; Ramautar et al., 2006; Vink et al., 2006; Verbruggen and Logan, 2009; Jahfari et al., 2010; Zandbelt and Vink, 2010) and the longer participants wait with responding to go-signals the greater the chance that they can stop their response when a stop-signal occurs (Logan and Cowan, 1984). Likewise, greater proactive response slowing is associated with faster reactive stopping (Chikazoe et al., 2009). Furthermore, the higher the stop-signal probability the slower activity in the primary motor cortex increases to response initiation (Jahfari et al., 2010), reflecting that the state of the motor system before the onset of a stop-signal determines whether or not a response can be stopped (Lo et al., 2009; van den Wildenberg et al., 2010).

Functional magnetic resonance imaging (fMRI) studies have shown that activation during proactive and reactive inhibition largely overlaps (Chikazoe et al., 2009; Jahfari et al., 2010; Zandbelt and Vink, 2010). This has led to the view that the whole neural network for reactive inhibition becomes already activated in anticipation of stopping (e.g. Aron, 2010). Typically, proactive inhibition has been measured as the effect of stop-signal probability on activation during go-signal trials, that is, trials in which stop-signals do not occur. For example, Chikazoe et al. (2009) identified brain regions involved in proactive inhibition by contrasting activation during go-signal trials in the 20% stop-signal probability context (i.e. trials in which stop-signals could occur, but ultimately did not) with activation during go-signal trials in the 0% stop-signal probability context (i.e. trials in which stop-signals never occurred). Recently, we took a similar approach but varied stop-signal probability in five steps from 0% to 33% (Zandbelt and Vink, 2010). Importantly, activation in these kinds of contrasts may not only reflect expectation of a stop-signal (evoked by the stop-signal probability cue), but also violation of this expectation because stop-signals do not occur on go-signal trials. These accounts could not be dissociated by previous studies, because the cue indicating stop-signal

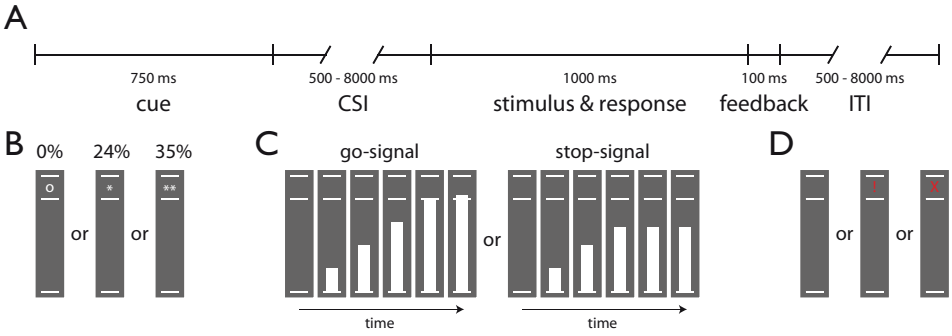



**Figure 1.** Delayed-response version of the stop-signal anticipation task. **(A)** Timeline of a trial. **(B)** Each trial started with the presentation of a cue for 750 ms that indicated the probability that a stop-signal would be presented (o, 0%, N = 85; *, 24%, N = 85; **, 35%, N = 85). **(C)** After a variable cue-stimulus interval (CSI, mean 4138 ms, range 500 - 8000 ms), a bar moved from the lower line towards the upper line, reaching the middle line in 800 ms. On go-signal trials (80%, N = 205), participants had to stop the bar as close to the middle line as possible, by pressing a button with the right thumb (i.e. the target response time was 800 ms). On stop-signal trials (20%, N = 50), the bar stopped moving automatically before reaching the middle line (i.e. stop-signal), indicating that a response had to be suppressed. The initial stop-signal delay (from the moment the bar started moving) was 500 ms and was adjusted in 33-ms steps according to a tracking procedure. Stop-signal trials were pseudorandomly interspersed between go-signal trials. **(D)** Feedback was presented for 100 ms if the response time was longer than 900 ms (!) or if an error was made (X). The intertrial interval (ITI) was on average 4038 ms and ranged from 500 to 7900 ms. The task lasted 42 m and 37 s.

probability and the go-signal were always presented simultaneously. Here, we addressed this problem, using a stop-signal task in which the stop-signal probability cue and the go-signal were separated in time (Figure 1). Therefore, we could distinguish the effect of stop-signal probability on activation during the cue, reflecting expectation of the stop-signal, from the effect of stop-signal probability on activation during the go-signal, reflecting expectation of the stop-signal or violation of that expectation.

## Materials & Methods

### *Participants*

22 healthy volunteers (mean age 23.5 years, range 20 - 28 years; 13 females) participated in this study. All participants were right-handed, had normal or corrected-to-normal vision, and gave written informed consent after having received complete description of the study. The study was approved by the University Medical Center Utrecht ethics committee and was performed in accordance with the Declaration of Helsinki.

*Delayed-response version of the stop-signal anticipation task*

Participants performed a delayed-response version of the stop-signal anticipation task (Zandbelt and Vink, 2010), which is described in Figure 1. Participants were trained on this task before the fMRI experiment.

*Data acquisition*

The experiment was performed on a 3.0 T MRI scanner (Philips Medical System, Best, the Netherlands) at the University Medical Center Utrecht. We collected 1600 whole-brain T2*-weighted echo planar images (EPI) with blood-oxygen level-dependent (BOLD) contrast in a single run and a T1-weighted image for within-subject registration purposes, using scan parameters identical to those described before (Zandbelt and Vink, 2010).

*Behavioral analysis*

Proactive inhibition was investigated by examining the effect of stop-signal probability on go-signal response time (RT). As an additional index of proactive inhibition, we computed the stop-signal probability slope, which is defined as the change in go-signal RT per stop-signal probability unit increase. As an index of reactive inhibition, we computed the stop-signal reaction time (SSRT). The SSRT was computed according to the integration method (Logan and Cowan, 1984), separately for each stop-signal probability level. We also examined stop accuracy for each stop-signal probability level for evaluation of the tracking procedure (see legend of Figure 1).

The effect of stop-signal probability on go-signal RT and SSRT was analyzed in two separate repeated-measures ANOVAs, with stop-signal probability as factor. The correlation between the stop-signal probability slope and the SSRT (pooled across stop-signal probability contexts) was analyzed using the Pearson correlation coefficient.

*fMRI analysis*

Functional images were analyzed with SPM5 (http://www.fil.ion.ucl.ac.uk/spm/software/spm5). Pre-processing was performed as described before (Zandbelt and Vink, 2010), involving correction for slice timing differences, realignment for head motion correction, spatial normalization to the Montreal Neurological Institute (MNI) template brain, and spatial smoothing to accommodate interindividual differences in neuroanatomy.

Statistical analysis was performed within the framework of the general linear model and followed a two-level procedure. We modeled the onsets of cue 0% (i.e. cue in the 0% stop-signal probability context), cue 24%, cue 35%, RT on go-signal 0% trials, RT on go-signal 24% trials, RT on go-signal 35% trials, RT on failed stop-signal trials, target RT on successful stop-signal trials, and explicit feedback. Each event was modeled as a delta function, except for the cues that were modeled as a boxcar with duration of the period between cue and stimulus onset. The data were high-pass filtered (cutoff: 128 s) to remove low-frequency drifts and a first-order autoregressive model was used to model the remaining serial correlations. We generated contrast images for cue 0%, cue 24%, cue 35%, go-signal 0%, go-signal 24%, and go-signal 35% (all against baseline). The effect of stop-signal probability on activation during the cue and during the go-signal cannot be contrasted directly, because cues were modeled as epochs whereas go-signals were modeled as events (Henson, 2007). To enable a direct comparison, we first standardized cue and go-signal contrast images to Z-score images and then computed an image of the effect of stop-signal probability on these Z-scores using linear regression, separately for the cue and the go-signal.

These images were entered into a second-level random-effects full factorial analysis, with trial component (cue versus stimulus) as a within-subject factor and the stop-signal probability slope as a between-subjects factor. This between-subjects factor was included to test the relation between the effect of stop-signal probability on activation and go-signal RT across participants during the cue versus during the go-signal. Statistical parametric maps were tested for significance using cluster-level inference (cluster-defining threshold of $P < .001$, cluster-probability of $P < .05$, family-wise error corrected for multiple comparisons). For a graphical representation of the experimental effects, we used the activated clusters to extract mean contrast estimates.

*Table I. Descriptive statistics for go-signal and stop-signal trials*

| Trial type | Stop-signal probability | | |
|---|---|---|---|
| | 0% | 24% | 35% |
| go-signal | | | |
| Accuracy (%) | 99.5 ± 1.6 | 99.2 ± 1.8 | 99.3 ± 1.4 |
| RT (ms) | 808 ± 14 | 821 ± 20 | 829 ± 21 |
| stop-signal | | | |
| Accuracy (%) | - | 49.3 ± 3.2 | 50.0 ± 2.7 |
| SSRT (ms) | - | 328 ± 20 | 336 ± 16 |
| Failed RT (ms) | - | 796 ± 27 | 793 ± 29 |

All figures represent mean ± s.d.; RT, response time; SSRT, stop-signal reaction time.

## Results

### *Task performance*

Table I shows descriptive statistics of task performance on go-signal and stop-signal trials, for each stop-signal probability context separately. First, we assessed whether participants waited longer with responding to go-signals as stop-signal probability increased (Figure 2A). Whereas go-signal RTs after a 0% stop-signal probability cue were close to the target RT of 800 ms, go-signal RTs became progressively slower as stop-signal probability increased (linear contrast, $F(1,21) = 36.61$, $P < .001$). This is consistent with previous studies manipulating stop-signal probability (Logan and Burkell, 1986; Ramautar et al., 2004; Vink et al., 2005; Ramautar et al., 2006; Vink et al., 2006; Verbruggen and Logan, 2009; Zandbelt and Vink, 2010) and suggests that participants slowed down proactively in anticipation of a stop-signal.

Next, we tested whether greater proactive slowing was associated with faster reactive stopping, as previously reported (Chikazoe et al., 2009). We examined the relationship between the stop-signal probability slope (i.e. the change in go-signal RT per stop-signal probability unit increase) and the stop-signal reaction time (SSRT) (Figure 2B). The stop-signal probability slope and the SSRT were negatively correlated ($r = -.46$, $P = .015$), confirming an inverse relationship between proactive and reactive inhibition across participants. Further, the SSRT (Table I) was similar to that in a previous report of the stop-signal anticipation task (Zandbelt and Vink, 2010) and did not differ between stop-signal probability contexts ($t(21) = 1.35$, $P = .19$), confirming others (Verbruggen and Logan, 2009). Finally,

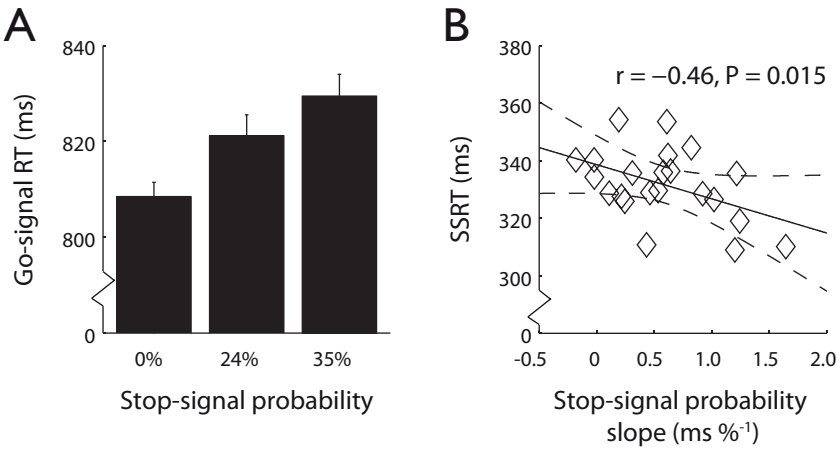



**Figure 2.** Stop-signal anticipation task performance. **(A)** Go-signal RT increased as a function of stop-signal probability. Bars represent mean go-signal RT, error bars indicate standard errors. **(B)** SSRT was negatively correlated with the stop-signal probability slope, the change in go-signal RT per stop-signal probability unit increase. Each data point represents a single subject. The regression line and the 95% confidence bands are given as solid and dashed lines, respectively.

we reproduced key findings that are essential for the model underlying SSRT estimation to hold (Logan and Cowan, 1984); RTs on unsuccessful stop-signal trials were faster than RTs on go-signal trials ($t(21) = 12.92$, $P < .001$) and stopping rates declined with later onset of the stop-signal ($t(21) = 14.56$, $P < .001$).

*Functional MRI*

In an initial analysis, we examined the effect of stop-signal probability on activation during the cue and the go-signal, separately (Supporting Information, Figure S1). During the cue, activation increased as a function of stop-signal probability in the left and right striatum, the supplementary motor complex (SMC), the midbrain, and the left and right insula. During the go-signal, there was a significant effect of stop-signal probability on activation in the right inferior parietal cortex (IPC) and the right inferior frontal cortex (IFC). Combined, the networks activated during the cue and go-signal show striking overlap with the networks reported by previous reports studying proactive inhibition (Chikazoe et al., 2009; Jahfari et al., 2010; Zandbelt and Vink, 2010)..

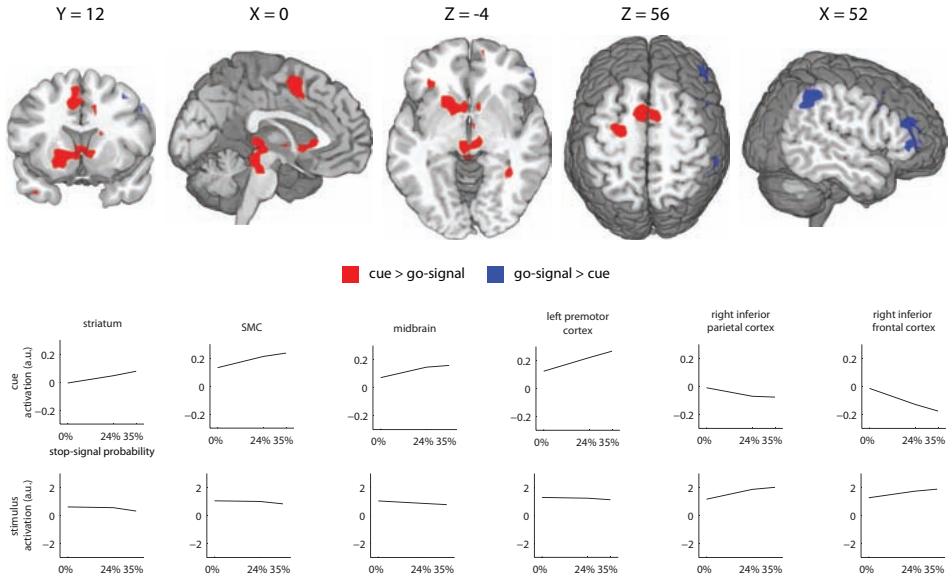



**Figure 3.** Effect of stop-signal probability on brain activation differs between cue and go-signal. Brain regions showing a significant increase in activation as a function of stop-signal probability during the cue versus the go-signal (red) or during the go-signal versus the cue (blue). Significant clusters of activation ($P < .05$, FWE-corrected) are displayed on a normalized brain (neurological orientation, left is left). Line graphs are shown to provide a graphical representation of the mean effect of stop-signal probability on activation during the cue (top row) and during the go-signal (bottom row).

These fMRI results appear to indicate that the network previously associated with proactive inhibition can be separated into two distinct components. To test this idea directly, we contrasted the effect of stop-signal probability on activation during the cue and the go-signal (Figure 3). Several regions showed a greater effect of stop-signal probability on activation during the cue than during the go-signal, including the left and right striatum, the SMC, the midbrain, and the left premotor cortex. There was a greater effect of stop-signal probability on activation during the go-signal versus the cue in the right IPC and the right IFC. These findings confirm that the neural network previously associated with proactive inhibition can be divided into two subcomponents.

Finally, we tested whether inter-individual differences in activation levels during the cue and the go-signal could be explained by between-subjects variation in the degree of proactive slowing. We tested the between-subjects relation between the effect of stop-signal probability on

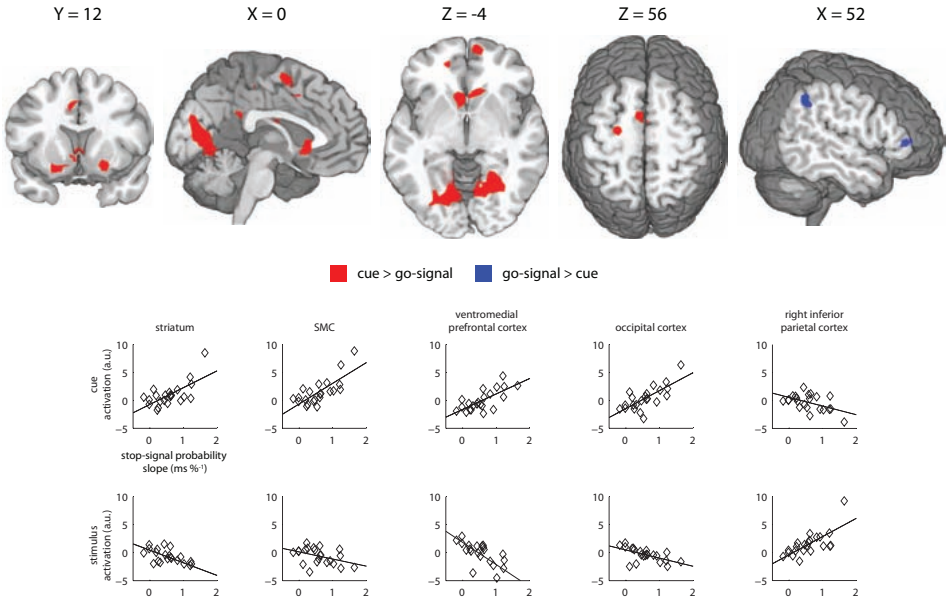



**Figure 4.** Effect of stop-signal probability on brain activation in relation to proactive slowing differs between cue and go-signal. Brain regions shown a significantly stronger positive relationship during the cue than during the go-signal increase in activation as a function of stop-signal probability during the cue versus go-signal (red) or during the go-signal versus the cue (blue). Significant clusters of activation ($P < .05$, FWE-corrected) are displayed on a normalized brain (neurological orientation, left is left). Scatter graphs are shown to provide a graphical representation of the relation between the behavioral and physiological sensitivity to increasing stop-signal probability during the cue (top row) and during the go-signal (bottom row).

activation and go-signal RT during the cue against this relation during the go-signal. (Figure 4). We found a stronger positive relationship during the cue than during the go-signal in the left and right striatum, the SMA, and in the occipital cortex, as well as in the ventromedial prefrontal cortex. In contrast, there was a stronger positive relationship between proactive slowing and activation during the go-signal in the right IPC. Correlations in the midbrain and left premotor cortex (during the cue), as well as the right IFC (during the go-signal) did not reach whole-brain corrected significance, even though these regions did activate as a function of stop-signal probability (Figure 3). Nevertheless, post-hoc exploratory analyses of activation in 6-mm spheres around the local maxima of these regions revealed a stronger positive relationship during the cue versus the go-signal in the midbrain ($P = .010$, small volume corrected, SVC) and the left premotor cortex ($P = .001$, SVC), as well as a stronger positive relationship during the go-signal versus the cue in the right IFC ($P = .002$, SVC). Thus,

participants showing the greatest degree of proactive slowing showed the strongest activation of the striatum, the SMC and the midbrain during the cue, and the strongest activation of the right IPC and right IFC during the go-signal.

## Discussion

We studied the neural network associated with proactive inhibition (i.e. expectation of stopping). Previous fMRI studies measured proactive inhibition as the effect of stop-signal probability on activation during go-signal trials. However, this activation may not only reflect expectation of a stop-signal (evoked by the stop-signal probability cue), but also violation of that expectation (evoked by the absence of an expected stop-signal after the go-signal). These studies could not dissociate expectation and violation, because the stop-signal probability cue and the go-signal were presented simultaneously. Here, we used a stop-signal task in which the stop-signal probability cue and the go-signal were separated in time. Therefore, we could distinguish the effect of stop-signal probability on activation during the cue from the effect of stop-signal probability on activation during the go-signal. We showed that the left and the right striatum, the supplementary motor complex (SMC), and the midbrain activated during the cue. In contrast, the right inferior parietal cortex (IPC) and the right inferior frontal cortex (IFC) activated during the go-signal. In both networks, greater activation was associated with greater proactive slowing across participants.

When added together, the networks activated during the cue and the go-signal correspond very well to the network observed in previous fMRI studies of proactive inhibition (Chikazoe et al., 2009; Jahfari et al., 2010; Zandbelt and Vink, 2010) as well as to the network activated during reactive inhibition (for review, see Chambers et al., 2009). Previous studies have therefore suggested that the whole network underlying reactive inhibition becomes activated already in anticipation of a stop-signal (Chikazoe et al., 2009; Aron, 2010; Jahfari et al., 2010; Zandbelt and Vink, 2010). The present findings appear to challenge this view in that only a part of this network becomes activated before a stop-signal occurs, whereas other regions, such as the right IFC and the right IPC, do not activate during the cue but only during the go-signal. In what follows, we will argue that the network activated during the cue is involved in processes related

to expectation of the stop-signal whereas the network activated during the go-signal is involved in processes associated with violation of expectations.

Cue-related activation in the striatum and the SMC has been associated with preparation for inhibition of motor responses (Apicella et al., 1992; Curtis and D'Esposito, 2003; Chen et al., 2010; Watanabe and Munoz, 2010). Anticipatory activation in the striatum and the SMC may reflect the act of increasing the threshold that triggers a motor response (i.e. response threshold). Participants increase the response threshold when they expect a stop-signal (Verbruggen and Logan, 2009) and there is evidence to suggest that the striatum and the SMC are involved in such response threshold adjustments (Lo and Wang, 2006; Stuphorn and Schall, 2006; Forstmann et al., 2008; Chen et al., 2010). So, our findings are consistent with the idea that the striatum and the SMC have a central role in proactive inhibition (Vink et al., 2005; Vink et al., 2006; Aron, 2010; Chen et al., 2010; Stuphorn et al., 2010; Zandbelt and Vink, 2010).

In addition, we found cue-related activation in the midbrain. This region harbors the ventral tegmental area and the substantia nigra pars compacta, the main dopaminergic cell groups in the midbrain. The midbrain activation we report might reflect increased dopaminergic signaling. This is consistent with the idea that midbrain dopaminergic neurons are fundamental to proactive control (Braver et al., 2007). Furthermore, our findings corroborate a study showing that midbrain fMRI signals predict response strategy adjustments in the stop-signal task (Boehler et al., 2010), possibly implemented by the striatum and the SMC. However, these interpretations are speculative and should be made with caution, because midbrain fMRI signals are at best indirectly associated with activity in midbrain dopaminergic neurons and may be confounded by the presence of nearby pulsatile blood vessels (D'Ardenne et al., 2008; Düzel et al., 2009).

Activation in the right IFC and right IPC also increased as a function of stop-signal probability. However, rather than during the cue, these effects occurred during the go-signal. Therefore, this activation could reflect either expectation of a stop-signal or violation of that expectation. The right IFC has indeed been implicated in proactive control (Braver et al., 2007), particularly in the maintenance of contextual information (e.g. stop-signal probability) to bias processing in pathways responsible for

task performance. However, if the right IFC maintains stop-signal probability then it should activate during the cue-stimulus interval, but it did not. Alternatively, the right IFC might implement proactive inhibition, but only from the time when a stop-signal can be expected (i.e. after the go-signal). This would explain why the right IFC activates during the go-signal rather than during the cue. Nevertheless, this appears unlikely, given previous stop-signal studies showing that activity in the right IFC is modulated after rather than before stop-signal onset (Swann et al., 2009) and that stimulation of the right IFC alters reactive inhibition, but not proactive inhibition (Verbruggen et al., 2010). Moreover, neither of these interpretations explains the meaning of right IPC activation. Thus, the right IPC and the right IFC do not appear to be involved in proactive inhibition.

Instead, go-signal-related activation of the right IPC and the right IFC could reflect that an expected stop-signal did not occur. Participants demonstrated proactive slowing, suggesting that they expected stop-signals. However, on the trials we analyzed (i.e. go-signal trials) this expectation was violated because no stop-signal occurred. Indeed, unexpected events activate the right IPC and the right IFC (Arrington et al., 2000; Corbetta et al., 2000; Asplund et al., 2010) and the more unexpected an event the larger the activation in these regions (Vossel et al., 2006; Shulman et al., 2009). It is likely that stop-signal expectation is updated over the course of a trial (i.e. it declines as the rising bar gets closer to the target line). The right IPC and the right IFC have also been implicated in such online updating of temporal expectations (Nobre et al., 2007; Coull, 2009). More generally, the right IPC and the right IFC constitute a network that is concerned with bottom-up processes (e.g. updating of expectations) rather than top-down processes (e.g. expectation of a stop-signal) (Corbetta and Shulman, 2002; Corbetta et al., 2008). Thus, stop-signal probability effects on right IPC and right IFC activation reported here and elsewhere (Chikazoe et al., 2009; Jahfari et al., 2010; Zandbelt and Vink, 2010) may reflect expectancy violation and updating of expectations rather than stop-signal expectation. Future studies, using techniques with millisecond temporal resolution such as magnetoencephalography, should examine the timing of activity in the right IPC and the right IFC. If the modulation of activity by stop-signal probability occurs time-locked to go-signal onset, then it probably reflects expectation of a stop-signal. However, if it

occurs around the time a stop-signal is presented, then it is more likely to indicate violation of expectation.

Our findings provide strong support for the involvement of the striatum, the SMC, and the midbrain in anticipation of stopping. We interpreted these results in terms of top-down control through response threshold adjustments, but there may be alternative explanations. For example, activation during proactive inhibition may also be interpreted in terms of conflict (Neubert and Klein, 2010). In the current task design, greater stop-signal probability automatically resulted in greater uncertainty and therefore greater response conflict. Future experiments should try to distinguish between these explanations by varying stop-signal probability independently from uncertainty.

*Conclusion*

We show that the neural network associated with proactive inhibition can be subdivided into two components. One component, including the striatum, the SMC, and the midbrain, activated during the cue, implicating this network in proactive inhibition. Another component, consisting of the right IPC and the right IFC, activated during the go-signal. Rather than being involved in proactive inhibition, this network may be involved in processes associated with violation of expectations.

## References

Apicella P, Scarnati E, Ljungberg T, Schultz W (1992) Neuronal activity in monkey striatum related to the expectation of predictable environmental events. J Neurophysiol 68:945-960.

Aron AR (2010) From Reactive to Proactive and Selective Control: Developing a Richer Model for Stopping Inappropriate Responses. Biol Psychiatry.

Arrington CM, Carr TH, Mayer AR, Rao SM (2000) Neural mechanisms of visual attention: object-based selection of a region in space. J Cogn Neurosci 12 Suppl 2:106-117.

Asplund CL, Todd JJ, Snyder AP, Marois R (2010) A central role for the lateral prefrontal cortex in goal-directed and stimulus-driven attention. Nat Neurosci 13:507-512.

Boehler CN, Bunzeck N, Krebs RM, Noesselt T, Schoenfeld MA, Heinze HJ, Münte TF, Woldorff MG, Hopf JM (2010) Substantia nigra activity level predicts trial-to-trial adjustments in cognitive control. J Cogn Neurosci.

Braver TS, Gray JR, Burgess GC (2007) Explaning the many varieties of working memory variation: dual mechanisms of cognitive control. In: Variation in Working Memory (Conway A, Jarrold C, Kane M, Miyake A, Towse K, eds), pp 76-106. Oxford: Oxford University Press.

Chambers CD, Garavan H, Bellgrove MA (2009) Insights into the neural basis of response inhibition from cognitive and clinical neuroscience. Neurosci Biobehav Rev 33:631-646.

Chen X, Scangos K, Stuphorn V (2010) Supplementary Motor Area Exerts Proactive and Reactive Control of Arm Movements. J Neurosci 30:14657-14675.

Chikazoe J, Jimura K, Hirose S, Yamashita K-i, Miyashita Y, Konishi S (2009) Preparation to inhibit a response complements response inhibition during performance of a stop-signal task. J Neurosci 29:15870-15877.

Corbetta M, Shulman GL (2002) Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 3:201-215.

Corbetta M, Patel G, Shulman GL (2008) The reorienting system of the human brain: from environment to theory of mind. Neuron 58:306-324.

Corbetta M, Kincade JM, Ollinger JM, McAvoy MP, Shulman GL (2000) Voluntary orienting is dissociated from target detection in human posterior parietal cortex. Nat Neurosci 3:292-297.

Coull JT (2009) Neural substrates of mounting temporal expectation. PLoS Biol 7:e1000166.

Curtis CE, D'Esposito M (2003) Success and failure suppressing reflexive behavior. J Cogn Neurosci 15:409-418.

D'Ardenne K, McClure SM, Nystrom LE, Cohen JD (2008) BOLD responses reflecting dopaminergic signals in the human ventral tegmental area. Science 319:1264-1267.

Düzel E, Bunzeck N, Guitart-Masip M, Wittmann B, Schott BH, Tobler PN (2009) Functional imaging of the human dopaminergic midbrain. Trends Neurosci 32:321-328.

Forstmann BU, Dutilh G, Brown S, Neumann J, von Cramon DY, Ridderinkhof KR, Wagenmakers EJ (2008) Striatum and pre-SMA facilitate decision-making under time pressure. Proc Natl Acad Sci USA 105:17538-17542.

Henson R (2007) Efficient experimental design for fMRI. In: Statistical Parametric Mapping. The Analysis of Functional Brain Images., 1 Edition (Friston KJ, Ashburner JT, Kiebel SJ, Nichols TE, Penny W, eds), pp 193-210. London: Academic Press.

Jahfari S, Stinear C, Claffey M, Verbruggen F, Aron A (2010) Responding with restraint: what are the neurocognitive mechanisms? J Cogn Neurosci 22:1479-1492.

Lo C, Wang X (2006) Cortico-basal ganglia circuit mechanism for a decision threshold in reaction time tasks. Nat Neurosci 9:956-963.

Lo C, Boucher L, Paré M, Schall JD, Wang X (2009) Proactive inhibitory control and attractor dynamics in countermanding action: a spiking neural circuit model. J Neurosci 29:9059-9071.

Logan GD, Cowan WB (1984) On the ability to inhibit thought and action: A theory of an act of control. Psychol Rev 91:291-327.

Logan GD, Burkell J (1986) Dependence and independence in responding to double stimulation. A comparison of stop, change, and dual-task paradigms. J Exp Psychol Hum Percept Perform 12:549-563.

Neubert F-X, Klein M (2010) What Is Driving Inhibition-Related Activity in the Frontal Lobe? J Neurosci 30:4830.

Nobre A, Correa A, Coull J (2007) The hazards of time. Curr Opin Neurobiol 17:465-470.

Ramautar JR, Kok A, Ridderinkhof KR (2004) Effects of stop-signal probability in the stop-signal paradigm: the N2/P3 complex further validated. Brain Cogn 56:234-252.

Ramautar JR, Slagter HA, Kok A, Ridderinkhof KR (2006) Probability effects in the stop-signal paradigm: the insula and the significance of failed inhibition. Brain Res 1105:143-154.

Shulman G, Astafiev S, Franke D, Pope D, Snyder A, Mcavoy M, Corbetta M (2009) Interaction of Stimulus-Driven Reorienting and Expectation in Ventral and Dorsal Frontoparietal and Basal Ganglia-Cortical Networks. J Neurosci 29:4392.

Stuphorn V, Schall JD (2006) Executive control of countermanding saccades by the supplementary eye field. Nat Neurosci 9:925-931.

Stuphorn V, Brown JW, Schall JD (2010) Role of supplementary eye field in saccade initiation: executive, not direct, control. J Neurophysiol 103:801-816.

Swann N, Tandon N, Canolty R, Ellmore TM, McEvoy LK, Dreyer S, DiSano M, Aron AR (2009) Intracranial EEG reveals a time- and frequency-specific role for the right inferior frontal gyrus and primary motor cortex in stopping initiated responses. J Neurosci 29:12675-12685.

van den Wildenberg WPM, Burle B, Vidal F, van der Molen MW, Ridderinkhof KR, Hasbroucq T (2010) Mechanisms and dynamics of cortical motor inhibition in the stop-signal paradigm: a TMS study. J Cogn Neurosci 22:225-239.

Verbruggen F, Logan GD (2009) Proactive adjustments of response strategies in the stop-signal paradigm. Journal of experimental psychology Human perception and performance 35:835-854.

Verbruggen F, Aron AR, Stevens MA, Chambers CD (2010) Theta burst stimulation dissociates attention and action updating in human inferior frontal cortex. Proc Natl Acad Sci USA 107:13966-13971.

Vink M, Ramsey NF, Raemaekers M, Kahn RS (2006) Striatal dysfunction in schizophrenia and unaffected relatives. Biol Psychiatry 60:32-39.

Vink M, Kahn RS, Raemaekers M, van den Heuvel M, Boersma M, Ramsey NF (2005) Function

of striatum beyond inhibition and execution of motor responses. Hum Brain Mapp 25:336-344.

Vossel S, Thiel CM, Fink GR (2006) Cue validity modulates the neural correlates of covert endogenous orienting of attention in parietal and frontal cortex. Neuroimage 32:1257-1264.

Watanabe M, Munoz DP (2010) Presetting basal ganglia for volitional actions. J Neurosci 30:10144-10157.

Zandbelt BB, Vink M (2010) On the role of the striatum in response inhibition. PLoS ONE 11:e13848.

## Supporting Information

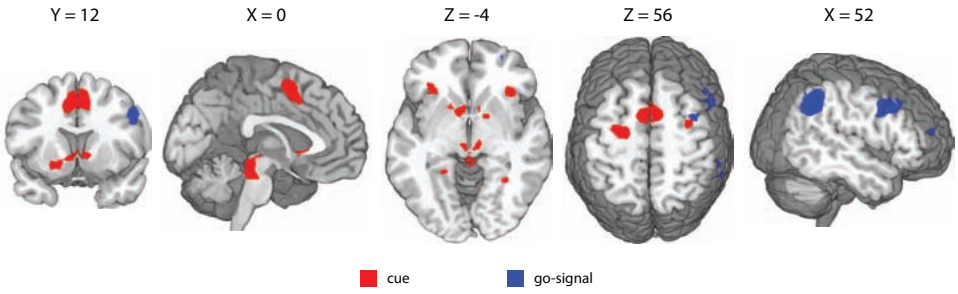



**Figure S1.** Effects of stop-signal probability on brain activation during the cue (red) and during the go-signal (blue). Significant clusters of activation ($P < .05$, FWE-corrected) are displayed on a normalized brain (neurological orientation, left is left).

# Reduced proactive inhibition in schizophrenia is related to cortico-striatal dysfunction and poor working memory

5

**Bram B. Zandbelt, Mariët van Buuren, René S. Kahn, Matthijs Vink**

*Under review*

Inhibitory control is central to executive functioning and appears deficient in schizophrenia. However, it is unclear how inhibitory control is affected, what the underlying neural mechanisms are, whether these deficits are related to the illness itself or to increased risk for the illness, and whether there is a relation to impairments in other executive functions. We used functional MRI to investigate two forms of inhibitory control: proactive inhibition (anticipation of stopping) and reactive inhibition (outright stopping). 24 schizophrenia patients, 24 unaffected siblings, and 24 healthy controls performed a modified version of the stop-signal paradigm. To assess the relation between performance on inhibitory control and other executive functions, we correlated inhibitory control indices with working memory span. Compared with controls, proactive inhibition was reduced in patients and siblings. Reactive inhibition was unaffected. Reduced proactive inhibition was associated with a failure to activate the right striatum, the right inferior frontal cortex and the left and right temporoparietal junction. Activation during reactive inhibition was unaffected. Those patients with the least proactive inhibition and the lowest activation in frontoparietal regions also showed the lowest working memory span. These results suggest that schizophrenia is associated with reduced proactive inhibition, probably resulting from cortico-striatal dysfunction. This deficit is related to an increased risk for schizophrenia and likely reflects a general executive function deficit rather than a specific inhibitory control impairment.

*We thank Mirjam Bloemendaal, Florian Bootsman, Max de Leeuw, and Anca Rapcencu for their assistance in data collection.*

## Introduction

Inhibitory control is central to executive functioning and may be deficient in schizophrenia. Several studies have reported impaired inhibitory control in schizophrenia (Kiehl et al., 2000; Raemaekers et al., 2002; Vink et al., 2005a; Enticott et al., 2008), but others have not (Rubia et al., 2001; Badcock et al., 2002; Nishimura et al., 2011). This may be due to the fact that these studies have used a variety of tasks measuring different aspects of inhibition (Aron, 2007). Furthermore, as most were behavioral studies, the neural mechanisms underlying impaired inhibitory control in schizophrenia are largely unknown. In addition, very few studies included siblings or relatives of patients (Raemaekers et al., 2006; Vink et al., 2006), although inclusion of this group could indicate whether inhibitory control deficits in schizophrenia are associated with the illness itself or with increased risk for that illness. Finally, impaired inhibitory control may reflect a more general deficit in executive functioning, possibly related to deficits in other domains, such as working memory (Roberts Jr. et al., 1994).

A typical task for studying inhibitory control is the stop-signal task (Verbruggen and Logan, 2008). In this paradigm, go-signals requiring a response are occasionally followed by a stop-signal, indicating that the planned response should be stopped. Inhibitory control in the stop-signal task involves reactive mechanisms triggered by the stop-signal (i.e. reactive inhibition), but also proactive mechanisms that are active before a stop-signal is presented (i.e. proactive inhibition) (Vink et al., 2005b; Aron, 2010; Zandbelt and Vink, 2010).

Here, we studied proactive and reactive inhibition in schizophrenia patients, unaffected siblings of patients, and controls. They underwent functional MRI while performing a stop-signal task designed to measure proactive and reactive inhibition (Fig. 1). To assess the relation between inhibitory control impairments and deficits in other executive functions, we correlated indices of proactive and reactive inhibition with working memory span.

First, we predicted that patients and siblings would be impaired in proactive inhibition, whereas reactive inhibition may be less affected. This is because proactive control, compared to reactive control, relies more heavily on context-processing and mesocortical dopaminergic projections (Braver et al., 2007), both of which are compromised in schiz-

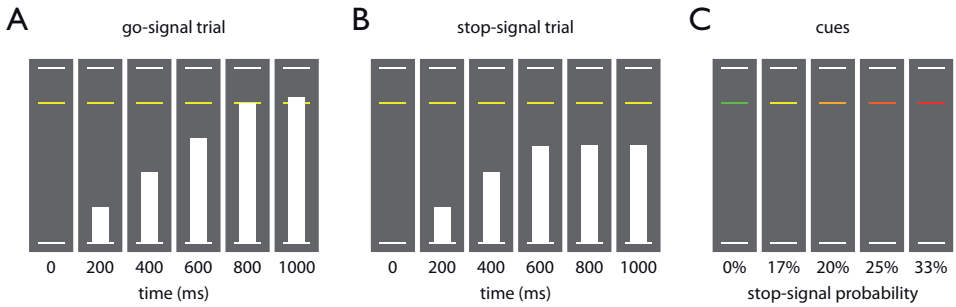



**Figure 1.** Stop-signal anticipation task. Three horizontal lines formed the background displayed continuously during the task. **(A)** In each trial, a bar moved at constant speed from the bottom up, reaching the middle line in 800 ms. The main task was to stop the bar as close to the middle line as possible by pressing a button with the right thumb (i.e. the target response time was 800 ms). These trials are referred to as go-signal trials. **(B)** In a minority of trials, the bar stopped moving automatically before reaching the middle line (i.e. the stop-signal), indicating that a response had to be stopped. These trials are referred to as Stop trials. **(C)** The probability that a stop-signal would occur was manipulated across trials and was indicated by the color of the target response line. There were five stop-signal probability levels: 0% (green), 17% (yellow), 20% (amber), 25% (orange), and 33% (red). Stop-signal delay (SSD), the interval between trial onset and presentation of the stop-signal, was initially 550 ms and varied from one stop-signal trial to the next according to a staircase procedure: if stopping was successful, then stopping was made more difficult on the next stop-signal trial by increasing SSD with 25 ms. The process was reversed when stopping failed. For more details on the stop-signal anticipation task, see Zandbelt & Vink (2010).

ophrenia (Davis et al., 1991; Servan-Schreiber et al., 1996). Second, we predicted that brain activation in patients and siblings, like task performance, would be reduced during proactive inhibition, but less so during reactive inhibition. Specifically, we expected reduced activation of the right striatum because this region has been associated with proactive control (Zandbelt and Vink, 2010; Aron, in press) and shows reduced activation in schizophrenia (Raemaekers et al., 2006; Vink et al., 2006). Third, we predicted that if reduced inhibitory control reflects a general deficit in executive functioning, then it should be associated with lower working memory span.

## Methods & Materials

### *Participants*

All participants gave written informed consent after having received complete description of the study, in accordance with procedures approved by the University Medical Center Utrecht (UMCU) ethics committee. Participants were 24 patients with schizophrenia (SZ), 24 unaffected siblings

*Table 1. Demographic characteritics of the diagnostic groups*

| | SZ (N = 24) | SB (N = 24) | HC (N = 24) | test statistic | p |
|---|---|---|---|---|---|
| Age (years) | 31.3 ± 3.6 | 29.9 ± 6.7 | 32.2 ± 5.9 | F = 1.12 | .33 |
| Sex (M/F) | 19/5 | 13/11 | 15/9 | $\chi 2 = 3.43$ | .18 |
| Handedness (EHI quotient) | .87 ± .17 | .85 ± .23 | .92 ± .11 | F < 1 | .42 |
| Parental education level (a.u.) | 4.8 ± 2.2 | 5.5 ± 2.4 | 4.8 ± 2.6 | F < 1 | .52 |

Age, handedness and education data represent mean ± s.d. EHI, Edinburgh handedness inventory (Oldfield, 1971)

of patients with schizophrenia (SB), and 24 healthy controls (HC). Demographic information of the diagnostic groups is displayed in Table 1.

Patients were outpatients (mean ± s.d. duration of illness: 9.0 ± 3.9 years) recruited from the Department of Psychiatry at the UMCU and participating in an ongoing longitudinal study (Genetic Risk and Outcome in Psychosis, GROUP (GROUP, 2011)). They fulfilled DSM-IV criteria for paranoid schizophrenia (American Psychiatric Association, 1994), as confirmed by a Schedules for Clinical Assessment in Neuropsychiatry (SCAN) interview (Wing et al., 1990). All patients were receiving atypical antipsychotic medication, except for one patient who was taking penfluridol (Table S1, mean ± s.d. daily chlorpromazine equivalent dose: 316 ± 246 mg). Further, eight patients received mood-stabilizing medications and five received anxiolytic medications. Clinical symptoms were evaluated with the Positive and Negative Syndrome Scale (Kay et al., 1987) on the day of the experiment (mean ± s.d ratings; positive scale, 15 ± 4; negative scale, 13 ± 3; general scale, 27 ± 6; total, 55 ± 9).

Siblings of patients were recruited from families of schizophrenia patients participating in an ongoing longitudinal study (GROUP) at the Department of Psychiatry at the UMCU. None of them had a history of psychiatric illness, as assessed by a SCAN interview.

Healthy controls were recruited from the community. They were matched with patients and siblings for sex, age, handedness and parental education level (Table 1). None of the controls had a history of psychiatric illness, as assessed with a Mini International Neuropsychiatric Interview Plus (Sheehan et al., 1998). They also had no family history of psychosis.

Due to poor task performance, data from two patients and one

healthy control had to be excluded, yielding 22 patients, 24 siblings and 23 controls in the analysis of task performance. Functional MRI data from two siblings and another healthy control had to be excluded because of excessive head motion during image acquisition, yielding 22 patients, 22 siblings, and 22 controls in the fMRI analysis. Finally, working memory span scores could not be obtained in three siblings and four controls.

*Working memory: Sternberg task*

Prior to the fMRI experiment, we measured working memory span using a modified version of the Sternberg verbal working memory task (Sternberg, 1966). Participants were instructed to memorize a set of letters (uppercase consonants) that was displayed for 4000 ms on a computer screen. After the memory set disappeared, a series of 25 probes (lowercase consonants) was presented. For each probe, participants had to indicate whether or not it had appeared in the memory set, by pressing one of two buttons on a response device. Each probe was onscreen for 1000 ms with an intertrial interval of 1000 ms. There was a 50% chance that a probe was a part of the memory set. No feedback was given during the task. Across the experiment, the memory set size varied from three to nine letters in a pseudorandom fashion. Each set size was presented twice, so that participants classified a total of 50 probes per memory set size. The total duration of the task was 13 minutes and 41 seconds.

*Inhibitory control: Stop-signal anticipation task*

During the fMRI experiment, participants performed a stop-signal task designed to measure proactive and reactive inhibition (Zandbelt and Vink, 2010). This task is explained in Figure 1.

*Image acquisition*

The experiment was performed on a 3.0 T MRI scanner (Philips Medical System, Best, the Netherlands) at the UMCU. We collected 622 whole-brain T2*-weighted echo planar images (EPI) with blood-oxygen level-dependent (BOLD) contrast in a single run and a T1-weighted image for within-subject registration purposes, using scan parameters identical to those described before (Zandbelt and Vink, 2010).

*Data analysis - Stop-signal anticipation task performance*

In keeping with previous studies (Logan and Burkell, 1986; Vink et al., 2005b; Vink et al., 2006; Verbruggen and Logan, 2009; Zandbelt and Vink, 2010), proactive inhibition was measured as the effect of stop-signal probability on go-signal response time. Impaired proactive inhibition is evidenced by a reduced effect of stop-signal probability on go-signal response time (reflecting weaker anticipation of a stop-signal) (Vink et al., 2006).

Reactive inhibition was studied in terms of the stop-signal reaction time (SSRT) and the slope of the normalized inhibition function, referred to as the ZRFT slope (Logan and Cowan, 1984). The SSRT is a measure of the latency of the inhibition process. The ZRFT slope is an index of the variability of the inhibition process. Impaired reactive inhibition is evidenced by a slower SSRT (reflecting a slower inhibitory process) or a flatter ZRFT slope (reflecting a more variable or a less often triggered inhibition process), or both (Logan, 1994).

Statistical analysis of proactive inhibition consisted of a repeated-measures ANOVA on mean go-signal response times, with stop-signal probability and group as factors. Statistical analysis of reactive inhibition involved two one-way ANOVAs on SSRT and ZRFT slope, both with group as a factor. Post-hoc tests were performed according to the Ryan-Einot-Gabriel-Welsh Q (REGWQ) procedure.

*Data analysis - fMRI*

Image data were analyzed using SPM5 software (http://www.fil.ion.ucl.ac.uk/spm/software/spm5/). Preprocessing and first-level statistical analysis were performed as described previously (Zandbelt and Vink, 2010). In brief, preprocessing involved correction for slice timing differences, realignment for head motion correction, spatial normalization to the Montreal Neurological Institute (MNI) template brain, and spatial smoothing to accommodate interindividual differences in neuroanatomy.

The fMRI data were modeled voxel-wise, using a general linear model, in which the following events were included as regressors: successful stop-signal trials, failed stop-signal trials, and go-signal trials with stop-signal probability > 0%. For these go-signal trials, we also included two parametric regressors modeling response time and stop-signal probability level. Regressors were created by convolving delta functions coding for each event's response time (or target response time for successful

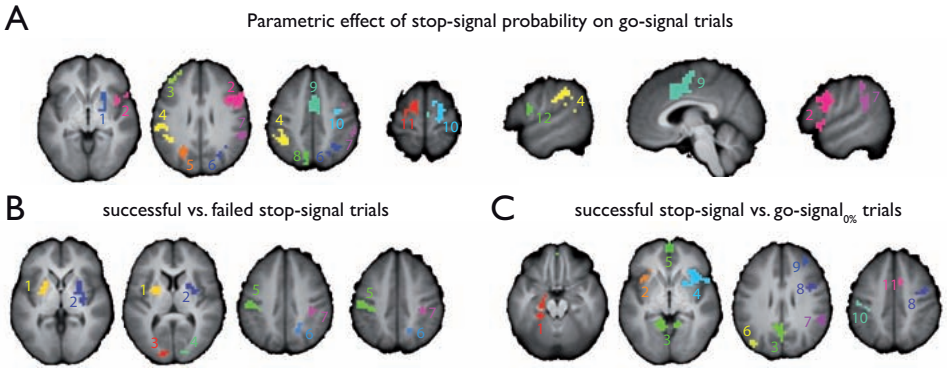



**Figure 2.** Regions-of-interest (ROIs) used to assess group differences in brain activation during proactive and reactive inhibition. All ROIs were defined based on data from a previous experiment (Zandbelt and Vink, 2010), in which an independent sample of healthy volunteers performed the same task. **(A)** The ROIs for the parametric effect effect of stop-signal probability on go-signal activation were defined using a cluster-level threshold (cluster-defining threshold, $P < .001$; cluster probability, $P < .05$, FWE-corrected). ROIs were the 1) right striatum, 2) right inferior frontal cortex, extending into the precentral gyrus, 3) left middle frontal gyrus, 4) left temporoparietal junction, 5) left superior parietal gyrus, extending into the angular gyrus, 6) right superior parietal gyrus, extending into the angular gyrus, 7) right temporoparietal junction, 8) left precuneus, 9) anterior cingulate gyrus, extending into the superior frontal gyrus, 10) right superior frontal gyrus, 11) left superior frontal gyrus, 12) left inferior frontal gyrus, and 13) right anterior insula (not shown). **(B)** The ROIs for the contrast Successful stop-signal versus Failed stop-signal were defined using a cluster-level threshold (cluster-defining threshold, $P < .001$; cluster probability, $P < .05$, FWE-corrected). ROIs were the 1) left putamen, 2) right putamen, 3) left middle occipital gyrus, 4) right middle occipital gyrus, 5) left pre/postcentral gyrus, 6) right precuneus, 7) right supramarginal gyrus. **(C)** The ROIs for the contrast Successful stop-signal versus go-signal 0% were defined using a more stringent voxel-level threshold was used ($P < .01$, FWE-corrected, additional extent threshol of $k = 10$ voxels), in order to obtain clusters of considerable size, but spanning no more than a few macroscopic regions. ROIs were the 1) left hippocampus and parahippocampal gyrus, 2) left insula, 3) left and right lingual gyrus and cuneus, 4) right insula and inferior frontal gyrus, 5) left and right superior frontal gyrus, 6) left angular gyrus, 7) right angular gyrus, 8) right precentral gyrus, 9) right middle frontal gyrus, 10) left pre/postcentral gyrus, 11) left and right superior frontal and cingulate gyrus.

stop-signal trials, see Figure 1 legend) with a canonical haemodynamic response function. The fMRI data were high-pass filtered to remove low-frequency drifts. A first-order autoregressive model was used to model the remaining serial correlations. For each participant, we computed three contrast images: 1) the parametric effect of stop-signal probability on go-signal activation (to assess proactive inhibition), 2) activation during successful stop-signal trials vs. failed stop-signal trials (to assess reactive inhibition), and 3) activation during successful stop-signal trials vs. go-signal trials in the 0% stop-signal probability context (to assess reactive inhibition). We computed two contrasts for reactive inhibition because there is no consensus on which contrast is most appropriate for investigating reactive inhibition.

On each set of contrast images we performed three group analyses. First, we assessed group activation differences in predefined regions-of-interest (ROIs) (Figure 2). ROIs were defined using data from a previous experiment (Zandbelt and Vink, 2010), in which an independent sample of healthy volunteers performed the same task (see Figure 2 legend for more details about ROI definition). From these ROIs, we extracted for each participant the mean activation level (i.e. parameter estimate). These were statistically analyzed in a multivariate analysis of variance (MANOVA) with group as a factor. In case the overall MANOVA was significant, post-hoc REGWQ tests were performed for each ROI showing a significant group effect. Second, whole-brain activations were visualized for each group separately, using one-sample t-tests. Third, group differences in whole-brain activation were tested (i.e. to identify regions showing group differences outside the predefined ROIs), using one-way analysis of variance (ANOVA) with group as a factor. Group statistical parametric maps, resulting from the second and third analyses, were tested for significance using cluster-level inference (cluster-defining threshold, $P < .001$, cluster-probability of $P < .05$, family-wise error corrected for multiple comparisons).

*Data analysis - Sternberg task performance*

Working memory span was defined as the largest memory set size in which performance was above 90% accuracy. Working memory span was analyzed using a Kruskal-Wallis test with group as a factor. Interrelationships between working memory span and behavioral indices of inhibitory control

as well as between working memory span and activation levels were evaluated with one-tailed Spearman rank correlations, because the direction of the relationship was predicted. Note that we used the stop-signal probability slope, defined as the change in go-signal response time per stop-signal probability unit increase, as a single-value behavioral index of proactive inhibition to assess the relationship with working memory span. Bonferroni-correction was applied to correct for multiple comparisons across ROIs.

## Results

*Proactive inhibition is reduced in patients and siblings*

We predicted that patients and siblings would be impaired in proactive inhibition. To test this hypothesis, we examined the effect of stop-signal probability on go-signal response time in patients, siblings, and controls (Figure 3A). Response time increased as a function of stop-signal probability (linear contrast, $F(1,66) = 133.7$, $P < .001$), but more importantly, this effect differed between groups ($F(2,66) = 4.32$, $P = .02$). Post-hoc tests revealed a smaller increase in response time as a function of stop-signal probability in patients relative to controls ($F(1,43) = 7.13$, $P = .01$), with siblings performing at an intermediate level between controls ($F(1,43) = 3.27$, $P = .08$) and patients ($F(1,43) = 1.48$, $P = .23$). An additional analysis of response time adjustments after stop-signal trials revealed no group differences (see Supplement 1), suggesting that reduced proactive inhibition unlikely results from general behavioral inflexibility.

*Reactive inhibition is not affected in patients and siblings*

We predicted that patients and siblings would be less impaired in reactive inhibition. To address this hypothesis, we examined the stop-signal reactione time (SSRT, Figure 3B) and the slope of the normalized inhibition function (ZRFT slope, Figure 3C) in patients, siblings, and controls. The SSRT did not differ between groups ($F(2,66) = 2.13$, $P = .13$), indicating that the inhibitory process in patients and siblings is not significantly slower than in controls. The ZRFT slope did also not differ between groups ($F(2,66) < 1$, $P = .65$), suggesting that the inhibitory process is not more variable or triggered less often in patients or siblings versus controls. The SSRT and ZRFT slope estimates were validated by showing that task performance was in accordance with the independence assumptions underlying the stop-signal paradigm and the race model (see Supplement 1).

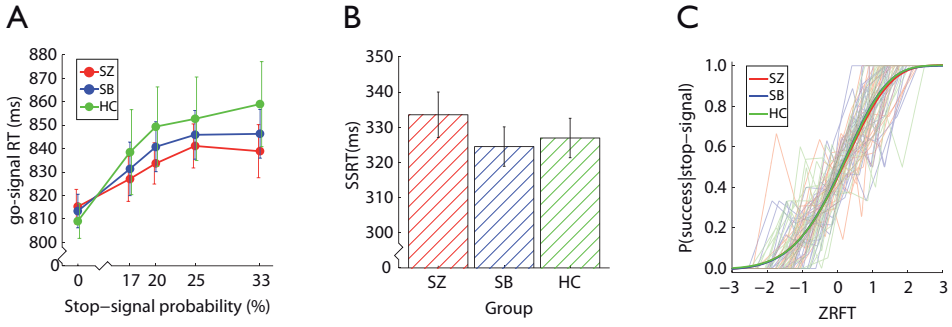



**Figure 3.** Task performance in patients, siblings, and controls. **(A)** Effect of stop-signal probability on go-signal response time across groups, for patients (SZ, red), siblings (SB, blue), and controls (HC, green). **(B)** Stop-signal reaction time in patients (SZ, red stripes), siblings (SB, blue stripes), and controls (HC, green stripes). **(C)** Normalized inhibition functions for patients (SZ, red), siblings (SB, blue), and controls (HC, green), plotting the probability of successful stopping given presentation of a stop-signal against the Z-transformed relative finishing time (ZRFT, see Methods). The smooth, opaque graphs represent the group mean normalized inhibition function; the transparent graphs depict normalized inhibition functions of individual participants. All error bars indicate 95% confidence intervals.

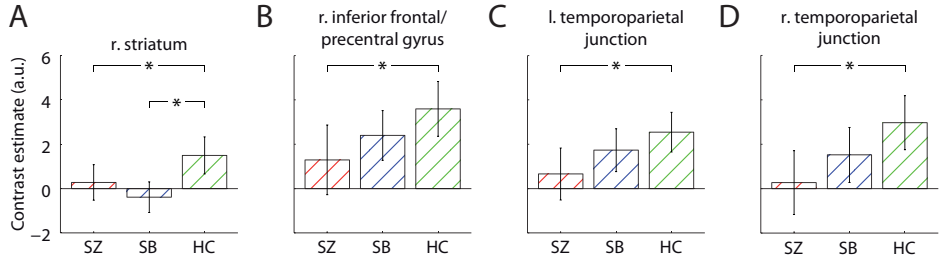



**Figure 4.** Regions-of-interest (ROIs) showing significant group activation differences during proactive inhibition. ROIs included the **(A)** right striatum, **(B)** right inferior frontal and precentral gyrus, **(C)** left temporoparietal junction, and **(D)** right temporoparietal junction. Bars represent group mean activation levels (i.e. parameter estimates) for the parametric effect of stop-signal probability on go-signal in patients (SZ, red stripes), siblings (SB, blue stripes), and controls (HC, green stripes). Error bars indicate 95% confidence intervals.

*Reduced proactive inhibition in patients and siblings is associated with cortico-striatal hypoactivation*

We predicted that brain activation in patients and siblings would be reduced during proactive inhibition, particularly in the right striatum. To address this hypothesis, we first examined group differences in the effect of stop-signal probability on activation during go-signal trials in 13 predefined regions-of-interest (ROIs). This ROI analysis revealed a significant main effect of group ($F(13,52) = 2.46$, $P = .011$). As shown in Figure 4, activation levels differed between groups in the right striatum ($F(2,63) = 6.51$, $P = .003$), the right inferior frontal cortex (IFC) ($F(2,63) = 3.23$, $P = .046$) and in the left and right temporoparietal junction (TPJ) ($F(2,63) = 3.71$, $P = .030$ and $F(2,63) = 4.63$, $P = .013$). Post-hoc analyses showed that, compared to controls, activation in the right striatum was significantly lower in both patients and siblings. Activation in the right IFC and left and right TPJ was significantly lower in patients as compared to controls, with activation in siblings at an intermediate level between patients and controls.

Next, we tested for activation differences outside these ROIs, using whole-brain analyses. Figure 5 shows brain regions in which activation increased as a function of stop-signal probability on go-signal trials, in patients, siblings, and controls, separately. Controls activated a network very similar to that reported previously (Zandbelt and Vink, 2010). The network activated in patients and siblings was much less widespread, lacking activation foci in frontal, temporal, parietal and subcortical regions, corroborating the findings from the ROI analysis. However, a direct comparison of activation levels in a voxel-wise whole-brain analysis did not reveal brain regions in which group differences were significant.

*Normal activation during reactive inhibition in patients and siblings*

We hypothesized that activation during reactive inhibition would be minimally affected in patients and siblings. To evaluate group activation differences, we performed two ROI analyses: one MANOVA tested activation during successful stop-signal versus failed stop-signal trials in seven regions (Fig. 2B), another MANOVA compared activation during successful stop-signal versus go-signal trials in 11 regions (Fig. 2C). Both MANOVAs did not reveal significant group differences (successful stop-signal versus failed stop-signal : $F(7,58) < 1$, $P = .75$; successful stop-signal versus go-

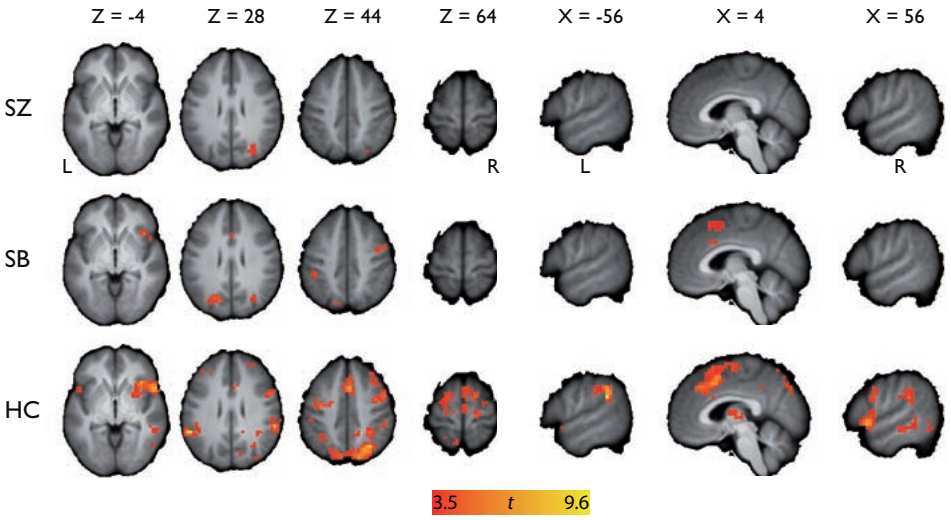



**Figure 5.** Whole-brain activation during proactive inhibition in patients, siblings, and controls. Brain regions in warm colors show a parametric increase in activation as a function of stop-signal probability. Significant activation clusters (P < .05, FWE-corrected) are displayed on the normalized and skull-stripped group-average brain (neurological orientation). SZ, schizophrenia patients; SB, siblings; HC, healthy controls; L, left; R, right.

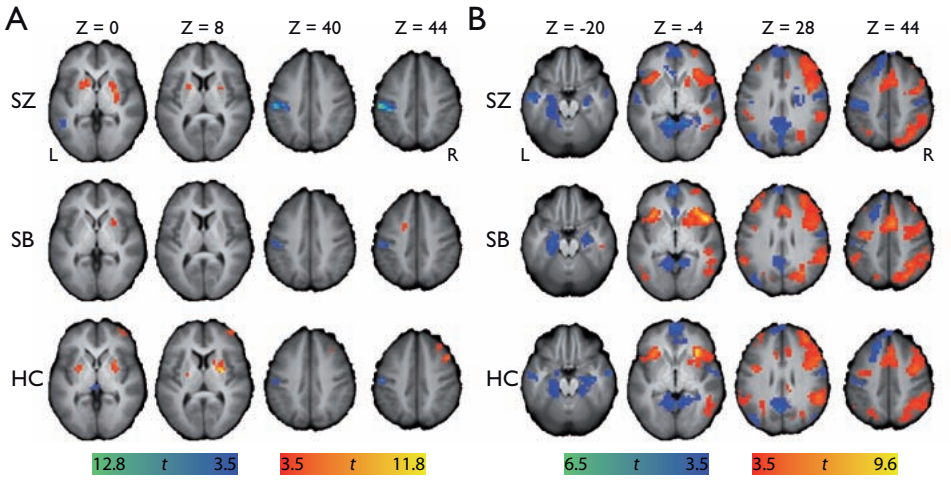



**Figure 6.** Whole-brain activation during reactive inhibition in patients, siblings, and controls. One-sample t-tests of (A) Successful stop-signal versus Failed stop-signal activation and (B) Successful stop-signal versus go-signal 0% activation, for patients (SZ, top panel), siblings (SB, middle panel), and controls (HC, bottom panel). Brain regions in warm colors are activated on Successful stop-signal trials, those in cool colors are deactivated on Successful stop-signal trials. Significant (de)activation clusters (P < .05, FWE-corrected) are displayed on the normalized and skull-stripped group-average brain (neurological orientation). L, left; R, right.

signal: $F(11,54) < 1$, $P = .48$).

We then examined whether brain regions outside these ROIs showed group activation differences. We compared groups on activation in the contrasts successful stop-signal versus failed stop-signal (Figure 6A) and successful stop-signal versus go-signal (Figure 6B). Note the striking similarity in activation pattern across groups for both contrasts. Also direct comparison of activation levels in voxel-wise whole-brain analyses did not reveal any brain regions with significant group differences.

*Reduced inhibitory control is associated with lower working memory span*

Inhibitory control may be related to deficits in other executive functions. We predicted that reduced inhibitory control would be associated with lower working memory span. First, we compared working memory span between groups (Figure 7A) and found that it differed significantly between groups ($\chi^2(2) = 21.00$ $P < .001$); post-hoc comparisons showed that working memory span in patients was significantly lower than in siblings and controls, consistent with meta-analytic findings (Lee and Park, 2005). We then examined whether there was a positive relationship between working memory span and behavioral indices of proactive inhibition (Figure 7B). Collapsed across groups, the stop-signal probability slope (i.e. the change in response time per stop-signal probability unit increase) was positively correlated with working memory span ($r_S = .33$, $P = .005$), indicating that poorer proactive inhibitory control was associated with lower working memory capacity. Within groups, this correlation reached significance in patients ($r_S = .54$, $P = .004$) only. Next, we tested correlations between working memory span and behavioral indices of reactive inhibition (Figure 7C-D). Collapsed across groups there was a significant correlation between working memory span and SSRT ($r_S = -.28$, $P = .013$), suggesting that slower reactive stopping was accompanied by lower working memory capacity. There was no significant correlation between working memory span and the ZRFT slope ($r_S = .09$, $P = .24$). Within each group alone, neither of these correlations reached significance.

*Reduced activation in the right IFC and left and right TPJ was associated with low working memory span in patients*

Finally, we analyzed correlations between working memory span and fMRI indices of proactive and reactive inhibition. Collapsed across groups, the

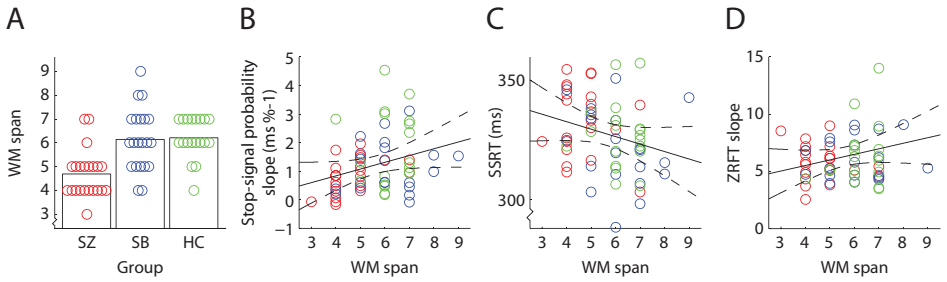



**Figure 7.** Relationship between working memory span and behavioral indices of proactive inhibition in patients, siblings, and controls. (**A**) Working memory (WM) span in patients (red), siblings (blue), and controls (green). Bars represent group mean spans, each circle represents a participant. (**B, C, D**) Stop-signal probability slope (**B**), stop-signal reaction time (**C**), and ZRFT slope (**D**) as a function of WM span in patients (red), siblings (blue), and controls (green). Solid lines depict regression lines, dashed lines represent 95% confidence bands, collapsed across groups.

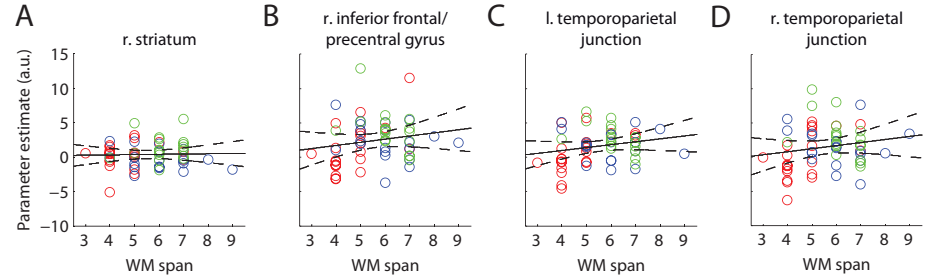



**Figure 8.** Relationship between working memory span and activation during proactive inhibition in predefined ROIs across patients, siblings and controls. Activation in (A) right striatum, (B) right inferior frontal and precentral gyrus, (C) left temporoparietal junction, and (D) right temporoparietal junction as a function of WM span in patients (red), siblings (blue), and controls (green). Each circle represents a participant. Solid lines depict regression lines, dashed lines represent 95% confidence bands, collapsed across groups.

correlation between working memory span and activation during proactive inhibition reached Bonferroni-corrected significance in none of the proactive inhibition ROIs. However, as shown in Figure 8, in the patient group we observed significant correlations in the right IFC ($r_S$ = .58, P = .002,), and the left and right TPJ ($r_S$ = .65, P = .001 and $r_S$ = .56, P = .003,), but not in the right striatum ($r_S$ = .12, P = .30). Correlations between working memory span and activation during reactive inhibition did not reach significance in any of the ROIs, neither collapsed across groups, nor within separate groups.

## Discussion

We used fMRI to investigate proactive inhibition (i.e. anticipation of stopping) and reactive inhibition (i.e. outright stopping) in patients with schizophrenia, unaffected siblings of patients, and matched controls. First, compared with controls, proactive inhibition was reduced in patients and siblings, whereas reactive inhibition was not significantly affected (Figure 3). Second, reduced proactive inhibition was associated with a failure to activate the right striatum, the right inferior frontal cortex (IFC) and the left and right temporoparietal junction (TPJ) (Figures 4-5). During reactive inhibition, activation levels did not differ significantly from controls (Figure 6). Third, those patients with the lowest working memory capacity also showed the least proactive inhibition (Figure 7) and the lowest activation levels in frontoparietal regions (Figure 8).

In line with previous observations (Raemaekers et al., 2002; Raemaekers et al., 2006; Vink et al., 2006), we found significantly reduced striatal activation during proactive inhibition not only in patients, but also in medication-free, unaffected siblings. This suggests that striatal dysfunction in schizophrenia is associated with an increased risk to develop the illness, rather than reflecting illness-related factors, such as antipsychotic treatment. These findings also support the view that the striatum is crucial for proactive inhibition (Vink et al., 2005b; Aron, 2010; Zandbelt and Vink, 2010) and may be central to prefrontal-dependent executive function deficits in schizophrenia (Graybiel, 1997; Simpson et al., 2010).

Patients and siblings showed reduced striatal activation during proactive, but not during reactive inhibition. We argue that this dissociation indicates that reduced striatal activation in schizophrenia reflects

disturbed dopaminergic signaling. First, pharmacological studies of inhibitory control (Eagle et al., 2007; Bari et al., 2009; Eagle and Baunez, 2009) and theoretical models of executive functioning (Braver et al., 1999; Braver et al., 2007) indicate that processes underlying proactive inhibition depend on dopamine, whereas processes underlying reactive inhibition do not. Second, the striatum receives dense dopaminergic input (Haber et al., 2000; Haber, 2003). Third, increased striatal dopamine synthesis is a hallmark of psychosis in schizophrenia (Howes and Kapur, 2009), but also occurs in non-psychotic patients who are stable on antipsychotic medication (McGowan et al., 2004) and non-psychotic first-degree relatives of patients (Huttunen et al., 2008). So, it is possible that the patients and siblings we studied had disturbed striatal dopaminergic signaling. Fourth, dopamine overactivity in schizophrenia patients and individuals at risk for psychosis is predominantly localized to the dorsal associative striatum (Howes et al., 2009; Kegeles et al., 2010), the region in which we found significantly reduced activation in patients and siblings as compared to controls. Future studies should test more directly whether (pharmacologically-induced) striatal hyperdopaminergia is sufficient to cause impairments in proactive inhibition.

Besides striatal dysfunction, patients and to a lesser extent siblings demonstrated reduced activation in the left and right TPJ and the right IFC. In the context of inhibitory control, these regions have been implicated in the monitoring and detection of behaviorally salient stimuli and the subsequent re-programming of actions (Schmajuk et al., 2006; Mars et al., 2007; Boehler et al., 2009; Boehler et al., 2010; Hampshire et al., 2010; Verbruggen et al., 2010). Thus, hypoactivation of the TPJ and IFC might reflect attenuated attentional processing of stop-signal probability cues, leading to reduced proactive inhibition. This is consistent with reports showing that patients and first-degree relatives are impaired in the use of contextual information to bias response tendencies (Servan-Schreiber et al., 1996; MacDonald et al., 2003; Chambon et al., 2008; Dias et al., 2011), which has been linked to reduced lateral prefrontal function (MacDonald and Carter, 2003; MacDonald et al., 2005; Delawalla et al., 2008; Barbalat et al., 2009). Alternatively, reduced TPJ and IFC activation may be a consequence rather than a cause of reduced proactive inhibition. Note that we measured proactive inhibition as the effect of stop-signal probability on

go-signal trials (i.e. trials in which stop-signals do not occur). Accordingly, activation in the TPJ and IFC may not only reflect expectation of a stop-signal, but also violation of this expectation. That is, the expectation of a stop-signal is likely updated over the course of a trial, in that the expectation decrease when it becomes apparent that a stop-signal will not occur. The TPJ and the IFC have been associated with such expectancy violations expectations (Arrington et al., 2000; Corbetta et al., 2000; Vossel et al., 2006; Shulman et al., 2009; Asplund et al., 2010) and online updating of temporal expectations (Nobre et al., 2007; Coull, 2009). Thus, reduced activation in the right IFC and the left and right TPJ in patients and siblings may also indicate that stop-signal expectation was lower in patients and siblings, possibly as a result of striatal hyperdopaminergia, due to which they updated stop-signal expectation less frequently than controls.

We showed an association between reduced proactive inhibition and lower working memory span in patients. Therefore, reduced inhibitory control in schizophrenia may reflect a general executive function deficit rather than an impairment confined to the domain of inhibitory control. Furthermore, reduced activation in the left and right TPJ and the right IFC during proactive inhibition was associated with a lower working memory span in patients. The interpretation of these correlations depends on the meaning of reduced frontoparietal activation in patients (see above). If reduced frontoparietal activation reflects a context processing deficit, then these correlations could reflect that proactive control can only be used if sufficient working memory capacity is available (Braver et al., 2007). Alternatively, if reduced frontoparietal activation is a consequence of reduced proactive inhibition, then these correlations may be indirect, reflecting that both working memory span and frontoparietal activation are related to reduced proactive inhibition.

We found no significant differences between patients, siblings and controls on reactive inhibition, neither in task performance nor in activation levels. These results confirm previous observations (Badcock et al., 2002; Bellgrove et al., 2006), but contrast with others (Enticott et al., 2008; Huddy et al., 2009; Thakkar et al., 2011). This discrepancy may be caused by differences in patient groups across studies. For example, Bellgrove et al. (2006) reported normal stop-signal reaction times (SSRTs) in patients

with paranoid schizophrenia (i.e. patients similar to ours), whereas they found slower SSRTs in patients with undifferentiated schizophrenia.

The stop-signal task (SST) has been selected as part of a cognitive battery to study executive functions in clinical trials (Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS), (Barch et al., 2009)), emphasizing the importance of studying inhibition in schizophrenia. However, whereas the SST measures reactive inhibition only, the stop-signal anticipation task (SSAT) probes both proactive and reactive inhibition. This is particularly relevant given that our data point to prominent behavioral and neural deficits in proactive inhibition in patients and siblings. Indeed, cognitive paradigms assessing both proactive and reactive inhibition have been suggested to be a better model for executive control in psychiatry than paradigms assessing reactive inhibition only (Aron, 2010).

In sum, we have shown that proactive inhibition is impaired in schizophrenia. Reduced proactive inhibition was accompanied by a failure to activate the striatum and frontoparietal regions. The presence of behavioral and neural inhibitory control deficits in unaffected siblings, suggests that these deficits are due to a predisposition to schizophrenia rather than due to the illness itself. Since reduced proactive inhibition in patients was associated with lower working memory capacity, inhibitory control deficits in schizophrenia may reflect a more general deficit in executive functions instead of a specific inhibitory control impairment. Together, our findings are consistent with the idea that executive function deficits in schizophrenia result from cortico-striatal dysfunction.

## References

American Psychiatric Association (1994) Diagnostic and statistical manual of mental disorders, DMS-IV, 4th Edition. Washington, DC: American Psychiatric Association.

Aron AR (2007) The neural basis of inhibition in cognitive control. Neuroscientist 13:214-228.

Aron AR (2010) From Reactive to Proactive and Selective Control: Developing a Richer Model for Stopping Inappropriate Responses. Biol Psychiatry.

Aron AR (in press) From reactive to proactive and selective control: developing a richer model for stopping inappropriate responses. Biol Psychiatry.

Arrington CM, Carr TH, Mayer AR, Rao SM (2000) Neural mechanisms of visual attention: object-based selection of a region in space. J Cogn Neurosci 12 Suppl 2:106-117.

Asplund CL, Todd JJ, Snyder AP, Marois R (2010) A central role for the lateral prefrontal cortex in goal-directed and stimulus-driven attention. Nat Neurosci 13:507-512.

Badcock JC, Michie PT, Johnson L, Combrinck J (2002) Acts of control in schizophrenia: dissociating the components of inhibition. Psychol Med 32:287-297.

Barbalat G, Chambon V, Franck N, Koechlin E, Farrer C (2009) Organization of cognitive control within the lateral prefrontal cortex in schizophrenia. Arch Gen Psychiatry 66:377-386.

Barch DM, Braver TS, Carter C, Poldrack RA, Robbins T (2009) CNTRICS final task selection: executive control. Schizophr Bull 35:115.

Bari A, Eagle DM, Mar AC, Robinson ESJ, Robbins TW (2009) Dissociable effects of noradrenaline, dopamine, and serotonin uptake blockade on stop task performance in rats. Psychopharmacology (Berl) 205:273-283.

Bellgrove MA, Chambers CD, Vance A, Hall N, Karamitsios M, Bradshaw JL (2006) Lateralized deficit of response inhibition in early-onset schizophrenia. Psychol Med 36:495-505.

Boehler CN, Appelbaum LG, Krebs RM, Hopf JM, Woldorff MG (2010) Pinning down response inhibition in the brain - conjunction analyses of the stop-signal task. Neuroimage 52:1621-1632.

Boehler CN, Munte TF, Krebs RM, Heinze H, Schoenfeld MA, Hopf J (2009) Sensory MEG responses predict successful and failed inhibition in a stop-signal task. Cereb Cortex 19:134.

Braver TS, Barch DM, Cohen JD (1999) Cognition and control in schizophrenia: a computational model of dopamine and prefrontal function. Biol Psychiatry 46:312-328.

Braver TS, Gray JR, Burgess GC (2007) Explaning the many varieties of working memory variation: dual mechanisms of cognitive control. In: Variation in Working Memory (Conway A, Jarrold C, Kane M, Miyake A, Towse K, eds), pp 76-106. Oxford: Oxford University Press.

Chambon V, Franck N, Koechlin E, Fakra E, Ciuperca G, Azorin JM, Farrer C (2008) The architecture of cognitive control in schizophrenia. Brain 131:962-970.

Corbetta M, Kincade JM, Ollinger JM, McAvoy MP, Shulman GL (2000) Voluntary orienting is dissociated from target detection in human posterior parietal cortex. Nat Neurosci 3:292-297.

Coull JT (2009) Neural substrates of mounting temporal expectation. PLoS Biol 7:e1000166.

Davis KL, Kahn RS, Ko G, Davidson M (1991) Dopamine in schizophrenia: a review and recon-

ceptualization. Am J Psychiatry 148:1474-1486.
Delawalla Z, Csernansky JG, Barch DM (2008) Prefrontal cortex function in nonpsychotic siblings of individuals with schizophrenia. Biol Psychiatry 63:490-497.
Dias EC, Butler PD, Hoptman MJ, Javitt DC (2011) Early Sensory Contributions to Contextual Encoding Deficits in Schizophrenia. Arch Gen Psychiatry.
Eagle D, Baunez C (2009) Is there an inhibitory-response-control system in the rat? Evidence from anatomical and pharmacological studies of behavioral inhibition. Neurosci Biobehav Rev 34:50-72.
Eagle DM, Tufft MRA, Goodchild HL, Robbins TW (2007) Differential effects of modafinil and methylphenidate on stop-signal reaction time task performance in the rat, and interactions with the dopamine receptor antagonist cis-flupenthixol. Psychopharmacology (Berl) 192:193-206.
Enticott PG, Ogloff JR, Bradshaw JL (2008) Response inhibition and impulsivity in schizophrenia. Psychiatry Res 157:251-254.
Graybiel AM (1997) The basal ganglia and cognitive pattern generators. Schizophr Bull 23:459-469.
GROUP (2011) Evidence that familial liability for psychosis is expressed as differential sensitivity to cannabis: an analysis of patient-sibling and sibling-control pairs. Arch Gen Psychiatry 68:138-147.
Haber S, Fudge J, Mcfarland N (2000) Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. J Neurosci 20:2369.
Haber SN (2003) The primate basal ganglia: parallel and integrative networks. J Chem Neuroanat 26:317-330.
Hampshire A, Chamberlain SR, Monti MM, Duncan J, Owen AM (2010) The role of the right inferior frontal gyrus: inhibition and attentional control. Neuroimage 50:1313-1319.
Howes OD, Kapur S (2009) The dopamine hypothesis of schizophrenia: version III - the final common pathway. Schizophr Bull 35:549-562.
Howes OD, Montgomery AJ, Asselin M-C, Murray RM, Valli I, Tabraham P, Bramon-Bosch E, Valmaggia L, Johns L, Broome M, McGuire PK, Grasby PM (2009) Elevated striatal dopamine function linked to prodromal signs of schizophrenia. Arch Gen Psychiatry 66:13-20.
Huddy VC, Aron AR, Harrison M, Barnes TRE, Robbins TW, Joyce EM (2009) Impaired conscious and preserved unconscious inhibitory processing in recent onset schizophrenia. Psychol Med 39:907-916.
Huttunen J, Heinimaa M, Svirskis T, Nyman M, Kajander J, Forsback S, Solin O, Ilonen T, Korkeila J, Ristkari T, McGlashan T, Salokangas RKR, Hietala J (2008) Striatal dopamine synthesis in first-degree relatives of patients with schizophrenia. Biol Psychiatry 63:114-117.
Kay SR, Fiszbein A, Opler LA (1987) The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 13:261-276.
Kegeles L, Abi-Dargham A, Frankle W, Gil R, Cooper T, Slifstein M, Hwang D-R, Huang Y, Haber S, Laruelle M (2010) Increased synaptic dopamine function in associative regions of the striatum in schizophrenia. Arch Gen Psychiatry 67:231.
Kiehl KA, Smith AM, Hare RD, Liddle PF (2000) An event-related potential investigation of response inhibition in schizophrenia and psychopathy. Biol Psychiatry 48:210-221.
Lee JD, Park S (2005) Working memory impairments in schizophrenia: a meta-analysis. J

Abnorm Psychol 114:599-611.
Logan G (1994) On the ability to inhibit though and action - a user's guide to the stop-signal paradigm. In: Inhibitory processes in attention, memory, and language (Dagenbach D, Carr TH, eds), pp 189-239. San Diego: Academic Press.
Logan GD, Cowan WB (1984) On the ability to inhibit thought and action: A theory of an act of control. Psychol Rev 91:291-327.
Logan GD, Burkell J (1986) Dependence and independence in responding to double stimulation. A comparison of stop, change, and dual-task paradigms. J Exp Psychol Hum Percept Perform 12:549-563.
MacDonald AW, Carter CS (2003) Event-related FMRI study of context processing in dorsolateral prefrontal cortex of patients with schizophrenia. J Abnorm Psychol 112:689-697.
MacDonald AW, Pogue-Geile MF, Johnson MK, Carter CS (2003) A specific deficit in context processing in the unaffected siblings of patients with schizophrenia. Arch Gen Psychiatry 60:57-65.
MacDonald AW, Carter CS, Kerns JG, Ursu S, Barch DM, Holmes AJ, Stenger VA, Cohen JD (2005) Specificity of prefrontal dysfunction and context processing deficits to schizophrenia in never-medicated patients with first-episode psychosis. Am J Psychiatry 162:475-484.
Mars R, Piekema C, Coles M, Hulstijn W, Toni I (2007) On the programming and reprogramming of actions. Cereb Cortex 17:2972-2979.
McGowan S, Lawrence A, Sales T, Quested D, Grasby P (2004) Presynaptic dopaminergic dysfunction in schizophrenia: a positron emission tomographic [18F]fluorodopa study. Arch Gen Psychiatry 61:134.
Nishimura Y, Takizawa R, Muroi M, Marumo K, Kinou M, Kasai K (2011) Prefrontal cortex activity during response inhibition associated with excitement symptoms in schizophrenia. Brain Res 1370:194-203.
Nobre A, Correa A, Coull J (2007) The hazards of time. Curr Opin Neurobiol 17:465-470.
Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9:97-113.
Raemaekers M, Ramsey NF, Vink M, van den Heuvel MP, Kahn RS (2006) Brain activation during antisaccades in unaffected relatives of schizophrenic patients. Biol Psychiatry 59:530-535.
Raemaekers M, Jansma JM, Cahn W, Van der Geest JN, van der Linden JA, Kahn RS, Ramsey NF (2002) Neuronal substrate of the saccadic inhibition deficit in schizophrenia investigated with 3-dimensional event-related functional magnetic resonance imaging. Arch Gen Psychiatry 59:313-320.
Roberts Jr. RJ, Hager LD, Heron C (1994) Prefrontal cognitive processes: working memory and inhibition in the antisaccade task. J Exp Psychol Gen 123:374-393.
Rubia K, Russell T, Bullmore ET, Soni W, Brammer MJ, Simmons A, Taylor E, Andrew C, Giampietro V, Sharma T (2001) An fMRI study of reduced left prefrontal activation in schizophrenia during normal inhibitory function. Schizophr Res 52:47-55.
Schmajuk M, Liotti M, Busse L, Woldorff MG (2006) Electrophysiological activity underlying inhibitory control processes in normal adults. Neuropsychologia 44:384-395.
Servan-Schreiber D, Cohen JD, Steingard S (1996) Schizophrenic deficits in the processing of context. A test of a theoretical model. Arch Gen Psychiatry 53:1105-1112.

Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC (1998) The mini-international neuropsychiatric interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 59 Suppl 20:22-33.

Shulman G, Astafiev S, Franke D, Pope D, Snyder A, Mcavoy M, Corbetta M (2009) Interaction of Stimulus-Driven Reorienting and Expectation in Ventral and Dorsal Frontoparietal and Basal Ganglia-Cortical Networks. J Neurosci 29:4392.

Simpson EH, Kellendonk C, Kandel E (2010) A Possible Role for the Striatum in the Pathogenesis of the Cognitive Symptoms of Schizophrenia. Neuron 65:585-596.

Sternberg S (1966) High-speed scanning in human memory. Science 153:652-654.

Thakkar KN, Schall JD, Boucher L, Logan GD, Park S (2011) Response inhibition and response monitoring in a saccadic countermanding task in schizophrenia. Biol Psychiatry 69:55-62.

Verbruggen F, Logan GD (2008) Response inhibition in the stop-signal paradigm. Trends Cogn Sci 12:418-424.

Verbruggen F, Logan GD (2009) Proactive adjustments of response strategies in the stop-signal paradigm. Journal of experimental psychology Human perception and performance 35:835-854.

Verbruggen F, Aron AR, Stevens MA, Chambers CD (2010) Theta burst stimulation dissociates attention and action updating in human inferior frontal cortex. Proc Natl Acad Sci USA 107:13966-13971.

Vink M, Ramsey NF, Raemaekers M, Kahn RS (2005a) Negative priming in schizophrenia revisited. Schizophr Res 79:211-216.

Vink M, Ramsey NF, Raemaekers M, Kahn RS (2006) Striatal dysfunction in schizophrenia and unaffected relatives. Biol Psychiatry 60:32-39.

Vink M, Kahn RS, Raemaekers M, van den Heuvel M, Boersma M, Ramsey NF (2005b) Function of striatum beyond inhibition and execution of motor responses. Hum Brain Mapp 25:336-344.

Vossel S, Thiel CM, Fink GR (2006) Cue validity modulates the neural correlates of covert endogenous orienting of attention in parietal and frontal cortex. Neuroimage 32:1257-1264.

Wing JK, Babor T, Brugha T, Burke J, Cooper JE, Giel R, Jablenski A, Regier D, Sartorius N (1990) SCAN. Schedules for Clinical Assessment in Neuropsychiatry. Arch Gen Psychiatry 47:589-593.

Zandbelt BB, Vink M (2010) On the role of the striatum in response inhibition. PLoS ONE 11:e13848.

6

# Discussion

In this chapter, we summarize the main findings of the research presented in this thesis. In addition, we discuss what these findings can tell us about the neural mechanisms underlying proactive and reactive inhibition in health and how these mechanisms may be affected in schizophrenia. Furthermore, limitations of our studies are described and suggestions for future studies are given.

## Summary of findings

In Chapter 2, we reported on the role of the striatum in inhibitory control. We investigated whether striatal activation during inhibitory control reflects 1) inhibition of the primary motor cortex (M1), 2) anticipation of an upcoming stop-signal, or 3) a slower build-up the response process on successful stop-signal trials than on go-signal or failed stop-signal trials. We showed that striatal activation and M1 deactivation during successful stopping not only co-occur, but are also functionally linked. This suggests that the striatum is engaged in inhibition of M1. We further demonstrated that stop-signal probability modulated striatal activation on go-signal trials and that striatal activation during inhibition predicted the degree of activation in several cortical regions, including the supplementary motor complex (SMC). These findings suggest that the striatum is involved in anticipatory processes and may exert proactive inhibition over M1 via these cortical regions. Finally, we showed that striatal activation on go-signal trials was not related to response time, indicating that striatal activation is not an index of the speed of the response process. Taken together, these findings implicate the striatum in proactive inhibition and in reactive inhibition.

In Chapter 3, we focused on two other key components of the inhibitory control network, the right inferior frontal cortex (rIFC) and the SMC. We combined repetitive transcranial magnetic stimulation (rTMS) and fMRI to examine the route through which the rIFC and SMC exert control over M1 and the relative position of the rIFC and the SMC with respect to each other. Both rIFC and SMC stimulation improved reactive inhibition by shortening the stop-signal reaction time (SSRT). We showed a common effect of rIFC and SMC stimulation on activation in the SMC, the right striatum, and left M1, implicating a cortico-basal ganglia pathway through the right striatum in reactive inhibition. In addition, rIFC stimulation altered SMC activation, but SMC stimulation did not alter rIFC activation, indicating that rIFC lies upstream from the SMC. In sum, these findings provide insight into the functional organization of the network subserving reactive inhibition, indicating that the rIFC exerts control over M1 via the SMC and the right striatum.

In Chapter 4, we took a closer look at the neural network of proactive inhibition. Previous studies, including ours in this thesis, identified the neural network of proactive inhibition as the set of brain regions in which activation during go-signal trials increased with stop-signal probability. However, such activation may not only reflect expectation of a stop-signal (i.e. proactive inhibition), but also violation of that expectation because stop-signals do not occur on go-signal trials. We attempted to study proactive inhibition in isolation, using a stop-signal task in which the presentation of the stop-signal probability cue and the go-signal were separated in time. We showed that the network previously associated with proactive inhibition could be subdivided into two components. Activation in the SMC, the striatum, and a region near the dopaminergic midbrain was modulated by stop-signal probability early in the trial (i.e. during the cue). This activation probably reflects anticipatory processes underlying proactive inhibition, such as modulating the responsiveness of M1. In contrast, activation in the rIFC and the right inferior parietal cortex increased as a function of stop-signal probability late in the trial (i.e. during the go-signal). We have argued that this most likely reflects processes associated with updating of expectations when these expectations are violated rather than proactive inhibition. Thus, our findings challenge

the common view that the whole network activated during reactive inhibition becomes already activated in anticipation of stopping.

In Chapter 5, we investigated proactive and reactive inhibition in schizophrenia. Specifically, we examined how proactive and reactive inhibition were affected, what the underlying neural mechanisms are, whether these deficits occur only in patients or also in unaffected siblings of patients, and whether there is a relation to impairments other executive functions, such as working memory. We showed that proactive inhibition is reduced in schizophrenia. This behavioral impairment was accompanied by a failure to activate the striatum, the rIFC, and the left and right temporoparietal junction (TPJ). Striatal dysfunction may point to disturbed striatal dopaminergic signaling. In light of the findings from Chapter 4, reduced rIFC and TPJ activation may be a consequence of reduced proactive inhibition, reflecting that patients and siblings had to update expectations less often than controls. We also found behavioral and neural proactive inhibition impairments in unaffected siblings of patients, albeit in a milder form. Therefore, proactive inhibition impairments in schizophrenia appear to be related to increased risk for the illness rather than reflecting illness-related factors. Finally, reduced proactive inhibition in patients was linked to poorer working memory, suggesting that reduced inhibitory control in schizophrenia may reflect a general executive function deficit rather than a specific impairment in inhibitory control. Together, these results indicate that schizophrenia is associated with reduced proactive inhibition probably resulting from striatal dysfunction.

## Neural mechanisms of proactive and reactive inhibition: the emerging picture

Together, these findings provide further insight into the neural mechanisms underlying proactive and reactive inhibition. In this thesis, we focused specifically on the main regions that are thought to exert inhibitory control over M1, including the rIFC, the SMC, the striatum, and the subthalamic nucleus (STN).

We have demonstrated that the rIFC is crucially involved in reactive inhibition (Chapter 3). In contrast, the rIFC does not appear to be engaged in proactive inhibition, because stimulation of this region did not alter

proactive inhibition (Chapter 3) and its response to increasing stop-signal probability occurred late rather than early in the trial (Chapter 4). Together, these findings fit with the idea that the rIFC, together with the TPJ, constitutes a network concerned with bottom-up (i.e. stimulus-driven) control only (Corbetta and Shulman, 2002; Corbetta et al., 2008; Verbruggen et al., 2010). We suggest that the rIFC is activated by behaviorally salient stimuli (e.g. stop-signals) and initiates the reactive inhibition process by interrupting activity in the network that prepares and executes motor responses, including the SMC, the basal ganglia, and M1.

In contrast to the rIFC, the SMC appears to be engaged both in proactive inhibition (Chapter 2 and 4) and reactive inhibition (Chapter 2 and 3). Yet, the precise role of the SMC in proactive and reactive inhibition remains unclear. It could be that the SMC modulates activity in the primary motor cortex, given that it has been implicated in the complete suppression of actions in response to stop-signals (reactive inhibition) as well as in the adjustment of the level of responsiveness of the motor system based on trial history (proactive inhibition) (Forstmann et al., 2008; Chen et al., 2009; Bogacz et al., 2010; Chen et al., 2010). Alternatively, the SMC may be involved in the detection of response conflict (Ridderinkhof et al., 2004; Sharp et al., 2010) that arises as a result of the co-activation of a response process and an inhibition process. These interpretations cannot be dissociated on the basis of the present findings.

Similar to the SMC, the striatum appears to be engaged both in proactive inhibition (Chapters 2, 4, and 5) and reactive inhibition (Chapters 2 and 3). In addition, our findings point to a role for striatal dopamine in proactive inhibition (Chapters 4 and 5). The striatum has been implicated in action selection (making a choice among multiple alternatives) and reinforcement learning (modifying expectations and behavior based on feedback-related dopamine release) (Houk and Wise, 1995; Mink, 1996; Cohen and Frank, 2009). Specifically, actions represented in the cortex (e.g. ‘go’ vs. ‘stop’ or ‘speeding up’ vs. ‘slowing down’) project to the striatum where they compete for selection (Brown et al., 2004; Frank, 2005). This action selection mechanism is under control of dopamine-driven reinforcement learning, such that, over time, successful actions are more likely to be repeated than unsuccessful actions. Indeed, these mechanisms are able to produce the striatal activations that we reported during proactive inhibition (i.e. due to increased competition for selection

between 'go' and 'stop') and reactive inhibition as measured by activation during successful stop-signal vs. go-signal trials (i.e. due to selecting a 'go' and a 'stop' action vs. selecting a 'go' action only) and successful vs. failure stop-signal trials (i.e. due to increased competition for selection on successful trials, either because a stop-signal was expected or due to stochastic processes).

The subthalamic nucleus is considered an important structure for (reactive) inhibition (Aron and Poldrack, 2006; Aron et al., 2007; Aron, 2010). However, apart from the fact that the STN was activated during reactive inhibition (Chapter 2 and 3), we did not find additional evidence implicating the STN in inhibitory control. This could be related to the fact that the STN is small relative to the spatial resolution of our fMRI images and that the fMRI signal in the vicinity of the STN may be distorted by iron-containing nuclei surrounding it (Drayer, 1988). As a consequence, no strong conclusions can be drawn from our findings about the role of the STN in inhibitory control.

In sum, the picture that emerges is that a cortico-basal ganglia network, including the SMC and the striatum, is involved in the top-down modulation of the responsiveness of M1 (i.e. proactive inhibition). When suddenly a stop-signal is presented, the rIFC detects the stop-signal and interrupts the ongoing response in M1 via the SMC and the right striatum (i.e. reactive inhibition).

## Neural mechanism of reduced proactive inhibition in schizophrenia

We demonstrated that proactive inhibition is reduced in schizophrenia and that it is accompanied by a failure to activate the striatum. This is in agreement with previous studies that have associated striatal dysfunction in schizophrenia with (proactive) inhibition impairments (Raemaekers et al., 2002; Raemaekers et al., 2006; Vink et al., 2006) and executive function deficits in general (Simpson et al., 2010). We tentatively suggest that striatal dysfunction in schizophrenia reflects disturbances in striatal dopaminergic signaling. This hampers the optimization of the action selection mechanism through reinforcement learning (Frank, 2008), such that this mechanism does not (or later) converge on an optimum. Indeed, this matches the pattern of behavioral results, showing that patients and siblings tend to adopt a suboptimal response strategy.

## Methodological considerations

The findings presented in this thesis should be interpreted in light of potential limitations. First, it is important to emphasize that findings from fMRI cannot provide conclusive evidence about the neural mechanisms of cognitive functions. As outlined in the Introduction, the hemodynamic signal measured with fMRI is an indirect measure of neural activity. Moreover, one should be aware that it reflects neuronal mass activity (i.e. one activation pixel in an fMRI activation map reflects an effect averaged over as many as ~ 6 million neurons) (Logothetis, 2008). Furthermore, fMRI alone cannot establish whether the contribution of a brain region to a cognitive function is crucial or more subsidiary (Robertson et al., 2003). Finally, inhibitory processes take place at the millisecond time scale, but the temporal resolution of fMRI is too low to determine whether activity in a brain region is sufficient for reactive inhibition. Thus, the present fMRI findings need to be confirmed by future studies using techniques that provide a more direct measure of neural activity, allow causal inferences, or have a superior temporal resolution.

Second, it is unclear whether the present findings from the stop-signal anticipation task generalize to inhibitory control as measured with the standard stop-signal task. In particular, the SSRT in the stop-signal anticipation task is substantially longer than in the standard stop-signal task. On the other hand, task performance is in agreement with the race model (Logan and Cowan, 1984; Verbruggen and Logan, 2009) and the activation patterns we observed for reactive inhibition are strikingly similar to those reported by studies using the standard stop-signal task (Vink et al., 2005; Aron and Poldrack, 2006; Leung and Cai, 2007; Ray Li et al., 2008; Boehler et al., 2010).

Third, it remains to be explored to what extent the findings from our relatively homogenous patient sample (in terms of diagnostic subtype and severity of clinical symptoms) are representative for the population of schizophrenia patients as a whole. In particular, we did not find reduced reactive inhibition in schizophrenia, whereas other studies did (Enticott et al., 2008; Huddy et al., 2009; Thakkar et al., 2011). This discrepancy may be due to differences in patient groups between studies, given that reactive inhibition deficits depend on diagnostic subtype (Bellgrove et al., 2006) and symptom severity (Thakkar et al., 2011).

## Future directions

The studies presented in this thesis have increased our insight into the neural mechanisms of proactive and reactive inhibition. In addition, these findings raise new questions that may be addressed in future studies.

*Temporal profile of reactive inhibition*

Despite the fact that reactive inhibition takes place at the millisecond time scale, little is known about the timing of activity during this process. Future studies should therefore explore the temporal profile of activity in key nodes of the inhibitory control network during reactive inhibition.

These studies are necessary to determine whether activity in brain regions is sufficient to contribute to reactive inhibition. For a region to be involved in reactive inhibition, its response to the stop-signal should occur within the time window of the SSRT (De Jong et al., 1990; Hanes et al., 1998; Paré and Hanes, 2003). Although such evidence has already been provided for the SMC (Chen et al., 2010), the rIFC (Swann et al., 2009), and M1 (Coxon et al., 2006), it is still lacking for the basal ganglia, including the striatum and the subthalamic nucleus. This issue may be addressed with single-cell and local field potential recordings from the basal ganglia in non-human primates performing the stop-signal task.

In addition, these studies could test our claim that during reactive inhibition the rIFC exerts control over M1 via the SMC. Two lines of evidence are required. First, the inhibitory effect of SMC on M1 should occur at a later time point than the inhibitory effect of rIFC on M1. Second, the inhibitory effect of SMC on M1 should be influenced by the rIFC. These predictions may be tested using paired-pulse TMS in humans performing the stop-signal task.

*Dissociating proactive inhibition from related cognitive processes*

The brain regions activated during proactive and reactive inhibition may have a direct inhibitory influence on M1, but it may very well be that their activation, in fact, reflects a process associated with the inhibition of a response, such as stop-signal detection and response selection (Chambers et al., 2009). Indeed, recent studies have separated cognitive subprocesses contributing to reactive inhibition (e.g. Hampshire et al., 2010; Sharp et al., 2010; Verbruggen et al., 2010) and future studies should do the same

for proactive inhibition. Specifically, in Chapter 4 we suggested that the effect of stop-signal probability on go-signal trial activation may not only relate to proactive inhibition, but also reflect expectancy violation (in the rIFC and rTPJ) or response conflict (in the SMC and the striatum).

Proactive inhibition may be dissociated from response conflict using an adapted version of the stop-signal anticipation task that includes stop-signal probability levels above 50%. That is, up to 50%, both inhibitory control and response conflict increase, but above 50%, the degree of inhibitory control increases, whereas the degree of response conflict decreases. Thus, if activation increases monotonously as a function of stop-signal probability, then it likely reflects proactive inhibition. However, if it follows an inverted U-shape, then it may indicate response conflict. These predictions can be tested in humans with fMRI.

Proactive inhibition may be dissociated from expectancy violation in studies combining the stop-signal anticipation task with magnetoencephalography or electrocorticography, both of which have a temporal resolution superior to fMRI. We predict that the modulation of rIFC and rTPJ activity by stop-signal probability occurs late in the trial, around the time point at which stop-signals are presented. This would support the claim that the activation we report reflects updating of expectations after these have been violated. In contrast, if the modulation of activity by stop-signal probability occurs time-locked to trial onset, then rIFC and rTPJ could be involved in proactive inhibition.

*Role of dopamine in proactive inhibition*

We have argued that proactive inhibition relies on striatal dopaminergic signaling and that disturbances in this process may explain reduced proactive inhibition in schizophrenia. Although this interpretation is supported by theoretical models of proactive control (Braver et al., 1999; Braver et al., 2007; Simpson et al., 2010), direct evidence supporting this claim is lacking. Future pharmacological manipulations of dopaminergic signaling could test whether elevated striatal dopaminergic function, such as occurs in schizophrenia, results in reduced proactive inhibition.

## Conclusion

The overall aim of this thesis was to increase the understanding of the neural mechanisms underlying proactive and reactive inhibition and how these mechanisms are affected in schizophrenia. First, our findings suggest that the rIFC is involved in reactive inhibition only, whereas the SMC and the striatum are engaged both in proactive and reactive inhibition. Therefore, our findings appear to challenge the common view that the whole neural network involved in outright stopping is recruited in anticipation of stopping. Second, our results provide insight into the mechanism underlying reactive inhibition, indicating that the rIFC exerts inhibitory control over M1 via a cortico-basal ganglia pathway that includes the SMC and the right striatum. Third, our findings suggest that reduced proactive inhibition in schizophrenia is associated with striatal dysfunction, possibly reflecting striatal dopaminergic abnormalities.

## References

Aron AR (2010) From Reactive to Proactive and Selective Control: Developing a Richer Model for Stopping Inappropriate Responses. Biol Psychiatry.

Aron AR, Poldrack RA (2006) Cortical and subcortical contributions to stop signal response inhibition: role of the subthalamic nucleus. J Neurosci 26:2424-2433.

Aron AR, Behrens TE, Smith S, Frank MJ, Poldrack RA (2007) Triangulating a cognitive control network using diffusion-weighted magnetic resonance imaging (MRI) and functional MRI. J Neurosci 27:3743-3752.

Bellgrove MA, Chambers CD, Vance A, Hall N, Karamitsios M, Bradshaw JL (2006) Lateralized deficit of response inhibition in early-onset schizophrenia. Psychol Med 36:495-505.

Boehler CN, Appelbaum LG, Krebs RM, Hopf JM, Woldorff MG (2010) Pinning down response inhibition in the brain - conjunction analyses of the stop-signal task. Neuroimage 52:1621-1632.

Bogacz R, Wagenmakers EJ, Forstmann BU, Nieuwenhuis S (2010) The neural basis of the speed-accuracy tradeoff. Trends Neurosci 33:10-16.

Braver TS, Barch DM, Cohen JD (1999) Cognition and control in schizophrenia: a computational model of dopamine and prefrontal function. Biol Psychiatry 46:312-328.

Braver TS, Gray JR, Burgess GC (2007) Explaning the many varieties of working memory variation: dual mechanisms of cognitive control. In: Variation in Working Memory (Conway A, Jarrold C, Kane M, Miyake A, Towse K, eds), pp 76-106. Oxford: Oxford University Press.

Brown JW, Bullock D, Grossberg S (2004) How laminar frontal cortex and basal ganglia circuits interact to control planned and reactive saccades. Neural Netw 17:471-510.

Chambers CD, Garavan H, Bellgrove MA (2009) Insights into the neural basis of response inhibition from cognitive and clinical neuroscience. Neurosci Biobehav Rev 33:631-646.

Chen CY, Muggleton NG, Tzeng OJ, Hung DL, Juan CH (2009) Control of prepotent responses by the superior medial frontal cortex. Neuroimage 44:537-545.

Chen X, Scangos K, Stuphorn V (2010) Supplementary Motor Area Exerts Proactive and Reactive Control of Arm Movements. J Neurosci 30:14657-14675.

Cohen MX, Frank MJ (2009) Neurocomputational models of basal ganglia function in learning, memory and choice. Behav Brain Res 199:141-156.

Corbetta M, Shulman GL (2002) Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 3:201-215.

Corbetta M, Patel G, Shulman GL (2008) The reorienting system of the human brain: from environment to theory of mind. Neuron 58:306-324.

Coxon JP, Stinear CM, Byblow WD (2006) Intracortical inhibition during volitional inhibition of prepared action. J Neurophysiol 95:3371-3383.

De Jong R, Coles MGH, Logan GD, Gratton G (1990) In search of the point of no return: the control of response processes. Journal of experimental psychology Human perception and performance 16:164-182.

Drayer BP (1988) Imaging of the aging brain. Part I. Normal findings. Radiology 166:785-796.

Enticott PG, Ogloff JR, Bradshaw JL (2008) Response inhibition and impulsivity in schizophrenia. Psychiatry Res 157:251-254.

Forstmann BU, Dutilh G, Brown S, Neumann J, von Cramon DY, Ridderinkhof KR, Wagenmakers EJ (2008) Striatum and pre-SMA facilitate decision-making under time pressure. Proc Natl Acad Sci USA 105:17538-17542.

Frank MJ (2005) Dynamic dopamine modulation in the basal ganglia: a neurocomputational account of cognitive deficits in medicated and nonmedicated Parkinsonism. J Cogn Neurosci 17:51-72.

Frank MJ (2008) Schizophrenia: a computational reinforcement learning perspective. Schizophr Bull 34:1008-1011.

Hampshire A, Chamberlain SR, Monti MM, Duncan J, Owen AM (2010) The role of the right inferior frontal gyrus: inhibition and attentional control. Neuroimage 50:1313-1319.

Hanes DP, Patterson WF, Schall JD (1998) Role of frontal eye fields in countermanding saccades: visual, movement, and fixation activity. J Neurophysiol 79:817-834.

Houk JC, Wise SP (1995) Distributed modular architectures linking basal ganglia, cerebellum, and cerebral cortex: their role in planning and controlling action. Cereb Cortex 5:95-110.

Huddy VC, Aron AR, Harrison M, Barnes TRE, Robbins TW, Joyce EM (2009) Impaired conscious and preserved unconscious inhibitory processing in recent onset schizophrenia. Psychol Med 39:907-916.

Leung HC, Cai W (2007) Common and differential ventrolateral prefrontal activity during inhibition of hand and eye movements. J Neurosci 27:9893-9900.

Logan GD, Cowan WB (1984) On the ability to inhibit thought and action: A theory of an act of control. Psychol Rev 91:291-327.

Logothetis N (2008) What we can do and what we cannot do with fMRI. Nature.

Mink JW (1996) The basal ganglia: focused selection and inhibition of competing motor programs. Prog Neurobiol 50:381-425.

Paré M, Hanes DP (2003) Controlled movement processing: superior colliculus activity associated with countermanded saccades. J Neurosci 23:6480-6489.

Raemaekers M, Ramsey NF, Vink M, van den Heuvel MP, Kahn RS (2006) Brain activation during antisaccades in unaffected relatives of schizophrenic patients. Biol Psychiatry 59:530-535.

Raemaekers M, Jansma JM, Cahn W, Van der Geest JN, van der Linden JA, Kahn RS, Ramsey NF (2002) Neuronal substrate of the saccadic inhibition deficit in schizophrenia investigated with 3-dimensional event-related functional magnetic resonance imaging. Arch Gen Psychiatry 59:313-320.

Ray Li CS, Yan P, Sinha R, Lee TW (2008) Subcortical processes of motor response inhibition during a stop signal task. Neuroimage 41:1352-1363.

Ridderinkhof K, Ullsperger M, Crone E, Nieuwenhuis S (2004) The Role of the Medial Frontal Cortex in Cognitive Control. Science 306:443.

Robertson EM, Théoret H, Pascual-Leone A (2003) Studies in cognition: the problems solved and created by transcranial magnetic stimulation. J Cogn Neurosci 15:948-960.

Sharp DJ, Bonnelle V, De Boissezon X, Beckmann CF, James SG, Patel MC, Mehta MA (2010) Distinct frontal systems for response inhibition, attentional capture, and error processing. Proc Natl Acad Sci USA.

Simpson EH, Kellendonk C, Kandel E (2010) A Possible Role for the Striatum in the Pathogenesis of the Cognitive Symptoms of Schizophrenia. Neuron 65:585-596.

Swann N, Tandon N, Canolty R, Ellmore TM, McEvoy LK, Dreyer S, DiSano M, Aron AR (2009)

Intracranial EEG reveals a time- and frequency-specific role for the right inferior frontal gyrus and primary motor cortex in stopping initiated responses. J Neurosci 29:12675-12685.

Thakkar KN, Schall JD, Boucher L, Logan GD, Park S (2011) Response inhibition and response monitoring in a saccadic countermanding task in schizophrenia. Biol Psychiatry 69:55-62.

Verbruggen F, Logan GD (2009) Models of response inhibition in the stop-signal and stop-change paradigms. Neurosci Biobehav Rev 33:647-661.

Verbruggen F, Aron AR, Stevens MA, Chambers CD (2010) Theta burst stimulation dissociates attention and action updating in human inferior frontal cortex. Proc Natl Acad Sci USA 107:13966-13971.

Vink M, Ramsey NF, Raemaekers M, Kahn RS (2006) Striatal dysfunction in schizophrenia and unaffected relatives. Biol Psychiatry 60:32-39.

Vink M, Kahn RS, Raemaekers M, van den Heuvel M, Boersma M, Ramsey NF (2005) Function of striatum beyond inhibition and execution of motor responses. Hum Brain Mapp 25:336-344.

7

# Nederlandse samenvatting

Het doel van dit proefschrift is het inzicht in de neurale mechanismen die ten grondslag liggen aan proactieve en reactieve inhibitie te vergroten. Daarnaast onderzochten we hoe deze mechanismen worden beïnvloed door schizofrenie.

Inhibitie verwijst naar het remmen of blokkeren van acties, bijvoorbeeld het vertragen van je pas in een drukke winkelstraat of stoppen voor een rood voetgangerslicht. In de recente literatuur worden twee vormen van inhibitie onderscheiden: proactieve inhibitie en reactieve inhibitie.

Proactieve inhibitie is het remmen van acties in voorbereiding op (of ter voorkoming van) het blokkeren van een actie. Het vertragen van je pas in een drukke winkelstraat om een botsing met een andere voetganger te voorkomen is een voorbeeld van proactieve inhibitie.

Reactieve inhibitie verwijst naar het blokkeren van acties. Stoppen voor een rood voetgangerslicht wanneer je de straat wilt oversteken is een voorbeeld van reactieve inhibitie.

Het onderzoek naar de neurale mechanismen van proactieve en reactieve inhibitie is niet alleen relevant om te begrijpen hoe de mens controle uitoefent over zijn gedrag, maar is ook van belang om hersenaandoeningen beter te kunnen begrijpen. Een aantal psychiatrische en neurologische stoornissen wordt namelijk gekenmerkt door symptomen die kunnen worden verklaard in termen van een inhibitieprobleem: impulsiviteit en aandachtsproblemen bij ADHD, het niet kunnen onderdrukken van tics bij Gilles de la Tourette, overmatig handenwassen en controleren bij dwangstoornissen en het doelloos herhalen van handelingen (perseveratie) bij schizofrenie.

## Achtergrond

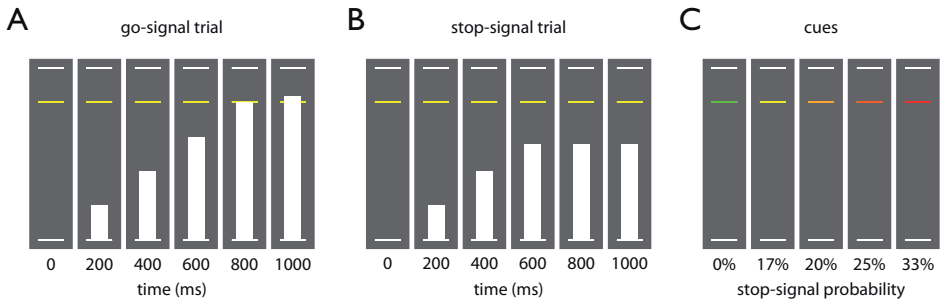
*Hoe werd inhibitie onderzocht?*

Om proactieve en reactieve inhibitie te kunnen onderzoeken hebben we een computertaak ontwikkeld, genaamd de stopsignaal anticipatie taak (SSAT). Deze taak (Figuur 1) bestaat uit een honderdtal opgaven, waarin een wit balkje vanaf een lijn onderaan het computerscherm naar een lijn bovenin het computerscherm beweegt (Figuur 1A). Tussen de onderste en de bovenste lijn bevindt zich een derde lijn, de doellijn. In een klein aantal van de opgaven stopt het witte balkje alvorens de doellijn te passeren (stopsignaal, Figuur 1B). De kans op een stopsignaal wordt aangegeven door de kleur van de doellijn: in geval van een groene, gele, lichtoranje, donkeroranje, en rode doellijn verschijnt het stopsignaal in respectievelijk 0%, 17%, 20%, 25% en 33% van de opgaven (Figuur 1C). De opdracht in de SSAT is eenvoudig: druk op een knop op het moment dat het balkje de doellijn passeert, maar druk niet als het balkje vroegtijdig stopt alvorens de doellijn te passeren.

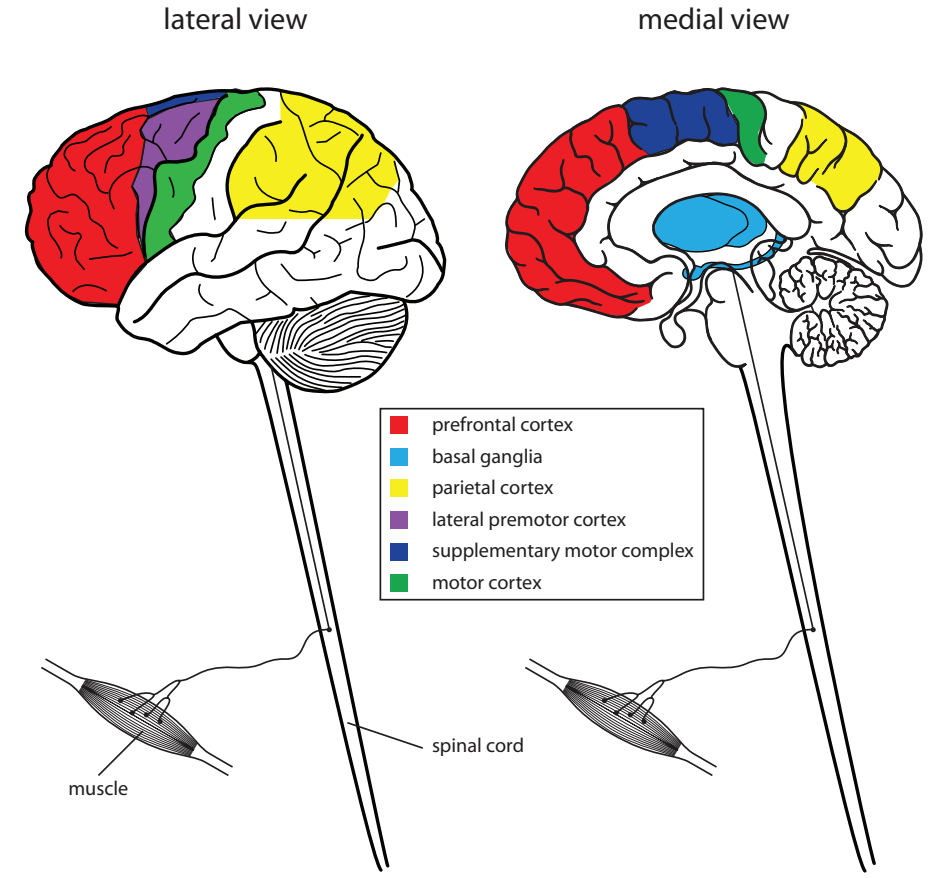
Je kunt de situatie die deze taak creëert vergelijken met de start van een 100 meter sprintwedstrijd bij atletiek. Het moment waarop het balkje omhoog begint te lopen komt overeen met de instructie 'klaar voor de start', het moment waarop het balkje aankomt bij de middelste lijn weerspiegelt de instructie 'af!'. Het stopsignaal kan vergeleken worden met een tegenstander die een valse start maakt, waardoor alle sporters hun race moeten afbreken. Tenslotte, een toename in de stopsignaalkans is vergelijkbaar met de situatie waarin reeds een valse start begaan is en de atleet zich bij de herkansing voorbereidt op een voorzichtigere start om een tweede valse start te voorkomen.

Proactieve inhibitie werd gemeten aan de hand van opgaven waarin geen stopsignaal verscheen ('go-signaal opgaven'). We onderzochten hoe de kans op een stopsignaal de reactietijd beïnvloedde. Een toename in de kans op een stopsignaal had in het algemeen een remmende invloed op de reactietijd.

Reactieve inhibitie werd gemeten aan de hand van de opgaven waarin wel een stopsignaal verscheen ('stopsignaal opgaven'). Het moment waarop het stopsignaal verscheen was variabel: soms verscheen het stopsignaal vroeg in de opgave (waardoor deelnemers meestal in staat waren om een respons te blokkeren), soms laat in de opgave (waardoor deelne-




**Figuur 1.** Grafische weergave van de stopsignaal anticipatie taak. (**A**) Voorbeeld van een 'go-signaal' opgave. De zes plaatjes tonen momentopnamen tijdens de opgave op respectievelijk 0, 200, 400, 600, 800, en 1000 ms na het begin van de opgave. Merk op dat het balkje vlak na de doellijn gestopt is, als gevolg van een respons van de deelnemer. (**B**) Voorbeeld van een stopsignaal opgave. Merk op dat het balkje halverwege de opgave gestopt is. (**C**) Voorbeeld van de weergave van stopsignaalkans condities.




**Figuur 2.** Hersengebieden betrokken bij het genereren, het remmen (proactieve inhibitie) en het blokkeren (reactieve inhibitie) van acties.

mers meestal niet in staat waren om een respons te blokkeren). Door het moment waarop het stopsignaal verscheen te variëren konden we een inschatting maken van de reactietijd van het reactieve inhibitieproces, de stopsignaal reactietijd (SSRT).

*Neurale mechanismen van het uitvoeren van acties*

Om de neurale mechanismen van het remmen (proactieve inhibitie) en blokkeren (reactieve inhibitie) van acties te kunnen begrijpen is het nuttig om eerst de mechanismen te bespreken die betrokken zijn bij het uitvoeren van een actie.

De totstandkoming van een actie is het resultaat van een samenwerking tussen verschillende hersengebieden (Figuur 2). Deze samenwerking is hiërarchisch georganiseerd: Hersengebieden hoog in de hiërarchie houden zich bezig met de abstracte planning van acties, terwijl gebieden lager in hiërarchie betrokken zijn bij concrete uitvoering van spiercontracties waardoor de actie wordt uitgevoerd. Deze hiërarchische organisatie kan worden geïllustreerd aan de hand van een voorbeeld: een honkbalspeler die een bal werpt naar een slagman.

De werper heeft als doel een bal in de slagzone te gooien die de slagman niet kan slaan. Dergelijke doelen en de middelen om deze doelen te bereiken worden gerepresenteerd in de prefrontale schors (rood in Figuur 2). Om zijn doel te bereiken kan de werper uit verschillende soorten worpen kiezen (bijvoorbeeld een curveball, knuckleball of een screwball). De werper zal de worp kiezen waarmee zijn doel naar de grootste waarschijnlijkheid wordt bereikt. Bij het maken van dergelijke keuzes zijn de basale kernen betrokken die in het midden van de hersenen liggen (turquoise in Figuur 2). Daarnaast moet de werper de richting en snelheid van zijn worp baseren op de positie van de slagman ten opzichte van zijn eigen positie. Hiervoor is een ruimtelijke representatie van de omgeving nodig die gegenereerd wordt in de parietaalkwab (geel in Figuur 2). Vervolgens moet de gekozen worp worden vertaald in een serie aaneengeschakelde bewegingen. De premotorschors, bestaande uit supplementaire motor cortex (SMC) en laterale premotorschors, zijn hiervoor verantwoordelijk (respectievelijk in paars en blauw). Deze informatie wordt naar de primaire motorschors (M1, groen in Figuur 2) gestuurd die dit abstracte motorische plan omzet in signalen waarmee de spieren, via de hersenstam en het ruggenmerg, worden aangestuurd en waardoor de bal uiteindelijk wordt geworpen.

In vergelijking tot de processen betrokken bij het genereren van acties is er minder bekend over de processen betrokken bij het remmen en blokkeren van acties. Men veronderstelt dat deze processen ook hiërarchisch georganiseerd zijn en dat dezelfde gebieden erbij betrokken zijn.

*Neurale mechanismen van het blokkeren van acties (reactieve inhibitie)*
Om een actie te blokkeren dient neuronale activiteit in M1 te worden onderdrukt. Activiteit in M1 wordt aangestuurd door een netwerk bestaande uit gebieden in de frontaalkwab (waaronder de rechter inferior frontal cortex (rIFC) en de SMC) en de basale kernen (waaronder het striatum en de subthalamische nucleus (STN)).

De rol van deze gebieden tijdens reactieve inhibitie is niet geheel duidelijk. De rIFC lijkt betrokken bij het detecteren van het stopsignaal en het aanpassen van het actieplan (dat wil zeggen: van het uitvoeren van een actie naar het blokkeren ervan). De SMC is mogelijk ook betrokken bij deze laatste functie. Daarnaast speelt de SMC een rol bij de directe modulatie van activiteit in M1 en de detectie van conflict dat ontstaat door de gelijktijdige activatie van twee tegenstrijdige actieplannen (, namelijk het uitvoeren en blokkeren van een actie). Dit conflict lijkt te worden opgelost in samenwerking met de basale kernen. De basale kernen, waartoe het striatum en de STN behoren, zijn verantwoordelijk voor het selecteren van acties uit verschillende mogelijkheden. Daarnaast wordt verondersteld dat het striatum en de STN betrokken zijn bij de implementatie van reactieve inhibitie. Echter, er is twijfel over de rol van het striatum in de implementatie van reactieve inhibitie; sommige onderzoekers menen dat het onwaarschijnlijk is dat het striatum bij reactieve inhibitie betrokken is. Deze kwestie werd onderzocht in Hoofdstuk 2.

Hoe bovengenoemde gebieden samenwerken tijdens reactieve inhibitie over M1 is een ander punt waarover een aantal onduidelijkheden bestaan. Ten eerste, over de positie van de rIFC ten opzichte van de SMC. Er zijn studies die suggereren dat de rIFC in hiërarchie boven de SMC staat en dat de rIFC via de SMC invloed uitoefent op M1. Andere studies beweren het tegenovergestelde, namelijk, dat de SMC via de rIFC M1 aanstuurt. Ten tweede, en zoals hierboven al genoemd, bestaat er onduidelijkheid over het feit of reactieve inhibitie plaatsvindt via het striatum of via de STN (of allebei). Sterker, de betrokkenheid van de basale kernen bij reactieve inhibitie staat niet onomstotelijk vast, aangezien rIFC en SMC

M1 ook direct kunnen aansturen. Deze onderwerpen kwamen aan bod in Hoofdstuk 3.

*Neurale mechanismen van het remmen van acties (proactieve inhibitie)*
Er is nog minder bekend over de neurale mechanismen van proactieve inhibitie. De studies die tot nu toe zijn verricht suggereren dat het netwerk dat betrokken is bij proactieve inhibitie ook bij reactieve inhibitie geactiveerd wordt.

De precieze rol van de rIFC, SMC, en het striatum in proactieve inhibitie blijft echter onduidelijk. Het is mogelijk dat de functies van deze gebieden tijdens proactieve inhibitie soortgelijk of zelfs identiek zijn aan hun functie tijdens reactieve inhibitie. Voor de SMC en het striatum is dat aannemelijk omdat hun rol tijdens reactieve inhibitie (modulatie van activiteit in M1 en het detecteren en oplossen van conflict) ook van toepassing is op proactieve inhibitie. Voor de rIFC ligt dit anders; de rol van de rIFC tijdens reactieve inhibitie lijkt voornamelijk het detecteren van een stopsignaal, maar in het geval van proactieve inhibitie is er helemaal geen stopsignaal dat gedetecteerd moet worden. In Hoofdstuk 4 werd dit vraagstuk nader onderzocht.

*Hebben mensen met schizofrenie een inhibitieprobleem?*
Tenslotte onderzochten we de neurale mechanismen van inhibitieproblemen bij schizofrenie. Schizofrenie is een chronische aandoening van de hersenen die ongeveer 1% van de wereldbevolking treft. Zowel erfelijkheid als omgevingsfactoren spelen een rol bij het ontstaan van schizofrenie. Schizofrenie wordt gekenmerkt door onder andere vervormde waarnemingen (hallucinaties) en gedachten (wanen) en door sociale dysfunctie. De klinische symptomen van schizofrenie uiten zich meestal tussen het 15e en 25e levensjaar. Naast deze klinische symptomen wordt schizofrenie gekenmerkt door verminderd functioneren in een aantal cognitieve functies, waaronder het werkgeheugen.

Ook van inhibitie wordt verondersteld dat het verminderd is bij schizofrenie. Echter, lang niet alle studies rapporteren inhibitieproblemen bij schizofreniepatiënten. Een mogelijke verklaring voor deze discrepantie tussen studies is dat er verscheidene inhibitietaken zijn gebruikt die verschillen in de vorm van inhibitie die zij meten. Daarnaast is weinig bekend

over de neurale basis van inhibitieproblemen bij schizofrenie, omdat de meerderheid van de onderzoeken tot op heden gedragsstudies betreft. Bovendien is het onduidelijk in hoeverre eventuele inhibitieproblemen bij schizofrenie gerelateerd zijn aan de ziekte (en bijbehorende factoren zoals medicatie) of een familiaire oorsprong hebben. Tenslotte is het onbekend of eventuele problemen in proactieve en reactieve inhibitie een specifiek inhibitieprobleem vormen of dat deze problemen samenhangen met problemen in een andere cognitief domein, zoals het werkgeheugen. Deze vier kwesties kwamen aan bod in Hoofdstuk 5.

## Bevindingen en interpretatie

*Hoofdstuk 2*

In Hoofdstuk 2 onderzochten we de rol van het striatum in inhibitie. Een aantal studies heeft activatie van het striatum gerapporteerd tijdens het blokkeren van een actie. Deze bevinding kan duiden op een actieve betrokkenheid van het striatum bij het onderdrukken van activiteit in M1, maar het kan ook een andere betekenis hebben. Dat een actie geblokkeerd kan worden kan ook voortkomen uit het feit dat een stopsignaal werd verwacht of omdat men toevalligerwijs traag was met reageren en daardoor voldoende tijd had om de geplande actie te blokkeren.

Net als eerdere studies vonden we striatum activatie tijdens het blokkeren van een actie. Daarnaast vonden we dat striatum activatie in verhouding stond tot de onderdrukking van activiteit in M1. Deze bevinding vormt een aanwijzing voor de betrokkenheid van het striatum bij reactieve inhibitie. Bovendien zagen we een toename in striatum activiteit naarmate de kans op een stopsignaal hoger werd. Ook bleek activiteit in het striatum tijdens het onderdrukken van een actie voorspellend te zijn voor activiteit in de rIFC en de SMC, gebieden die reactieve inhibitie mogelijk implementeren. Deze resultaten suggereren dat het striatum tevens betrokken is bij proactieve inhibitie. Tenslotte vonden we geen aanwijzingen voor de bewering dat striatum activiteit samenhangt met variatie in reactiesnelheid.

De conclusie van deze studie luidt dat het striatum een belangrijke structuur is voor zowel proactieve als reactieve inhibitie.

*Hoofdstuk 3*

In Hoofdstuk 3 werd de bijdrage van twee andere componenten van het inhibitienetwerk onderzocht: de rechter IFC en de SMC. Hoewel er sterke aanwijzingen zijn voor de betrokkenheid van deze gebieden bij reactieve inhibitie is het niet bekend hoe deze gebieden controle uitoefenen op M1. Door activiteit in de rIFC en SMC te beïnvloeden door middel van hersenstimulatie (repetitieve transcraniële magnetische stimulatie, rTMS) en de effecten daarvan op hersenactiviteit te meten kon worden bepaald in welke andere hersengebieden van het inhibitienetwerk er veranderingen optreden. Hieruit kan worden afgeleid welke gebieden een cruciale rol spelen bij proactieve en reactieve inhibitie en hoe deze gebieden samenwerken en komen tot het remmen of blokkeren van een actie.

De resultaten lieten zien dat stimulatie van zowel de rIFC en de SMC (ten opzichte van placebo stimulatie) reactieve inhibitie verbeterde (de SSRT werd korter), terwijl proactieve inhibitie niet waarneembaar veranderde. Bovendien was M1 na rIFC en SMC stimulatie sterker gedeactiveerd (in lijn met een sterkere onderdrukking) tijdens reactieve inhibitie. Deze bevindingen tonen aan dat de interventie met rTMS succesvol was. De meest interessante resultaten werden echter gevonden in de hersenactiviteit van de gestimuleerde gebieden (de rIFC en de SMC) en het striatum. Terwijl rIFC stimulatie een invloed had op activiteit in zowel de SMC als de rIFC, beïnvloedde SMC stimulatie alleen maar activiteit in de SMC. Deze bevinding suggereert dat de rIFC de SMC aanstuurt in plaats van andersom. Daarnaast vonden we een effect van zowel rIFC als SMC stimulatie op activiteit in het rechter striatum. Deze bevinding laat zien dat reactieve inhibitie over M1 via het rechter striatum loopt.

De conclusie van deze studie is dat de rIFC en de SMC reactieve controle uitoefenen over M1 via het rechter striatum, waarbij de rIFC in hiërarchie boven de SMC staat.

*Hoofdstuk 4*

In Hoofdstuk 4 werden de neurale mechanismen van proactieve inhibitie nader bestudeerd. Kenmerkend voor de studies tot op heden is dat proactieve inhibitie nooit afzonderlijk werd onderzocht. Dat wil zeggen, de gemeten hersenactiviteit had betrekking op zowel de voorbereiding op het blokkeren van een actie (d.w.z. proactieve inhibitie) als de uitvoering van die actie. Wanneer men zich voorbereidt op het blokkeren van een

actie en de actie blijkt toch te moeten worden uitgevoerd dan zal in het actieplan waarschijnlijk een wijziging plaatsvinden (van stoppen naar uitvoeren). We hebben daarom een nieuwe variant van de SSAT ontwikkeld waarmee activiteit gerelateerd aan de voorbereiding op het blokkeren van een actie en het uitvoeren de actie onderscheiden konden worden.

De resultaten lieten zien dat onder meer het striatum en de SMC actief werden tijdens de voorbereiding op het blokkeren van een actie. De rIFC en een gebied in de parietaalkwab werden daarentegen actief tijdens het uitvoeren van een actie.

Kortom, het striatum en de SMC zijn waarschijnlijk betrokken bij proactieve inhibitie. De rIFC en de rechter parietaalkwab lijken daarentegen niet betrokken bij proactieve inhibitie; zij signaleren waarschijnlijk het uitblijven van een verwacht stopsignaal.

*Hoofdstuk 5*

In Hoofdstuk 5 werd onderzocht in welke mate proactieve en reactieve inhibitie zijn aangedaan bij schizofrenie en welke veranderingen in hersenactiviteit daarmee samengaan. We onderzochten zowel patiënten met schizofrenie als hun gezonde broers en zussen en namen naast de stopsignaal anticipatie taak ook een werkgeheugentaak af.

De resultaten van dit onderzoek lieten verminderde proactieve inhibitie zien bij zowel schizofreniepatiënten als hun gezonde broers en zussen, terwijl reactieve inhibitie niet was aangedaan. Deze problemen in proactieve inhibitie gingen samen met verminderde hersenactiviteit in vier hersengebieden: het rechter striatum, de rechter IFC en de linker en rechter TPJ. Een interessante bevinding was dat deze gebieden tijdens reactieve inhibitie wél normaal functioneerden. Kortom, van deze hersengebieden kan niet worden gesteld dat ze in het algemeen slecht functioneren bij schizofrenie. Tenslotte vonden we een verband tussen de ernst van inhibitieproblemen en werkgeheugenproblemen bij patiënten met schizofrenie. Dit wijst erop dat inhibitieproblemen bij schizofrenie voortkomen uit een meer algemeen cognitief disfunctioneren.

Samenvattend, inhibitieproblemen bij schizofrenie lijken voornamelijk betrekking te hebben op proactieve inhibitie, hebben een familiaire oorsprong, en zijn vermoedelijk het gevolg van cortico-striatale dysfunctie.

## Beperkingen

De resultaten in dit proefschrift dienen te worden geïnterpreteerd in het licht van een aantal beperkingen.

Ten eerste dient voorzichtigheid in acht genomen te worden bij het trekken van conclusies op basis van resultaten verkregen met functionele MRI, de techniek die werd gebruikt om hersenactiviteit te meten. Hersenactiviteit gemeten met functionele MRI geeft slechts een indirecte weergave van neuronale activiteit. Daarnaast is de gemeten hersenactiviteit de resultante van miljoenen hersencellen. Bovendien kan met functionele MRI onvoldoende worden vastgesteld in hoeverre de hersenactiviteit in een bepaald gebied essentieel is voor hersenfuncties zoals inhibitie. Tenslotte is de temporele resolutie (dat wil zeggen: de mate waarin twee (hersen)processen in tijd van elkaar te onderscheiden zijn) van functionele MRI relatief laag (seconden) ten opzichte van de schaal waarop hersencellen communiceren (milliseconden). Hierdoor kan met functionele MRI niet worden bepaald of de activiteit in een bepaald hersengebied vroeg genoeg optreedt om een bijdrage te leveren aan een proces zoals reactieve inhibitie, waarin timing van cruciaal belang is.

Ten tweede is het de vraag of de groep schizofrenie patiënten die bestudeerd is in dit onderzoek representatief is voor de populatie schizofreniepatiënten als geheel. Schizofrenie is een heterogene stoornis: het ziektebeeld verschilt niet alleen tussen patiënten maar ook binnen een patiënt over de verschillende stadia van de ziekte. Echter, de patiënten die deelnamen vormden een relatief homogene groep: zij bevonden zich min of meer in hetzelfde stadium van de ziekte (gemiddeld zo'n tien jaar na hun eerste psychose), hun symptomen waren relatief mild ten tijde van het onderzoek, en allen hadden de diagnose paranoïde schizofrenie. Het is mogelijk dat bij patiënten in een ander stadium van de ziekte (bijvoorbeeld tijdens een psychose) niet alleen proactieve inhibitie maar ook reactieve inhibitie aangedaan is.

## Vervolgonderzoek

De studies in dit proefschrift hebben bijgedragen aan het inzicht in de neurale mechanismen van proactieve en reactieve inhibitie. Daarnaast roepen de resultaten vragen op voor vervolgonderzoek.

Zoals hierboven al beschreven is functionele MRI niet optimaal voor het bestuderen van de temporele aspecten van het inhibitieproces.

Dit betekent dat de in Hoofdstuk 3 geopperde cascade van gebeurtenissen tijdens reactieve inhibitie (rIFC detecteert het stopsignaal en implementeert het inhibitieproces via interacties met de SMC en het striatum om uiteindelijk activiteit in M1 te blokkeren) gevalideerd dient te worden met technieken met een betere tijdsresolutie.

Een tweede lijn van vervolgonderzoek heeft betrekking op het ontrafelen van de subprocessen van proactieve inhibitie en reactieve inhibitie. Recente studies zijn begonnen met het in kaart brengen van subprocessen van reactieve inhibitie. Vervolgstudies moeten ditzelfde doen voor proactieve inhibitie om zo de mechanismen die ten grondslag liggen aan beide vormen van inhibitie beter te kunnen begrijpen.

## Conclusie

De resultaten in dit proefschrift geven inzage in de neurale mechanismen van proactieve en reactieve inhibitie. Een netwerk bestaande uit het striatum en de SMC lijkt betrokken bij de modulatie van activiteit in de primaire motorschors (M1) in de voorbereiding op het blokkeren van een actie (proactieve inhibitie). Wanneer er plotseling een stopsignaal verschijnt en reactieve inhibitie nodig is lijkt de rIFC het stopsignaal te detecteren en de geplande actie via de SMC en het striatum te blokkeren. Patiënten met schizofrenie hebben verminderde proactieve inhibitie. Dit inhibitieprobleem is vermoedelijke het gevolg van verstoorde hersenactiviteit in de frontaal cortex en het striatum.

8

# Dankwoord

Het volbrengen van dit promotietraject was niet mogelijk geweest zonder de bijdrage van een heleboel mensen.

Als eerste wil ik alle deelnemers aan mijn studies bedanken; zonder hun inspanning was er weinig te onderzoeken geweest.

Mijn co-promotor en promotor voor hun begeleiding:
Matthijs Vink, ondanks de bijna vijf jaar is het promotietraject voorbij gevlogen. Bedankt voor alle vrijheid en het vertrouwen dat je me hebt gegeven, voor je kritische kanttekeningen bij mijn manuscripten en dat je me vanaf de eerste dag achter de Matlab command line hebt gezet. Ik heb veel geleerd. Mij begeleiden was misschien niet altijd even makkelijk ('Wacht maar, tot je een AiO krijgt zoals jij'), maar ik denk dat we tevreden kunnen zijn met het eindresultaat. Ik hoop op een vruchtbare samenwerking in de toekomst!

René Kahn, bedankt voor uw snelle en bondige commentaar op mijn manuscripten. Ik weet het, mijn schrijfstijl is niet de uwe; heel erg fijn dat ik toch de vrijheid kreeg om mijn eigen stempel op de teksten te drukken.

De leden van de beoordelingscommissie:
De professoren Peter Burbach, Roshan Cools, Sarah Durston, Richard Ridderinkhof en Iris Sommer wil ik hartelijk danken voor het lezen en beoordelen van dit proefschrift.

Talloze collega's hebben hun bijdrage geleverd:
Mariët van Buuren, collega en kamergenoot vanaf (bijna) de eerste maand. Ik vond het erg leuk en prettig om met je samen te werken. Bedankt voor al je feedback op mijn werk, het uitproberen van mijn Matlab knutsels en de leuke gesprekken bij de vele liters koffie. Fijn dat je mijn paranimf wil zijn!

Een aantal studies in dit proefschrift had niet tot stand kunnen komen zonder de hulp van mijn stagiaires Janna Marie Hoogendam en Mirjam Bloemendaal. Dames, bedankt voor al het werk dat jullie hebben verzet! Ik heb jullie met veel plezier begeleid en bewonder jullie leergierigheid, kritische blik, doorzettingsvermogen en werklust. Janna Marie, fijn dat je mijn paranimf wilt zijn!

Naast de hulp bij de praktische uitvoering was het prettig om te kunnen profiteren van andermans kennis. Ik heb veel geleerd van Bas Neggers en Thomas Gladwin. Bas, bedankt voor je advies op het gebied van MRI en TMS en voor je hulp bij het opzetten van de (helaas alweer verdwenen) journal club. Je enthousiasme voor de wetenschap is aanstekelijk; ga zo door! Thomas, ik heb veel van je geleerd over statistiek, Matlab en Engelse taal, waarvoor dank. Alex Sack at Maastricht University: thank you for the hands-on TMS crash course, it was very useful!

Ook de medebewoners van de kantoortuin, collega's van de afdeling en de fMRI onderzoekers uit Utrecht en elders hebben bijgedragen. Bedankt voor al jullie feedback op onderzoeksvoorstellen, hulp bij het verzamelen van proefpersonen en data, interpretatie van mijn resultaten, gesprekken bij de koffie-automaat en de leuke tijd bij congressen: Anca Rapcencu, Anupam Sah (thanks for the lively discussions and your thought-provoking questions about my studies), Anna Kroes, Anna Hedman, Antoin de Weijer, Astrid van der Schot, Cédric Koolschijn, Christian Widschwendter, Daan Baas, Dora Hermes, Erika van Hell, Erno Hermans, Esther Mesman, Florian Bootsman, Floris Klumpers, Gerry Jager, Inge van Soelen (dank voor de zaterdagkoffies), Jiska Peper, Kelly Diederen, Maartje Aukes, Martijn van den Heuvel, Marijn Struiksma, Martijn Mulder (dank voor de leuke discussies en je creatieve onderzoeksvoorstellen), Mathijs Raemaekers, Matthijs Bossong, Max de Leeuw, Muriel Panouillères, Neeltje van Haren, Nick Ramsey (bedankt voor je supervisie tijdens mijn stage), Nicoletta van Veelen, Peter Bos, Rachel Brans, Remko van Lutterveld, René Mandl, Stefan du Plessis, Sven Stringer, Tamar van Raalten, Thomas Scheewe, Tjerk Gutteling.

Een speciale dank voor de collega's van NICHE! Sarah Durston, heel veel dank dat ik de maanden tussen het afronden van mijn proefschrift en de start van mijn postdoc mocht doorbrengen in jouw lab. Marieke Langen, bedankt voor de korte maar leuke tijd; je was een hele fijne ka-

mergenoot. Janna van Belle, bedankt voor de straffe espresso's en de levendige discussies; ik vond het leuk met je samen te werken. Ook Dienke Bos, Juliette Weusten, Patrick de Zeeuw, Rosanne van Diepen, Sanne de Wit, Sarai van Dijk: bedankt voor de fijne tijd bij NICHE.

Vincent Kersten en Yumas el Hankouri: bedankt voor het creeëren en onderhouden van de digitale trapveldjes; het was er fijn spelen!

Emmy Drost, Elly Schreurs, Jen Sopacua, Marion van Osnabrugge, en de dames van receptie 34: bedankt voor het regelen van de administratieve zaken rondom mijn promoietraject.

De MRI laboranten Gerrit Melis en Niels Blanken: heel fijn dat jullie beschikbaar waren voor de praktische zaken rond het scannen.

De standby-neurologen: Suzanne Koudijs, Tom Snijders en Casper van Oers: bedankt voor jullie kundige TMS-adviezen. Wat ben ik blij dat ik (en jullie) die diazepam zetpillen nooit heb hoeven toedienen bij mijn proefpersonen ...

Daarnaast wil ik hen bedanken die aan het prille begin van mijn wetenschappelijke loopbaan stonden:

Sabine Spijker en Guus Smit: Ik geloof dat ik een goede keus heb gemaakt om het bij drie maanden moleculaire neurobiologie te laten, maar jullie invulling van labmeetings, seminars, en cursussen zijn nog altijd een voorbeeld.

Wil Smeets: bedankt dat je wilde lobbyen bij het Donderscentrum in Nijmegen om mij een aantal cursussen in neuroimaging te laten volgen; ze zijn zeker van pas gekomen.

Serge Rombouts: bedankt voor het leggen van de contacten in Utrecht, waardoor ik eerst een stage kon doen en later promovendus werd.

Lars-Olof Wahlund, Olof Lindberg, Per Östberg, Eva-Lena Engman, and Lisa Botes at Karolinska Institutet: I can't tell how often I look back upon my time spent in Stockholm; it was a great place to work and to live.

… en hen bij wie ik na dit promotietraject aan de slag ga:

Jeffrey Schall, Gordon Logan, and Thomas Palmeri at Vanderbilt University: I'm looking forward to learning more about action control from an electrophysiological, psychological, and modeling point of view.

En tenslotte, mijn lieve vrienden en familie:

Ingeborg & Harm, wat fijn dat jullie er waren. Bedankt voor jullie luisterend oor, kritische vragen en inzichten, en samen met Ruben & Eelke, voor de vele avonden smullen met de eetclub. Ook Belinda & Rogier en Lies, bedankt voor het brengen van het nodige vertier.

Jeffrey & Alice, Tieti & Henri, Jos, Jort, Janneke & Heddy: Bedankt voor alle ongedwongen weekenden met goede koffie, lekker eten en leuke verhalen in het oosten des lands. Na zo'n weekend was ik weer helemaal opgeladen voor de rest van de week.

Papa en mama, Daan & Eva: wat heb ik veel van jullie geleerd. De discussies in huize Zandbelt waren een uitstekende leerschool voor het wetenschappelijke debat. Papa & mama, bedankt voor jullie onvoorwaardelijke vertrouwen en ondersteuning en jullie nieuwsgierigheid naar mijn werkzaamheden. Daan & Eva, bedankt voor jullie hulp bij het maken van de layout en het drukken van dit proefschrift.

Lieve Jorien, jouw relativeringsvermogen verlichtte de soms taaie fasen van het promotietraject. Dank je wel voor alle vrijheid die je me geeft en de spiegel die je mij zo af en toe voorhoudt; je verrijkt mijn leven. Ik bewonder je moed om uit je comfort-zone te stappen en samen aan een nieuw avontuur te beginnen in Nashville. Ik houd van je.

9

# List of publications

Zandbelt BB, Vink M (2010), 'On the role of the striatum in response inhibition', PLoS ONE, vol. 5 no. 11, pp. e13848.

van Buuren M, Gladwin TE, Zandbelt BB, Kahn RS, Vink M (2010), 'Reduced functional coupling in the default-mode network during self-referential processing', Human Brain Mapping, vol. 31, no. 8, pp. 1117-1127.

Looi JC, Svensson L, Lindberg O, Zandbelt BB, Ostberg P, Orndahl E, Wahlund LO (2009), 'Putaminal volume in frontotemporal lobar degeneration and Alzheimer disease: differential volumes in dementia subtypes and controls', American Journal of Neuroradiology, vol. 30, no. 8, pp. 1552-1560.

van Buuren M, Gladwin TE, Zandbelt BB, van den Heuvel M, Ramsey NF, Kahn RS,Vink M (2009), 'Cardiorespiratory effects on default-mode network activity as measured with fMRI', Human Brain Mapping, vol. 30, no. 9, pp. 3031-3042.

Lindberg O, Ostberg P, Zandbelt BB, Oberg J, Zhang Y, Andersen C, Looi JC, Bogdanovi_ N, Wahlund LO (2009), 'Cortical morphometric subclassification of frontotemporal lobar degeneration', American Journal of Neuroradiology, vol. 30, no. 6, pp. 1233-1239.

Looi JC, Lindberg O, Zandbelt BB, Ostberg P, Andersen C, Botes L, Svensson L, Wahlund LO (2008), 'Caudate nucleus volumes in frontotemporal lobar degeneration: differential atrophy in subtypes', American Journal of Neuroradiology, vol. 29, no. 8, pp. 1537-1543.

Zandbelt BB, Gladwin TE, Raemaekers M, van Buuren M, Neggers SF, Kahn RS, Ramsey NF, Vink M (2008), 'Within-subject variation in BOLD-fMRI

signal changes across repeated measurements: quantification and implications for sample size', Neuroimage, vol. 42, no. 1, pp. 196-206.

Raemaekers M, Vink M, Zandbelt B, van Wezel RJ, Kahn RS, Ramsey NF (2007), 'Test-retest reliability of fMRI activation during prosaccades and antisaccades', Neuroimage, vol. 36, no. 3, pp. 532-42.

10

# Curriculum vitae

Bram Zandbelt was born on November 1, 1982 in Hengelo, The Netherlands. In 2001, he graduated from high school and started a Bachelor's degree program in biomedical sciences at VU University Amsterdam (VUA). As part of this program, he did an internship in molecular neurobiology in the Department of Molecular Neurobiology at VUA. Supervised by dr. Sabine Spijker and prof. dr. Guus Smit, he studied morphine-induced changes in synaptic proteins in the rat's nucleus accumbens.

After obtaining a Bachelor of Science degree, he enrolled in the Master's degree program in Neurosciences at VUA. He did an internship in functional neuroimaging in the Department of Psychiatry at University Medical Center Utrecht with dr. Matthijs Vink and dr. Nick Ramsey, in which he investigated the reliability of functional magnetic resonance imaging. Furthermore, he did an internship in structural neuroimaging in the Department of Neurobiology, Care Sciences and Society at Karolinska Institutet, Stockholm, Sweden. Supervised by prof. dr. Lars-Olof Wahlund, he investigated the possibility to distinguish various forms of frontotemporal dementia and Alzheimer's disease on the basis of hippocampal and entorhinal cortex volumes. Finally, he wrote a literature thesis on the application of functional magnetic resonance imaging for detecting Alzheimer's disease under supervision of prof. dr. Philip Scheltens and dr. Serge Rombouts at the Alzheimer Center of the VU Univeristy medical center.

After obtaining a Master of Science degree in November 2006, he joined the Department of Psychiatry at the University Medical Center Utrecht as a PhD candidate. Under supervision of dr. Matthijs Vink and prof. dr. René Kahn, he explored the neural mechanisms of proactive and reactive inhibition in healthy volunteers and schizophrenia patients. On September 8, 2011 he will defend his thesis entitled "Neural mechanisms of proactive and reactive inhibition - studies in healthy volunteers and schizophrenia patients'. From October 2011, Bram will work as a post-doctoral researcher in the lab of prof. dr. Jeffrey Schall in the Department of Psychology at Vanderbilt University where he will study computational models of inhibitory control.

## Curriculum vitae

Bram Zandbelt werd op 1 november 1982 geboren in Hengelo. Hij doorliep de middelbare school op Twickel Hengelo waar hij in 2001 slaagde voor het VWO examen. Datzelfde jaar begon hij met de bacheloropleiding Biomedische wetenschappen aan de Vrije Universiteit Amsterdam. Hij volgde een stage moleculaire neurobiologie op de afdeling Moleculaire Neurobiologie van de Vrije Universiteit Amsterdam. Onder supervisie van dr. Sabine Spijker en prof. dr. Guus Smit deed hij onderzoek naar de invloed van morfine op expressieprofielen van synaptische eiwitten in de nucleus accumbens van de rat.

Na het voltooien van de bacheloropleiding in 2004 volgde hij de masteropleiding Neurowetenschappen, eveneens aan de Vrije Universiteit Amsterdam. In het kader van deze opleiding volgde hij een stage functionele neuroimaging op de afdeling Psychiatrie van het Universitair Medisch Centrum Utrecht. Onder supervisie van dr. Matthijs Vink en dr. Nick Ramsey onderzocht hij de betrouwbaarheid van functionele MRI. Daarnaast deed hij een stage structurele neuroimaging op de afdeling Neurobiologie, Verpleegingswetenschap en Samenleving van het Karolinska Institutet. Onder leiding van prof. dr. Lars-Olof Wahlund onderzocht hij de mogelijkheid om verschillende vormen van frontotemporale dementie en de ziekte van Alzheimer te kunnen onderscheiden op basis van hersenvolumes van de hippocampus en de enthorinale cortex. Tenslotte schreef hij een masterthese over de toepassing van functionele MRI bij de opsporing van de ziekte van Alzheimer onder leiding van dr. Serge Rombouts en prof. dr. Philip Scheltens van het Alzheimercentrum van het Vrije Universiteit medisch centrum.

Na het afronden van de masteropleiding begon hij in november 2006 aan een promotietraject op de afdeling Psychiatrie van het Universitair Medisch Centrum Utrecht. Onder leiding van dr. Matthijs Vink en prof. dr. René Kahn deed hij onderzoek naar de neurale mechanismen van proactieve en reactieve inhibitie in gezonde vrijwilligers en schizofrenie patiënten. Op 8 september 2011 zal hij zijn proefschrift “Neurale mechanismen van proactieve en reactieve inhibitie - studies in gezonde vrijwilligers en schizofreniepatiënten” verdedigen.

Vanaf oktober 2011 is hij als post-doctoraal onderzoeker verbonden aan Vanderbilt University, waar hij in het lab van prof. dr. Jeffrey Schall onderzoek zal doen naar computermodellen van inhibitie.