Free won't

Neurobiological bases of the development of intentional inhibition

ISBN 9789462950580

Cover design: Proefschriftmaken.nl|Uitgeverij BOXPress
Cover image: © 2014 AK3D ®
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Neurobiological bases of the development of intentional inhibition

Proefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof. mr. C.J.J.M. Stolker,
volgens besluit van het College voor Promoties
te verdedigen op donderdag 22 januari 2015
klokke 16.15 uur

door

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geboren te Uden
in 1986

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Chapter 1
General introduction

This chapter is based on:
Schel, M.A., Scheres, A., & Crone E.A. (in press) New perspectives on self-control development: Highlighting the role of intentional inhibition. *Neuropsychologia*

1.1 Scope

Self-control can be defined as the ability to exercise control over one's action, thoughts and emotions (Casey & Caudle, 2013). Self-control abilities are crucial for successful functioning in all aspects of human life (e.g. social situations, educational and work environments). The development of self-control is an important aspect of cognitive development through childhood and adolescence (Diamond, 2013), and has far-reaching implications during this important developmental period. That is, self-control is important for learning (e.g. self-control helps concentrating on the task at hand and not getting distracted by the environment), for making optimal decisions (e.g., healthy food-related or financial decisions), for keeping friendships (e.g. self-control helps in not reacting impulsively and hitting someone, when being teased), and for social skill development (e.g. self-control helps to inhibit the impulse to cut in line) (Diamond, 2013).

At the core of self-control lies the ability to intentionally inhibit one's actions. Intentional inhibition has been defined as a late 'veto' mechanism (Filevich, Kühn, & Haggard, 2012; Haggard, 2008). By means of this late 'veto' mechanism, one can cancel action execution of an already initiated action at the last possible moment, as given in by an internal thought process (Filevich, et al., 2012; Haggard, 2008). Thus, intentional inhibition differs from stimulus- or externally driven inhibition[1] in that it is driven by an internally generated process, rather than an external stimulus which tells you to stop your behavior. To date self-control development has been primarily studied from the perspective of externally driven inhibition (for a review, see Diamond, 2013), yet, intentional inhibition is clearly present in many aspects of children's life, such as when inhibiting the tendency to get up of your chair and walk around in the classroom based on internally set goals, or when trying to finish a tedious task without supervision. In addition, given that intentional inhibition lies at the core of self-control, that is to say, most of our action control is driven by internal motives, problems in intentional inhibition have wide-ranging implications, such as for childhood psychological and psychiatric disorders, such as Attention Deficit Hyperactivity Disorder (ADHD) (Moffitt et al., 2011) or conduct disorder (Fergusson, Boden, & Horwood, 2013).

Therefore, the main goal of this thesis is to gain insight in the development of intentional inhibition. In this chapter, a theoretical background for the empirical studies on intentional inhibition presented in this thesis will be given. First, the existing behavioral and neuroscientific literature on the development of self-control, with a focus on what is currently known about externally guided inhibition will be reviewed. Next, a framework for studying the development of intentional inhibition will be given. Finally, the literature discussing self-control in emotionally and/or motivationally relevant contexts will be described. Together, this overview leads to a set of studies on intentional inhibition presented in this thesis.

[1] The terms stimulus-driven and externally driven inhibition both refer to inhibition that is driven by and external stimulus. Therefore, the terms stimulus-driven and externally driven inhibition will be used interchangeably in this thesis.

1.2 Externally guided inhibition

One of the most studied components of self-control development involves the ability to control one's actions and stop actions when the environment requires one to do so, also referred to as inhibition (Diamond, 2013; Zelazo et al., 2003). There are marked improvements in inhibition in infancy (Diamond, 2013), early childhood (Zelazo, et al., 2003) and school-aged children (van der Molen, 2000), which has been interpreted as protracted development of executive control functions. Executive control is often used as an umbrella term to refer to our ability to control our thoughts and actions in order to attain future goals, and inhibition is a key component of executive control (Diamond, 2013). As such, inhibition is thought to lie at the core of cognitive development (Diamond, 2013).

Most research on the development of inhibition has focused on the development of stimulus-driven inhibition. In these experiments, inhibition is typically preceded by an external stimulus or cue, which signals that one has to stop an already initiated or prepotent action. Research with two experimental paradigms has contributed significantly to our knowledge of the mechanisms underlying stimulus-driven inhibition, namely the stop-signal paradigm and the go/nogo paradigm. In the stop-signal paradigm participants are presented with a simple stimulus (e.g. a left or right pointing arrow) to which they have to respond as quickly as possible. On a limited number of trials (i.e. about 25 % of all trials) a stop signal (e.g. a loud noise or a color-change of the stimulus) is presented after the stimulus has come online. By varying the delay between presentation of the stimulus and presentation of the stop-signal, it is possible to calculate the Stop Signal Reaction Time (SSRT), that is the time one needs to inhibit an already initiated response (Band, van der Molen, & Logan, 2003; Logan & Cowan, 1984). The go/nogo paradigm also examines the inhibition of prepotent responses (Casey et al., 1997). In this paradigm participants are presented with a stream of stimuli (e.g. different letters) to which they have to respond by means of a button press. However, one stimulus (e.g. the X) is instructed to be a nogo-stimulus. This nogo-stimulus is presented on a limited numbers of trials (i.e. around 20 % of all trials), and when this nogo-stimulus is presented participants have to inhibit a prepotent response to the presentation of a new stimulus (Casey, et al., 1997). In contrast to the stop-signal paradigm, the go/nogo paradigm does not allow for a calculation of the SSRT. Instead, the dependent variable in the go/nogo paradigm is the number of false alarms (i.e. the number of times a participant does not inhibit when a nogo-stimulus is presented).

Cross-sectional developmental comparison studies using these paradigms have shown that stimulus-driven inhibition has a protracted development (Casey, et al., 1997; Cohen et al., 2010; Durston et al., 2002; Rubia, Smith, Taylor, & Brammer, 2007). Studies using the stop-signal paradigm have found that even though children are already able to inhibit, the SSRT continues to become faster across development (between 6-30 years of age) (Cohen, et al., 2010; Ridderinkhof, Band, & Logan, 1999; Williams, Ponesse, Schachar, Logan, & Tannock, 1999). Furthermore, studies using the go/nogo paradigm have shown that even though 6 to 10 year-old children are already able to inhibit, they are more susceptible to the effects of prepotency of

responding (Durston, Thomas, Yang, et al., 2002). That is to say, when a nogo-trial was preceded by a larger number of go-trials, thereby increasing the prepotency of responding, children experienced more difficulty inhibiting responding to that nogo-stimulus (Durston, Thomas, Yang, et al., 2002). Taken together, young children are already able to inhibit, but not to the same level as adults and not in a stable level across the full duration of a paradigm (Diamond, 2013; Luna, Padmanabhan, & O'Hearn, 2010). This ability continues to improve across childhood and adolescence, with mature performance levels being reached in early (11 years of age) (Huizinga, Dolan, & van der Molen, 2006) to late adolescence (18 years of age) (Luna, et al., 2010).

In terms of neural correlates, studies in adults have shown that a specific network of brain regions is active when participants perform a stop-signal task. This network involves the dorsal and ventral prefrontal cortex (specifically right inferior frontal gyrus (IFG)), the anterior cingulate cortex (ACC)/pre-supplementary motor area (SMA) and parts of the basal ganglia, including the subthalamic nucleus (STN) (see Figure 1) (Aron & Poldrack, 2006; Ridderinkhof, Forstmann, Wylie, Burle, & van den Wildenberg, 2011; Verbruggen & Logan, 2008). Individual differences analyses have shown that activity in rIFG and STN correlates with SSRT, suggesting that these are core regions for successful response inhibition (Aron, Behrens, Smith, Frank, & Poldrack, 2007; Aron & Poldrack, 2006). In addition, functional and structural network analyses have found that increased connectivity between rIFG and STN is related to successful response inhibition performance (Aron, et al., 2007; Forstmann et al., 2012; Jahfari et al., 2011; King et al., 2012).

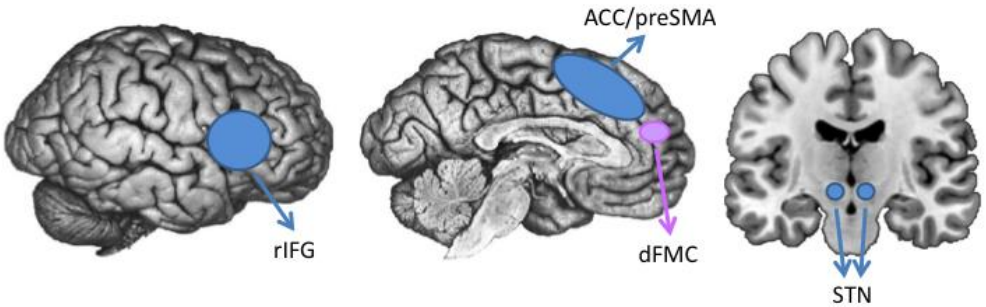

Figure 1. Brain regions associated with externally guided inhibition (in blue) and internally guided inhibition (in purple).
Note. rIFG = right inferior frontal gyrus, ACC/preSMA = anterior cingulate cortex/presupplementary motor area, dFMC = dorsal fronto-median cortex, STN = subthalamic nucleus.

Compared to adults, children show different activity during externally driven response inhibition. Specifically, some studies have shown that 8 to 12 year-old children use left lateralized PFC regions whereas adults use right lateralized regions (Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002), some studies reported

more activity in dorsolateral prefrontal cortex in 8 to 12 year-old children compared to adults (Velanova, Wheeler, & Luna, 2008), and others reported more activity in ventrolateral PFC in adults than in 6 to 10 year-old children (Durston, Thomas, Yang, et al., 2002). Together, these changes can be characterized as a shift from diffuse to focal activity (Durston, Thomas, Yang, et al., 2002). In other words, in childhood, widespread inhibition related activation was observed across lateral prefrontal cortex (Durston, Thomas, Yang, et al., 2002; Luna, et al., 2010), whereas with increasing age this activation became more focalized to the rIFG (Durston, Thomas, Yang, et al., 2002; Luna, et al., 2010). These findings are consistent with structural neuroimaging studies showing that regions in the lateral prefrontal cortex are the last to mature in terms of loss of grey matter volume, which is an index of neuronal maturation (Giedd, 2004; Shaw et al., 2008; Sowell et al., 2004), and slowly developing white matter maturation in the prefrontal cortex and its connections (Paus, 2010; Paus et al., 2001).

These findings fit well with studies focusing on other components of executive control which also rely on lateral prefrontal cortex, such as working memory (e.g. Crone, Wendelken, Donohue, van Leijenhorst, & Bunge, 2006; Finn, Sheridan, Kam, Hinshaw, & D'Esposito, 2010; Jolles, Kleibeuker, Rombouts, & Crone, 2011), task switching (e.g. Christakou et al., 2009; Crone, Donohue, Honomichl, Wendelken, & Bunge, 2006), and attention (Smith, Halari, Giampetro, Brammer, & Rubia, 2011). These studies also reported that prefrontal cortex activity is developing protractedly in childhood and adolescence, which has been interpreted in terms of increased interactive specialization of brain regions important for higher order cognitive processes (Johnson, 2011). In sum, there is substantial evidence that response inhibition, measured by the inhibition of behavior based on external signals, lies at the core of cognitive development (Diamond, 2013), matures slowly across development (Diamond, 2013; Luna, et al., 2010), and is associated with immature activity in the prefrontal cortex (Luna, et al., 2010).

1.3 Intentionally guided inhibition

Many of our daily activities involve stopping actions based on internally generated (i.e., intentional) stop signals, rather than explicit external stimuli telling us to stop our actions. Despite the clear importance of the intentional component of inhibition, intentional inhibition has remained largely unstudied within developmental psychology and developmental cognitive neuroscience. Since intentional inhibition is not preceded by an external stimulus or cue, and does not result in any behavioral output, there are obvious difficulties in studying intentional inhibition. In daily life, however, the need to inhibit is not constantly signaled by external cues, and therefore, understanding the mechanisms of intentional inhibition is of clear importance.

A framework for studying intentional inhibition

A useful framework for studying intentional inhibition is the factorial organization of action control (Filevich, et al., 2012). According to this framework both the motivation for action and the motivation for inhibition can be externally or internally

guided (see Table 1). Importantly, in daily life, action and inhibition decisions are often based on a combination of external and internal motivations. For instance in our previous example of children having to intentionally inhibit the tendency to get up of your chair and walk around in the classroom, external factors such as teacher expectations also play a role. Within experimental research, internal and external motivations for action and inhibition are separated by the presence or absence of an external cue signaling action or inhibition (Filevich, et al., 2012).

Table 1. Factorial organization of action control.

		Action	
		Externally guided	**Internally guided**
Inhibition	**Externally guided**	Stop walking when a green traffic light suddenly turns red.	Stop teasing a classmate when a teacher suddenly appears.
	Internally guided	Resisting the impulse to take another biscuit from the biscuit box standing in front of you.	Resisting the impulse to scratch your itchy skin caused by eczema.

Stimulus-driven inhibition involves the externally guided inhibition of both externally and internally guided action. However, as outlined above, traditionally most research has focused on externally guided inhibition of externally guided action. Intentional inhibition on the other hand involves the internally guided inhibition of both externally and internally guided action. When studying intentional inhibition there are three main difficulties (Filevich, et al., 2012). First, intentional inhibition does not result in any behavioral output. Thus, on the behavioral level one can only examine whether someone has intentionally inhibited or not. However, concluding that intentional inhibition has happened on the basis of no behavioral output is problematic (see the third point). Therefore, psychophysiological and neuroimaging measures are particularly useful in the study of intentional inhibition, since they can help identify the covert processes associated with inhibition. A second difficulty in the study of intentional inhibition is that intentional inhibition is an internal process, which is not triggered by an external stimulus or cue. This means that intentional inhibition cannot be easily manipulated in an experimental task. Third, according to our definition of intentional inhibition, intentional inhibition involves the inhibition of an action. However, on the behavioral level we cannot distinguish between an action that was inhibited at the last possible moment and an action that was never prepared. In the latter case, we would speak of early decision not to prepare an action. This

process is linked more to action selection than to inhibition (Haggard, 2008). Early decisions not to prepare an action are more likely in paradigms where there is no strong motivation for acting (Filevich, et al., 2012). Therefore, paradigms designed to measure intentional inhibition should include a strong motivation or prepotency for acting.

The marble paradigm is a valuable paradigm to study intentional inhibition, which was first developed by Kühn and colleagues (2009). In this paradigm, a white marble is rolling down a ramp. As soon as the marble starts rolling, the marble changes color to green. Participants are instructed to respond to the rolling marble as quickly as possible, to prevent the marble from dropping from the ramp and crashing. This green marble condition creates a prepotency for responding. On a number of trials (around 35 %, this differs slightly between experiments), the rolling marble does not change color and remains white. In this case, participants are free to choose to either respond or inhibit. However, since responding is prepotent, inhibiting taxes the late 'veto' mechanism.

In the first four empirical chapters of this thesis (chapters 2 to 5) the marble task is combined with heart rate and neuroimaging techniques to gain insight in the processes involved in intentional inhibition.

Heart rate

A useful measure for studying the covert processes underlying intentional inhibition is the study of phasic heart rate changes. Beat-to-beat heart rate changes are controlled by both the sympathetic and the parasympathetic autonomic nervous system (Berntson, Quigley, & Lozano, 2007). The sympathetic and parasympathetic systems differ in the latency by which they influence beat-to-beat changes. The sympathetic system has a relatively long-term effect on beat-to-beat changes, that is, it takes the sympathetic system several seconds to increase the heart rate. The parasympathetic system on the other hand, has a more direct influence on the heart and can decrease the heart rate quickly. This short-latency parasympathetic heart rate deceleration has been interpreted as indicative of an orienting reflex (Bradley, 2009).

Parasympathetic-driven phasic heart rate changes are shown to be a sensitive index of cognitive control processes in general (Crone, Somsen, Van Beek, & Van Der Molen, 2004; Crone et al., 2003; Jennings, Van der Molen, & Debski, 2003), and response activation and inhibition processes specifically (Jennings & van der Molen, 2002; van der Molen, 2000; Van der Veen, Van der Molen, & Jennings, 2000). During preparation and/or anticipation of a speeded response (a go-stimulus in a go/nogo or stop-signal paradigm), a pattern of heart rate deceleration is typically observed (Jennings & van der Molen, 2002, 2005; Jennings, van der Molen, Somsen, & Terezis, 1990). This pattern of anticipatory heart rate deceleration is interpreted as indicative of the central inhibition of action representations (Jennings & van der Molen, 2002, 2005). This anticipatory heart rate deceleration is followed by acceleratory recovery when a response is made (Jennings & van der Molen, 2005; Jennings, et al., 1990). However, during inhibition, the shift from anticipatory heart rate deceleration to acceleratory recovery is delayed, and heart rate continues to decelerate (Börger & van der Meere, 2000; Jennings & van der Molen, 2005; Jennings, van der Molen, Pelham,

Debski, & Hoza, 1997; van der Molen, 2000; Van der Veen, et al., 2000). This continued deceleration is implicated to be indicative of midbrain inhibition of action (Jennings, van der Molen, & Stenger, 2008; Van der Veen, et al., 2000).

In this thesis phasic heart rate changes are examined as an index of the development of intentional inhibition (chapter 2). Also, to gain further insight in the role of the central autonomic network in intentional action control, in chapter 4 phasic heart rate changes are examined in combination with changes in neural activation as measured by fMRI.

fMRI

A second method, which is useful for unraveling the covert processes involved in intentional inhibition, is neuroimaging. Concretely, fMRI studies can generate more specific hypotheses about the underlying mechanisms involved in externally driven and intentional inhibition. With fMRI it is possible to examine which brain regions are activated during task performance, by taking advantage of the BOLD (Blood Oxygenation Level Dependent) signal.

The first fMRI study specifically designed to measure intentional inhibition made use of a free choice paradigm involving the internally generated inhibition of internally generated action (Brass & Haggard, 2007). In this paradigm, participants were asked to always prepare and perform a simple action (i.e. a key press) at the time of their choice. Importantly, participants were instructed to withhold this action at the last possible moment on some freely chosen trials. On every trial, also when their action was inhibited, participants reported the time at which they felt they were about to perform their action. This reported time, also in the absence of action, formed the event modeled in the fMRI analysis. This analysis showed specific activation during intentional inhibition in the dorsal fronto-median cortex (dFMC), a brain region not implicated in stimulus-driven inhibition (see Figure 1) (Brass & Haggard, 2007). However, the free choice paradigm differs in two aspects from traditional stimulus-driven inhibition experiments, which focus on externally guided inhibition of externally guided action. That is to say, in this free choice paradigm both the decision to act and the decision to inhibit was internally guided.

Kühn and colleagues introduced the marble paradigm, which only differs in the internal initiation of inhibition from the traditional stimulus-driven inhibition paradigms, in an fMRI study in adults (2009). The critical contrast focused on brain regions that were more active during intentional decisions to inhibit compared to intentional decisions to act. This study also showed specific activation in the dFMC during intentional inhibition (Kühn, et al., 2009), comparable in location to the study by Brass & Haggard (2007).

In this thesis, fMRI is used in chapters 3 to 5. In chapter 3 fMRI is used to examine whether intentional and externally guided inhibition can be dissociated on the neural level. In chapter 4 fMRI is combined with the study of phasic heart rate changes to examine the role of the central autonomic network in intentional action control. Finally, in chapter 5 fMRI is used to examine the neural bases of the development of intentional inhibition.

1.4 Self-control in context

The studies described so far have all examined self-control in a relatively neutral context. In daily life however, we often experience strong motivations for action and inhibition, and inhibition rarely happens in an affectively neutral context. For instance, previous research has shown that externally guided inhibition performance improves when participants are motivated by external rewards, such as money (Leotti & Wager, 2010). Externally guided inhibition has also been shown to be influenced by affective context (Tottenham, Hare, & Casey, 2011). In this study, participants were instructed to respond to face stimuli expressing a certain emotion and inhibit responding to faces expressing a different emotion. Four different emotional expressions were included, three negative emotions (fear, anger and sadness), and one positive emotion (happiness), and in each block a different emotional face was coupled with neutral faces. In a developmental sample (5 to 28 year-olds) it was found that response inhibition performance was most negatively influenced by emotions for which emotion recognition was worst, namely for anger and sadness (Tottenham, et al., 2011). Another study has shown that also irrelevant emotional background stimuli, appeared to influence response inhibition performance (Cohen-Gilbert & Thomas, 2013).

In this thesis it is examined whether intentional inhibition performance is also affected by affective context and how this might differ across development (chapter 6).

1.5 Outline of this thesis

The main goal of this thesis is to gain insight in the development of intentional inhibition. In the majority of the empirical chapters (chapter 2 to 5) the marble task is combined with heart rate and neuroimaging techniques to gain insight in the processes involved in intentional inhibition. This approach allowed examining the covert process, which are not visible with only performance measures, involved in the development of intentional inhibition.

In chapter 2, the development of intentional inhibition was examined in a cross-sectional study with 3 age groups (8-10, 11-12, and 18-26). In this study phasic heart rate changes were examined as a measure of the covert processes underlying intentional inhibition.

The study presented in chapter 3 examined the differences and similarities in underlying neural correlates between intentionally and externally guided inhibition in a sample of young adults (18-26). For this means participants performed both the marble task, as a measure of intentional inhibition, and the stop-signal task, as a measure of externally guided inhibition, while inside the MRI scanner. In chapter 4, the role of the central autonomic network involved in intentional action control was further examined in a combined fMRI and heart rate study. For this study heart rate was measured continuously, while participants performed the marble task in the MRI scanner.

The development of intentional inhibition was further examined in the study presented in chapter 5. This study examined the neural correlates of intentional inhibition in a group of children (10-12) and a group of young adults (18-26). In this study individual differences in self-reported impulsivity were also related to intentional inhibition performance and the underlying correlates.

In the final empirical chapter (chapter 6) the development of inhibition within an affective context was examined in a large developmental sample (6-26). In this chapter two tasks are presented, one examining externally guided inhibition in an affective context and one examining externally guided and intentional inhibition in an affective context.

Finally, chapter 7 summarizes the results of all the empirical studies presented in this thesis. Implications of the results are discussed and suggestions for future research are presented.

Chapter 2
Developmental change in intentional action and inhibition: A heart rate analysis

This chapter is published as:
Schel, M.A., & Windhorst, D.A., & van der Molen, M.W., & Crone, E.A. (2013). Developmental change in intentional action and inhibition: A heart rate analysis. *Psychophysiology, 50*, 812-819.

2. A heart rate analysis of intentional inhibition

Abstract

The ability to inhibit is a major developmental dimension. Previous studies examined developmental change in instructed inhibition. The current study, however, focused on intentional inhibition. We examined heart rate responses to intentional action and inhibition, with a focus on developmental differences. Three age groups (8-10, 11-12, and 18-26 year-olds) performed a child-friendly marble paradigm in which they had to choose between intentionally acting on, or inhibiting a prepotent response. As instructed, all age groups chose to intentionally inhibit on approximately 50 percent of the intentional trials. A pronounced heart rate deceleration was observed during both intentional action and intentional inhibition, but this deceleration was most pronounced for intentional inhibition. Heart rate responses did not differentiate between age groups, suggesting that intentional action and inhibition reach mature levels early in childhood.

2.1 Introduction

The ability to control our actions is of critical importance for optimal functioning in daily life. Control over our actions can be both externally driven, such as when a traffic light turns red, and internally driven, such as when deciding not to scratch an itchy mosquito bite. Externally driven action control has been extensively studied using several different paradigms, such as stop-signal tasks (Logan & Cowan, 1984) go/nogo tasks (Casey, et al., 1997), and task-switching tasks (Monsell, Sumner, & Waters, 2003). In these paradigms a stimulus indicates whether participants should inhibit a prepared or prepotent response. Successful performance on these tasks appears to rely on a lateral prefrontal-parietal network in the brain (Aron, Robbins, & Poldrack, 2004; Bunge, Hazeltine, Scanlon, Rosen, & Gabrieli, 2002), specifically the right inferior frontal gyrus which seems to be prominently involved in the inhibition of motoric actions (Aron, 2011; Verbruggen & Logan, 2008).

Internally driven action control, on the other hand, has been less extensively studied, most likely because of the obvious difficulty in observing internal triggers for action. The limited number of studies in this area examined the 'what ' and 'when' components of intentional action selection (Brass & Haggard, 2008; Haggard, 2008). Tasks examining the what-component of intentional action focused on voluntary action selection (e.g. participants are instructed to voluntarily select between two response options), whereas tasks examining the when-component focused on voluntary action planning (e.g. participants are instructed to decide when they want to execute an instructed response). In contrast to externally driven action control, voluntary action selection and action planning are thought to rely on a different network in the brain, specifically involving the medial frontal cortex (Lau, Rogers, Haggard, & Passingham, 2004; Lau, Rogers, & Passingham, 2006).

Recently, research into internally driven action control focused on a third component of intentional action selection, namely the 'whether' component (Brass & Haggard, 2008; Haggard, 2008). The 'whether' component captures the process of deciding between intentionally performing or intentionally inhibiting a prepared action (Brass & Haggard, 2007, 2008; Filevich, et al., 2012). Intentional inhibition has been conceptualized as a late veto process; a final check before action execution (Brass & Haggard, 2007; Filevich, et al., 2012; Kühn, et al., 2009). Since there is no external stimulus and no overt behavior in intentional inhibition, the process of intentional inhibition proved to be quite difficult to investigate. Recently, however, two studies examined the neural correlates of intentional inhibition using paradigms in which participants were instructed to always prepare an action, but to choose to inhibit executing this prepared action on a number of trials. These studies indicate that intentional inhibition is supported by a specific brain area in medial frontal cortex, which can be dissociated from the areas involved in intentional action selection and planning, namely the dorsal fronto-median cortex (Brass & Haggard, 2007; Kühn, et al., 2009).

In the present study, we examined intentional action and inhibition by taking advantage of phasic heart rate changes, based on prior research showing that phasic heart rate is a sensitive measure of response activation and inhibition processes

(Crone, et al., 2004; Crone, et al., 2003; Jennings, Brock, van der Molen, & Somsen, 1992; Jennings & van der Molen, 2005; Jennings, et al., 1997). A score of studies showed that during the anticipation and preparation of a speeded response (e.g. a go-response in a go/nogo task) heart rate decelerates (Jennings & van der Molen, 2002; Van der Veen, et al., 2000). This anticipatory heart rate deceleration is proposed to support the central inhibition of action representations (Jennings & van der Molen, 2002, 2005). When a response is made, anticipatory heart rate deceleration is followed by an acceleratory recovery (Jennings & van der Molen, 2002; Van der Veen, et al., 2000). The shift from anticipatory deceleration to acceleratory recovery is dependent on reaction time vis-à-vis the R-wave of the ECG, with shifts occurring earlier when the interval between the R-wave to the behavioral response is short (i.e., within 350 ms) while later shifts occur with longer R-wave to response intervals (Jennings & Wood, 1977; Somsen, Jennings, & van der Molen, 2002). The pattern of anticipatory deceleration followed by acceleratory recovery is delayed when a response is inhibited; during response inhibition continued heart rate deceleration is observed (Börger & van der Meere, 2000; Jennings, et al., 1992; Van der Veen, et al., 2000). The continued heart rate deceleration during action inhibition is interpreted to reflect midbrain inhibition of action (Jennings, et al., 1992; Jennings, et al., 2008; Van der Veen, et al., 2000). Until now, the existing heart rate literature only focused on the processes of external action control and inhibition, not on the processes of intentional action and inhibition. Therefore, the present study was set out to examine heart rate response patterns associated with intentional action and inhibition.

We chose to examine heart rate responses to intentional inhibition by focusing on developmental differences. It is well established that externally driven action control has a protracted developmental trajectory (Bunge, Dudukovic, et al., 2002; Durston, Thomas, Yang, et al., 2002). The ability to inhibit is present in early childhood (Ridderinkhof, et al., 1999; Williams, et al., 1999), but this ability continues to improve through adolescence (Luna, et al., 2010; van de Laar, van den Wildenberg, van Boxtel, & van der Molen, 2011; van den Wildenberg & van der Molen, 2004). Inhibition-related heart rate deceleration has already been observed in children aged 5 to 12 (Jennings, et al., 1997; van der Molen, 2000). However, inhibition-related heart deceleration was delayed in the youngest children, suggesting that with age children become more efficient in recruiting inhibitory mechanisms (van der Molen, 2000). Currently the development of intentional action and inhibition has not been examined, most likely because of a lack of valid child-friendly paradigms.

Here, we adopted the recently developed marble task (Kühn, et al., 2009), in which participants have to decide between intentionally responding or intentionally inhibiting responding to a rolling marble, to examine the developmental pattern of intentional action and inhibition. During the task, heart rate was measured continuously so as to allow for an examination of the temporal dynamics of internal action control. We expected to observe anticipatory heart rate deceleration associated with the central inhibition of action representations (Jennings & van der Molen, 2002, 2005) during both intentional action and intentional inhibition to allow for an intentional decision to be made. During intentional action trials we expected to observe a shift from anticipatory deceleration towards acceleratory recovery associated

with response activation and execution (Jennings & van der Molen, 2002). In contrast, during intentional inhibition trials we expected to observe continued heart rate deceleration associated with response inhibition until task completion (Börger & van der Meere, 2000; Jennings, et al., 1992; Jennings, et al., 1997; Van der Veen, et al., 2000). Furthermore, with regard to the developmental pattern we expected to observe an early development of intentional action and inhibition abilities (Ridderinkhof, et al., 1999; Williams, et al., 1999), but a possible delay in reaching the maximum inhibition related heart rate deceleration in the youngest children (van der Molen, 2000).

2.2 Method

Participants

Sixty healthy participants across three age groups participated in the experiment. Three participants were excluded from the study, one because of technical difficulties, one because of misunderstanding of the experimental task, and one because of deviant heart rate responses. The final sample consisted of twenty-four children between 8-10 years of age (14 females, M = 9.42, SD = .63), fifteen early adolescents between 11-12 years of age (6 females, M = 12.22, SD = .44), and eighteen adults between 18-26 years of age (10 females, M = 21.91, SD = 2.55). A chi-square test revealed no significant differences in gender distributions between age groups (p = .51). Children were recruited from a primary school in the Netherlands and informed consent was obtained from a primary caregiver. Adult participants were recruited from Leiden University and signed informed consent before participation in the experiment. All participants completed the Raven Standard Progressive Matrices (Raven SPM) to obtain an estimate of their cognitive functioning (Raven, Raven, & Court, 1998). Age groups did not differ in estimated IQ scores, F (2, 56) = 1.97, p = .15, η_p^2 = .07.

Task

The marble task was adapted from Kühn et al. (2009), and optimized for heart rate recording. Each trial (see Figure 1) started with the presentation of a fixation screen (white cross against a black background) with duration jittered between 1400 and 2000 ms. The fixation screen was followed by a screen showing a white ramp with a white marble on top presented against black background. After a variable duration of 1400 to 2000 ms the marble started rolling down the ramp and participants could stop the marble from crashing by pressing a button. Finally, a feedback screen, showing trial outcome, was presented for 1000 milliseconds. There were two task conditions: a green marble and a white marble condition.

In the green marble condition, the white marble changed to green as soon as it started rolling. The task was programmed in such a way that participants viewed 16 rapidly presented static pictures showing the marble at successive locations on the ramp, which was experienced as a rolling movement. Participants were instructed to stop the marble from crashing by pressing a response button with their right index finger. When participants were successful at stopping the marble, they were presented with a feedback screen showing the location where they had stopped the marble.

When participants were not successful at stopping the marble, they were presented with a feedback screen showing a shattered marble beneath the ramp. The speed of the marble was adjusted by a staircase procedure. At the start of the experiment, the static pictures were presented for 30 milliseconds each. When participants were successful at stopping the marble the duration was decreased with 10 milliseconds, making the task more difficult. When participants were not successful at stopping the marble in time the duration was increased with 10 milliseconds, making the task easier. The staircase procedure was allowed to fluctuate between 20 and 80 milliseconds, allowing a response window between 320 and 1280 milliseconds.

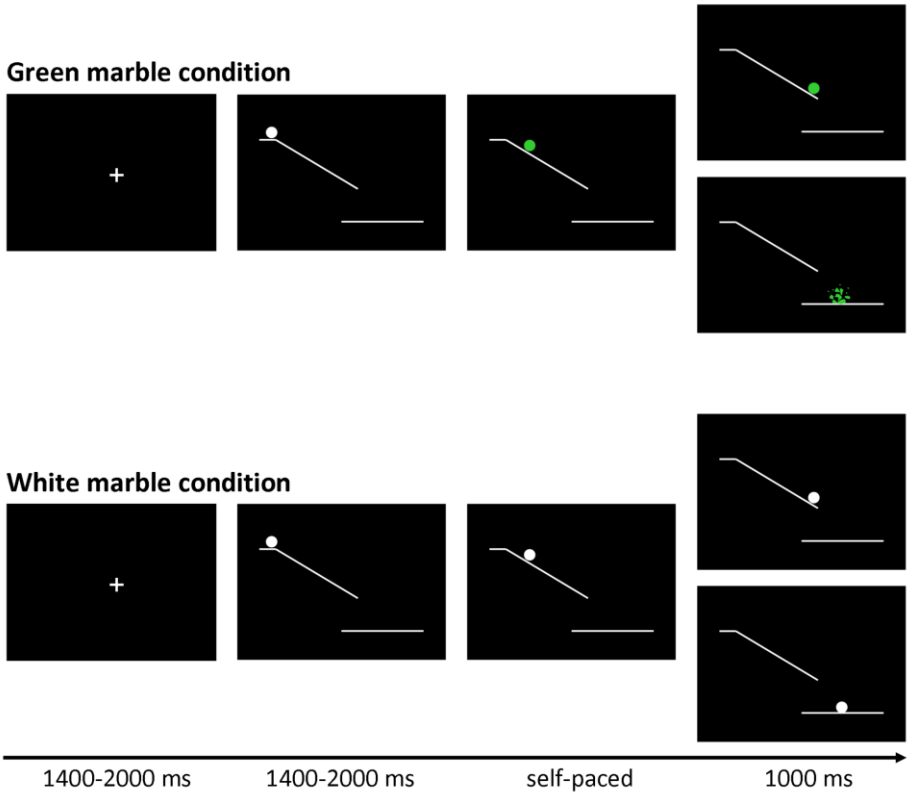

Figure 1: Trial structure. Stimuli were presented at a black background. At the beginning of each trial a white marble on top of a ramp was presented. After a variable delay (jittered between 1400 and 2000 ms) the marble started to roll down the ramp, and could change color to green.

In the white marble condition, the marble did not change color and participants were instructed to choose between responding and inhibiting. When participants responded, they were presented with a feedback screen showing the location were they had stopped the marble. When participants inhibited, they were shown a feedback screen showing the white marble at the bottom of the ramp. In order to motivate participants to balance the frequency of responding and inhibiting,

they were told that the stopped and non-stopped marbles would fall in different baskets. Participants were instructed to collect an approximately equal amount of marbles in each basket, but were not allowed to count or use a sequencing strategy. At the end of each block participants were shown how many marbles they had collected in each basket.

In order to give participants sufficient time to decide between responding and inhibiting the speed of the white marble rolling down the ramp was set considerably slower. The speed of the sequentially presented static white marble pictures was set to the speed currently reached in the green marble condition plus 30 milliseconds. Consequently the duration of the sequentially presented static white marble pictures was allowed to fluctuate between 50 and 110 milliseconds, allowing a response window between 800 and 1760 milliseconds.

The experiment consisted of two blocks of 80 trials (160 trials in total). Each block consisted of 48 green and 32 white marble trials. The larger proportion of green trials was included to create a prepotent action tendency, so that intentional inhibition would involve a late veto on an already prepared action. Trials were presented in a pseudo-randomized order so that each white marble trial was preceded by 0, 1, 2, or 3 green marble trials. The pseudo-randomized interleaving of green (instructed) and white (intentional) trials discouraged participants from strategically adopting a pattern of intentional action and inhibition, such as act-inhibit-act-inhibit etc.

Procedure

All participants were tested individually in a laboratory or an empty classroom. Before testing participants were instructed on the marble task. It was stressed that participants were not supposed to use a specific strategy to decide when to stop the white marble. Care was taken that all participants understood the instructions and were able to perform the task. All participants completed a practice block of 10 trials. Hereafter, participants completed the two test-blocks. Including instructions, the task took approximately 20 minutes to complete. After completion of the task participants were asked whether they had used a specific strategy in the task. Finally, participants completed the Raven SPM.

Data Recording and Analysis

During the task, the electrocardiogram (ECG) was measured continuously using the Biopac System at a sample frequency of 400 Hz. The ECG was recorded from three AgAg/Cl electrodes, attached via the modified lead-2 placement (one electrode directly under the right collar bone, one electrode between the two lower left ribs, and the ground electrode directly right of the navel). Inter Beat Intervals were defined as the length between consecutive R-peaks. The R-peaks were detected with the program Physiospec (developed by Technical Support Group UvA Psychology). The recorded Inter Beat Intervals (IBIs) were screened for physiologically impossible readings and artifacts (i.e. R-peaks not detected or other peaks seen as R-peaks). These were corrected by adjusting specific parameters in the program that extracted the IBIs from the digitized ECGs. Five consecutive IBIs were selected around the onset of marble motion; the IBI concurrent with the onset of marble motion (IBI 0), two IBIs

preceding the onset of marble motion (IBI -2 and IBI -1), and two IBIs following the onset of marble motion (IBI 1 and IBI 2). In order to obtain an index of phasic heart rate change (IBI difference) IBIs were referenced to IBI-2. Preliminary analysis of IBI-2 revealed no significant differences in IBI length between the different test conditions, confirming that there were no a priori differences between these conditions reflected in heart rate. Statistical analyses were performed using repeated measures ANOVA. Huynh-Feldt corrections for violations of the assumption of sphericity were used when necessary (Jennings, 1987; Vasey & Thayer, 1987).

2.3 Results

Behavior

An Age group (3) ANOVA for the number of go-responses on the green trials showed that with increasing age participants became more successful at responding to the green marble in time, F (2, 56) = 20.02, $p < .001$, $\eta_p^2 = .43$. Post-hoc Tukey tests showed that adults were more successful at responding fast to the green marble compared to both children ($p < .001$) and early adolescents ($p < .01$) (see Figure 2). Children and early adolescents did not differ significantly in their ability to respond to the green marble in time ($p = .078$).

On average participants decided to inhibit responding to the white marble on 43.64 percent of the trials. Age groups did not differ in this regard, F (2, 56) = .826, $p = .44$, $\eta_p^2 = .03$ (children: M = 42.58 (SD = 15.99), early adolescents: M = 41.35 (SD = 15.69), adults: M = 46.96 (SD = 6.00)) (see Figure 2). This finding indicates that all age groups performed the intentional inhibition task as instructed.

The use of strategies was evaluated by computing the Random Number Generation 2 (RNG2) index using Towse and Neil's (1998) RgCalc program. The RNG2 index is an adaptation of the Random Number Generation (RNG) index (Evans, 1978) optimized for two-choice response sequences, which considers the randomness of the sequence (Neuringer, 1986). A mean RNG2 index of .784 (SD = .025) was observed. Age groups did not differ in RNG2 index, F (2, 56) = 2.55, $p = .088$, $\eta_p^2 = .09$ (children: M = .789 (SD = .021), early adolescents: M = .790 (SD = .038), adults: M = .774 (SD = .007)). To examine the randomness the participants' RNG2 index was compared with a RNG2 index computed over a set of randomly generated sequences of go and nogo-responses. For the randomly generated set of go- and nogo-response sequences a mean RNG2 index of .770 (SD = .001) was observed. Adults' RNG2 index did not differ form the RNG2 index for the randomly generated set of go- and nogo- responses ($p = .10$), indicating that their choice behavior was not guided by unwanted rules (e.g., alternating between go vs nogo). RNG2 indexes of both children and early adolescents differed significantly from the RNG2 index for the randomly generated set of go- and nogo- responses (all p's < .05), indicating that children's and early adolescents' choice behavior deviated from pure randomness.

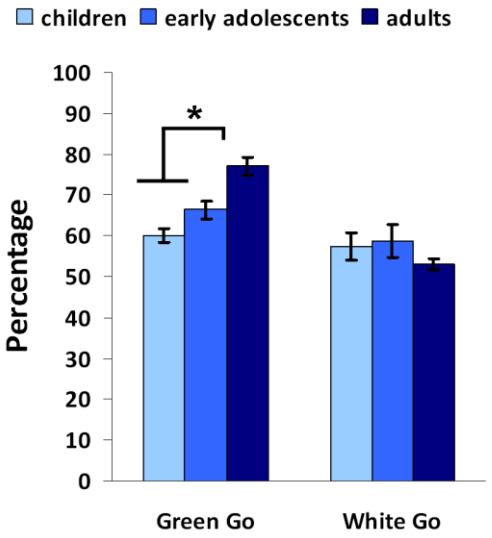

Figure 2: Percentage of go-responses in the green and white marble conditions.

Reaction times were shorter for the green marble trials (M = 283.92, SE = 6.85) than for the white marble trials (M = 358.77, SE = 11.78), F (1, 54) = 97.39, p < .001, η_p^2 = .64. Overall, reaction times decreased with age, F (2, 54) = 3.47, p < .05, η_p^2 = .11. Post-hoc Tukey tests showed that children were slower compared to adults (p < .05). Reaction times did not differ between children and early adolescents (p = .41) and between early adolescents and adults (p = .50). However, no interaction with condition was observed (p = .68). Together, these results indicate that all age groups performed the task accurately, but that adults were more efficient in doing so, as indicated by faster responses to green trials and more random choice behavior on the white trials.

Heart Rate

IBIs were computed separately for the stimulus-driven green-go condition, omissions on the stimulus-driven green trials, and the intentional white-go and white-nogo conditions. To test for differences in heart rate responses between the stimulus-driven and intentional conditions, an Age group (3) x Condition (2: green and white) x Response (2: go and nogo) x IBI (4) repeated measures ANOVA was performed. This analysis resulted in a main effect of IBI, F (3, 162) = 58.80, p < .001, η_p^2 = .52, ε = .67. As can be seen in Figure 3, heart rate decelerated (i.e., slowed) in anticipation of stimulus presentation, followed by an acceleratory recovery. A Condition x IBI interaction, F (3, 162) = 17.39, p < .001, η_p^2 = .24, ε = .83, indicated that heart rate deceleration was more pronounced for the intentional compared to the stimulus-driven conditions. A Response x IBI interaction, F (3, 162) = 28.00, p < .001, η_p^2 = .34, ε = .86, indicated that the shift from anticipatory deceleration to acceleratory recovery occurred earlier for go compared to nogo responses. Furthermore, a

Condition x Response x IBI interaction, F (3, 162) = 7.10, p < .001, η_p^2 = .12, ε = .93, was observed, indicating that heart rate patterns associated with go vs. nogo responses differed depending on the condition (green/white) in which they were made. No interactions with Age group were found (all 2-, 3- and 4-way interactions, p's > .1), demonstrating that heart rate responses to the different conditions were similar across age groups.

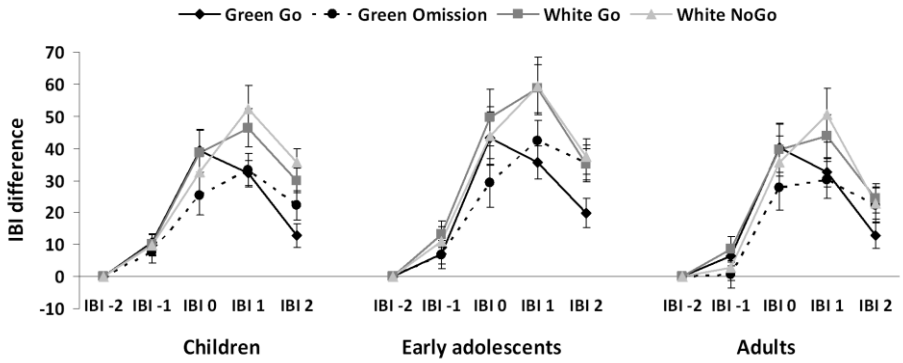

Figure 3: Stimulus-locked heart rate changes associated with stimulus-driven action, omissions on stimulus-driven action trials, intentional action and intentional inhibition. IBI 0 refers to the IBI during which the marble started to roll down the ramp. An increase in IBI difference scores indicates heart rate deceleration, and a decrease in IBI difference scores indicates heart rate acceleration.

Follow-up ANOVAs for the green stimulus-driven and white intentional conditions separately, showed that within the stimulus-driven condition the shift from anticipatory deceleration to acceleratory recovery occurred earlier for go compared to nogo responses, F (3, 168) = 31.08, p < .001, η_p^2 = .36, ε = .88. For nogo responses heart rate continued to decelerate during IBI 1, indicative of a lapse of attention. In the intentional condition heart rate deceleration was more pronounced for intentional inhibition compared to intentional action, F (3, 168) = 5.93, p < .002, η_p^2 = .10, ε = .90. Follow-up ANOVAs for the go and nogo responses separately, showed that for the nogo responses heart deceleration was more pronounced in the white intentional compared to the green stimulus-driven condition, F (3, 168) = 9.11, p < .001, η_p^2 = .14, ε = .90. Furthermore, heart rate deceleration was also more pronounced and continued during IBI 1 for the intentional white-go compared to the stimulus-driven green-go responses, F (3, 168) = 21.66, p < .001, η_p^2 = .28, ε = .84. Together, these results show that heart rate deceleration was more pronounced for the intentional conditions and that this heart rate deceleration was strongest in the intentional inhibition condition.

However, one alternative explanation for the continued heart rate deceleration in the intentional action condition is the possibility of a longer R-wave to response interval for the white-go compared to the green-go condition (Jennings & Wood, 1977; Somsen, et al., 2002). Since reaction times in the white-go condition were slower compared to the green-go condition, it might be that responses in the

white-go condition occurred later in the interbeat interval, resulting in a longer R-wave to response interval. To control for this alternative explanation, we performed a response-locked analysis (Jennings, et al., 1990). For this analysis five IBIs were selected around the moment of responding, IBI -2 to IBI 2, the moment of responding occurred during IBI 0. IBIs were referenced to IBI -2 to create IBI difference scores. Preliminary analysis of raw IBI -2 values revealed no significant difference in IBI -2 length between the white-go and the green-go conditions, confirming that there were no a priori differences between those conditions reflected in heart rate.

To test for differences in heart rate responses between the white-go and the green-go conditions, an Age group (3) x Condition (2) x IBI (4) repeated measures ANOVA was performed. Importantly, this analysis showed again a more pronounced heart rate deceleration for the white-go compared to the green-go condition, F (3, 162) = 9.86, $p < .001$, $\eta_p^2 = .15$, $\varepsilon = .88$ (see Figure 4), indicating that indeed heart rate deceleration is most pronounced for the intentional conditions. Again, no interaction with Age group was found (3-way interaction, $p = .26$), demonstrating that this pattern was similar across age groups.

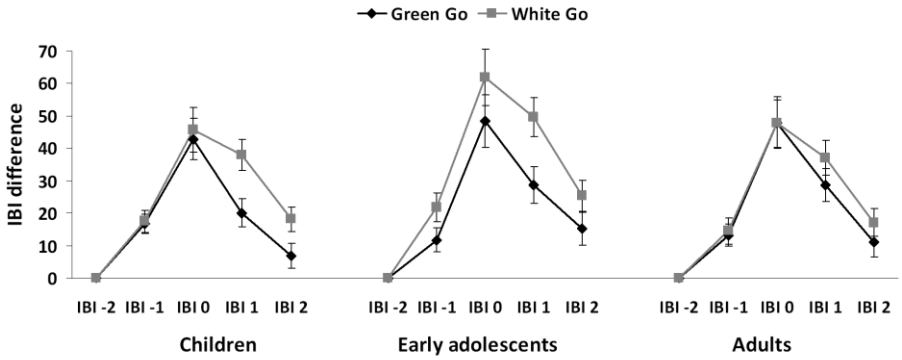

Figure 4: Response-locked heart rate changes associated with stimulus-driven action and intentional action. IBI 0 refers to the IBI during which the participant responded. An increase in IBI difference scores indicates heart rate deceleration, and a decrease in IBI difference scores indicates heart rate acceleration.

2.4 Discussion

In the present study, we examined the cardiac concomitants of intentional action and inhibition. Participants, divided in three age groups, performed a marble paradigm, in which they had to decide between intentionally inhibiting responding and intentionally responding to a rolling marble in the context of prepotent go responses, while their heart rate was measured continuously.

The behavioral results showed that all age groups followed task instructions; on average, age groups intentionally inhibited on 43.46% of the trials, which is close to

criterion (50%). The observation that in our study even the 8-to-10-year-olds were able to intentionally inhibit a prepotent response concurs with previous studies showing an early development of the ability to inhibit (Ridderinkhof, et al., 1999; Williams, et al., 1999). Importantly, analysis of the RNG2 index (Evans, 1978; Neuringer, 1986) indicated that participants did not use a simple alternation strategy to decide whether or not to inhibit responding to the white marble. Adults' choice behavior did not differ from a randomly generated response sequence whereas the choice behavior of children and early adolescents did, which is consistent with previous research showing a protracted development of random sequence generation (Towse & Mclachlan, 1999).

Consistent with the results of Kühn and colleagues (2009) we observed longer reaction times for the intentional go-responses compared to the stimulus-driven go-responses, indicating that the intentional decision process takes more time. Children and early adolescents responded slower compared to adults on both the stimulus-driven and the intentional trials, indicating that children and early adolescents were less efficient in performing the go-task. Even though a tracking system was used to adapt speed of responding to average reaction times on the stimulus-driven trials, children and adolescents were still less able to respond to this deadline on all trials, suggesting that there was more variability in their response times (Tamnes, Fjell, Westlye, Ostby, & Walhovd, 2012). Importantly, for the reaction times no interaction between condition (stimulus-driven, intentional) and age group was found, indicating that intentional go-responses were not disproportionally more difficult than stimulus-driven go-responses for children and early adolescents compared to adults.

The observed pattern of anticipatory heart rate deceleration and acceleratory recovery in our task is consistent with the standard pattern found in the stimulus-driven action control literature (Jennings, et al., 1992; Jennings & van der Molen, 2002, 2005; van Boxtel, van der Molen, Jennings, & Brunia, 2001; Van der Veen, et al., 2000). In addition, during intentional inhibition a pronounced continued heart rate deceleration was observed. This is in line with previous heart rate studies focusing on stimulus-driven inhibition (van Boxtel, et al., 2001; Van der Veen, et al., 2000), in which also heart rate deceleration following action inhibition was observed. Interestingly, we also observed a continued heart rate deceleration during intentional action, although less pronounced as for intentional inhibition, suggesting that heart rate is also sensitive to volitional decisions. The observed heart rate deceleration during intentional action remained significant when a response-locked analysis was performed to control for possible differences in R-wave to response intervals between the stimulus-driven and the intentional conditions.

The findings suggest that heart rate deceleration in the context of the current intentional action and inhibition paradigm is an index of a supervisory attention system for the central regulation of voluntary behavior (Jennings & van der Molen, 2002; Norman & Shallice, 1986). The observation of heart rate deceleration in the context of intentional action is consistent with earlier results showing heart rate deceleration when delaying action (Jennings, et al., 2003). In the intentional action condition participants are also delaying their action until they have made a final decision whether or not to act. The same is true for the intentional inhibition

condition; in this case participants are also delaying their action until they have made a final decision whether or not to act, but here the final decision is an inhibition instead of an overt action.

We did not observe developmental differences in intentional action and inhibition, indicating that the mechanics for intentional action and inhibition are already in place in middle childhood. Notably, the pattern of heart rate responses suggested that there were also no developmental differences across the age groups examined in the efficiency of recruiting the inhibitory mechanism. One possible explanation for this observation could be the mediating role of internal motivation. When one intentionally decides to inhibit, internal motivation to inhibit will be higher compared to when an external stimulus signals that one has to inhibit. Previous research has shown that motivation indeed plays an important role in inhibition (Groom et al., 2010; Leotti & Wager, 2010; Sinopoli, Schachar, & Dennis, 2011). For example, inhibitory performance improves when monetary incentives are used (Leotti & Wager, 2010; Sinopoli, et al., 2011). Motivation also has a positive effect on electrophysiological markers of response inhibition (Groom, et al., 2010). This finding is consistent with our observation that children and early adolescents showed adult-like heart rate response patterns for the internally motivated intentional conditions.

One limitation to the present study is the relatively restricted age range. Future studies should include younger age groups for a full assessment of developmental change in intentional inhibition. Most likely, this will require some further adaptations of the marble task making it even more child-friendly than the current version.

Taken together, the present study was the first to examine heart rate responses to intentional action and inhibition. Both intentional action and intentional inhibition resulted in heart rate deceleration, although the deceleration was larger for intentional inhibition than for intentional action. Thus, both volitional processes and inhibition may drive heart rate deceleration. This extends the existing heart rate literature, by showing that not only externally driven effortful processing, but also internally driven volitional processing, affects heart rate responses. The finding that heart rate responses to intentional action and inhibition are in place in middle childhood may indicate that internally driven choices may form a basic part of the supervisory attention system which comes online early in development.

Chapter 3
Neural correlates of intentional and stimulus-driven inhibition: A comparison

This chapter is published as:
Schel, M.A., Kühn, S., Brass, M., Haggard, P., Ridderinkhof, K.R., & Crone, E.A. (2014). Neural correlates of intentional and stimulus-driven inhibition: A comparison. *Frontiers in Human Neuroscience, 8*, 27.

3. Intentional versus externally driven inhibition

Abstract

People can inhibit an action because of an instruction by an external stimulus, or because of their own internal decision. The similarities and differences between these two forms of inhibition are not well understood. Therefore, in the present study the neural correlates of intentional and stimulus-driven inhibition were tested in the same subjects. Participants performed two inhibition tasks while lying in the scanner: the marble task in which they had to choose for themselves between intentionally acting on, or inhibiting a prepotent response to measure intentional inhibition, and the classical stop signal task in which an external signal triggered the inhibition process. Results showed that intentional inhibition decision processes rely on a neural network that has been documented extensively for stimulus-driven inhibition, including bilateral parietal and lateral prefrontal cortex and pre-supplementary motor area. We also found activation in dorsal frontomedian cortex and left inferior frontal gyrus during intentional inhibition that depended on the history of previous choices. Together, these results indicate that intentional inhibition and stimulus-driven inhibition engage a common inhibition network, but intentional inhibition is also characterized by additional context-dependent neural activation in medial prefrontal cortex.

3.1 Introduction

In daily life, most people experience and exercise a degree of voluntary control over their actions. The concept of intentional action is well recognized in the neuroscience literature. Several studies have focused on the voluntary choice between alternative actions (the so-called "what-component" of intentional action generation), and the voluntary choice of when to initiate action (the "when–component") (Brass & Haggard, 2008). Neuroimaging research has shown that the processes of intentional action selection and planning are supported by a medial prefrontal network, including the rostral cingulate zone and pre-supplementary motor area (preSMA) (Lau, et al., 2004; Lau, et al., 2006).

A recent novel line of research has suggested that the inhibition of actions, like the generation of actions, can also be either intentionally driven or stimulus-driven. Intentional inhibition has been conceptualized as a late "veto-process", a final check-and-brake function before action execution (Filevich, et al., 2012; Kühn, et al., 2009). It has been proposed as a third component in models of intentional action generation, the so-called "whether–component" (Brass & Haggard, 2008). In contrast to the "what" and "when" components of the model of intentional action generation, the "whether" component is difficult to examine, especially on a behavioral level, since intentional inhibition (i.e. internally driven inhibition) involves no external imperative stimulus, and does not result in any overt behavior. Two recent studies aimed to investigate intentional inhibition by asking participants to prepare actions, but then to occasionally cancel them at the last possible moment prior to action. These studies revealed a distinct neural network that was more activated in intentional inhibition than in intentional action, including the dorsal frontomedian cortex (dFMC) (Brass & Haggard, 2007; Kühn, et al., 2009).

In contrast to the scarce literature on intentional inhibition, most studies of action inhibition have focused on stimulus-driven inhibition (i.e. externally driven inhibition). Within neuroscience research stimulus-driven inhibition has been extensively studied using different paradigms, such as go/nogo tasks (Casey, et al., 1997) and stop-signal tasks (Logan & Cowan, 1984). In these paradigms an external stimulus signals that participants have to inhibit a prepotent or already prepared response. Successful performance on these stimulus-driven inhibition paradigms appears to rely on a fronto-striatal network (Aron, 2011; Aron & Poldrack, 2006; Ridderinkhof, et al., 2011; Verbruggen & Logan, 2008). Within this network, specifically, the right inferior frontal gyrus (rIFG) and preSMA have been implicated as crucial for the inhibition of motoric responses (Aron, et al., 2004; Chikazoe, 2010; Jahfari et al., 2012; Jahfari, et al., 2011). Importantly, stimulus-driven inhibition is influenced by preceding contexts, such that participants are more likely to make errors in inhibiting when an inhibition trial is preceded by a larger number of go-trials (Durston, Thomas, Worden, Yang, & Casey, 2002; Durston, Thomas, Yang, et al., 2002). Also activation in key regions, such as the rIFG becomes stronger during inhibition following a larger number of go-trials (Durston, Thomas, Worden, et al., 2002; Durston, Thomas, Yang, et al., 2002). Stimulus-driven inhibition benefits from a number of distinct methodological advantages, including a well-circumscribed

experimental task, and its mechanisms and dynamics are detailed by well-developed computational models (Aron & Poldrack, 2006). However, one recent review has noted that stimulus-driven inhibition may not capture the crucial operations of cognitive inhibitory control in everyday life, and particularly in social contexts. Explicit stop-signals are relatively rare in real life, and society (including legislation) assumes that healthy adults have the capacity to decide for themselves when to refrain from an action (Aron, 2011).

Despite the large literature on stimulus-driven inhibition, to date no study directly compared stimulus-driven inhibition and intentional inhibition. Nevertheless, understanding whether self-generated decisions to inhibit action are different from stimulus-driven decisions, remains an important question, both for the scientific understanding of inhibitory control, and for potential therapies for conditions such as impulsivity, harmful behavior, or shyness. In particular, is the neural network supporting stimulus-driven inhibition (lateral prefrontal cortex/ preSMA) also involved in intentional inhibition, or is a different neural network involved in intentional inhibition (including dFMC)? Additionally, is intentional inhibition dependent on preceding context, as has been previously observed for stimulus-driven inhibition (Durston, Thomas, Worden, et al., 2002; Durston, Thomas, Yang, et al., 2002)?

The present study is the first to test the neural correlates of intentional and stimulus-driven inhibition within the same subjects. To this end, participants performed two inhibition tasks while lying in the scanner; the marble task to measure intentional inhibition (Kühn, et al., 2009) and the stop-signal task to measure stimulus-driven inhibition (Logan & Cowan, 1984). In the marble task, participants have to intentionally inhibit an externally triggered prepotent response. A marble begins to roll down a slope. If the marble turns green as it begins to roll, they must rapidly press a button to stop it from rolling down. If the marble remains white, they may choose whether to press and stop it, or inhibit pressing and let it roll down. The contrast of crucial interest for the marble task was the contrast between the two possible outcomes of intentional decisions: i.e., inhibition vs action. We hypothesized that this contrast would show additional neural activity in dFMC as was previously shown by Kühn et al. (2009). Interestingly, this activation is not normally reported in the equivalent contrast for stimulus-driven inhibition. Secondly, in the current study, the marble task was used to identify the neural network supporting the intentional inhibition decision process, by contrasting trials in which participants intentionally decide to inhibit with trials in which participants are instructed to respond (green marble trials). These neural regions were compared with the contrast of successful stopping versus executing an action in the stop signal task by means of a conjunction analysis. We hypothesized that the fronto-striatal inhibition network (Aron & Poldrack, 2006; Ridderinkhof, et al., 2011) would be involved in both the intentional and the stimulus-driven inhibition decision process.

3.2 Method

Participants

Twenty-four healthy right-handed adults between 18-26 years of age (13 females, *M* = 21.49, *SD* = 2.36) participated in the experiment. All participants had normal or corrected-to-normal vision, and no neurological or psychiatric impairments according to self-report. Before participating in the experiment, all participants signed informed consent. In accordance with guidelines of the Leiden University Medical Center, all anatomical scans were reviewed by a radiologist. No anomalous findings were reported. To obtain an estimate of cognitive functioning participants completed two subtests of the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1981a); similarities and block design. Estimated IQ scores were within the normal range (*M* = 111.33, *SD* = 6.93).

Experimental Tasks

Participants performed two response inhibition tasks while lying in the MRI scanner. The tasks were presented in a fixed order. Participants first performed the marble task as a measure of intentional inhibition, followed by the stop-signal task as a measure of stimulus-driven inhibition.

Marble task. The marble task was adapted from Kühn et al. (2009). Each trial (see Figure 1) started with the presentation of a fixation screen (white cross against a black background) with duration jittered between 1400 and 2000 ms. The fixation screen was followed by a screen showing a white ramp with a white marble on top presented against black background. After a variable duration of 1400 to 2000 ms the marble started rolling down the ramp and participants could stop the marble from crashing by pressing a button. Finally, a feedback screen, showing trial outcome, was presented for 1000 milliseconds. There were two task conditions: a green marble and a white marble condition.

In the green marble condition, the white marble changed to green as soon as it started rolling. The task was programmed in such a way that participants viewed 16 rapidly presented static pictures showing the marble at successive locations on the ramp, which was experienced as a rolling movement. Participants were instructed to stop the marble from crashing by pressing a response button with their right index finger. When participants were successful at stopping the marble, they were presented with a feedback screen showing the location where they had stopped the marble. When participants were not successful at stopping the marble, they were presented with a feedback screen showing a shattered marble beneath the ramp. The speed of the marble was adjusted by a staircase-tracking procedure. At the start of the experiment, the static pictures were presented for 30 milliseconds each. When participants were successful at stopping the marble the duration was decreased with 10 milliseconds, making the task more difficult. When participants were not successful at stopping the marble in time the duration was increased with 10 milliseconds, making the task easier. The staircase procedure was allowed to fluctuate between 20 and 80 milliseconds, allowing a response window between 320 and 1280 milliseconds.

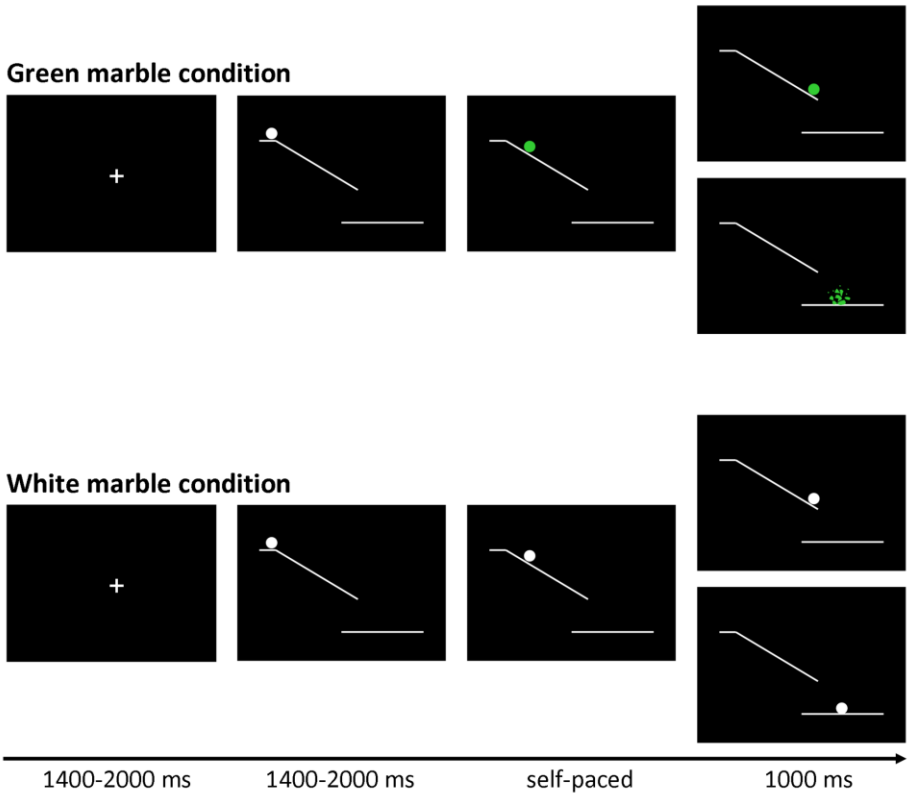

Figure 1: Trial structure of the marble task. Stimuli were presented on a black background. At the beginning of each trial a white marble on top of a ramp was presented. After a variable delay (jittered between 1400 and 2000 ms) the marble started to roll down the ramp, and could change color to green.

In the white marble condition, the marble did not change color and participants were instructed to choose between responding and inhibiting. When participants responded, they were presented with a feedback screen showing the location where they had stopped the marble. When participants inhibited, they were shown a feedback screen showing the white marble at the bottom of the ramp. In order to motivate participants to balance the frequency of responding and inhibiting, they were told that the stopped and non-stopped marbles would fall in different baskets. Participants were instructed to collect an equal amount of marbles in each basket, but were not allowed to count or use a sequencing strategy; therefore participants were instructed to make an independent decision every time the marble stayed white. At the end of each block participants were shown how many marbles they had collected in each basket. As will be described in the results section, the participants were successful in following the instruction to stop the marble on approximately 50% of the trials.

In order to give participants sufficient time to decide between responding and inhibiting the speed of the white marble rolling down the ramp was set considerably slower. The speed of the sequentially presented static white marble pictures was set to the speed currently reached in the green marble condition plus 30 milliseconds. Consequently the duration of the sequentially presented static white marble pictures was allowed to fluctuate between 50 and 110 milliseconds, allowing a response window between 800 and 1760 milliseconds.

The experiment consisted of three blocks of 80 trials, each block consisting of 48 green and 32 white marble trials. Trials were presented in a pseudo-randomized order so that each white marble trial was preceded by 0, 1, 2, or 3 green marble trials. The large proportion of fast-paced green trials served two functions. First, the fast-paced green trials lead to a prepotent tendency for action. This was desirable, so that intentional inhibition of action would involve a late brake on an already-prepared action, rather than an early decision not to initiate action preparation. Second, the randomized interleaving of intentional (white) and instructed (green) trials discouraged participants from strategically pre-deciding a pattern of intentional action, such as act-inhibit-act-inhibit etc.

Stop-Signal Task. The stop-signal task (Logan & Cowan, 1984) was presented in a visual form. Each trial started with the presentation of a green left- or rightwards pointing arrow. Participants were instructed to make a speeded response to the direction of the arrow, for the leftwards pointing arrow participants had to press a button with their left index finger and for the rightwards pointing arrow participants had to press a button with their right index finger. The arrow disappeared when participants responded or after 1500 milliseconds had passed. Following the presentation of the arrow a fixation cross was presented with a duration jittered between 2000 and 4000 milliseconds. When participants responded to the arrow, the duration of the fixation cross was extended by 1500 milliseconds minus the reaction time, in order to keep the duration of the task stable between participants.

On a limited number of stop-trials (25 %) a stop-signal was presented. In this case the arrow suddenly changed color to red. This color change indicated that participants had to inhibit responding to the direction of the arrow. Stop-signal delay (SSD) was adjusted using a staircase-tracking procedure to guarantee a 50 % inhibition rate (Lappin & Eriksen, 1966). At the beginning of the task SSD was set at 250 milliseconds. When participants successfully inhibited SSD was increased by 50 milliseconds to make the task more difficult, when participants were not able to inhibit responding SSD was decreased by 50 milliseconds to make the task easier.

The experiment consisted of two blocks of 128 trials, each block consisting of 96 go-trials and 32 stop-trials. Trials were presented in a pseudo-randomized order so that each stop-trial was preceded by 1, 2, 4, or 5 go-trials.

Data Acquisition

Scanning was performed with a standard whole-head coil on a 3.0 Tesla Philips scanner at the Leiden University Medical Center. The marble task consisted of 3 event-related runs, each lasting approximately 6 minutes, and the stop-signal task

consisted of 2 event-related runs, both lasting approximately 5 minutes. Functional data were acquired using T2*-weighted echo-planar imaging (EPI). The first 2 volumes of each run were discarded in order to allow for equilibration of T1 saturation effects (TR = 2.2 sec, TE = 30 msec, sequential acquisition, 38 slices of 2.75 mm, field of view 220 mm, 80 x 80 matrix, in-plane resolution 2.75 mm). After the functional runs a high-resolution 3D T1-FFE scan for anatomical reference was obtained (TR = 9.760 ms; TE = 4.59 ms, flip angle = 8 degrees, 140 slices, 0.875 × 0.875 × 1.2 mm^3 voxels, field of view = 224 × 168 × 177 mm^3). Head motion was restricted by using foam inserts between the head and the head coil. Visual stimuli were projected onto a screen in the magnet bore that could be viewed through a mirror attached to the head coil.

Behavioral Data Analysis

For the marble task, repeated measures analyses of variance were performed to examine the effect of preceding context on intentional inhibition. Planned comparisons were performed between the different numbers of preceding green trials, to examine which conditions differed from each other.

The use of response selection strategies on the marble task was evaluated by computing the Random Number Generation 2 (RNG2) index using the program RgCalc (Towse & Neil, 1998). The RNG2 index is an adaptation of the RNG index (Evans, 1978) optimized for two-choice response sequences, which considers the randomness of the sequence (Neuringer, 1986). RNG2 scores can range from 0 (null predictability) to 1 (complete predictability).

For the stop-signal task, the Stop signal reaction time (SSRT) was calculated according to the horse-race model of stopping (Logan & Cowan, 1984) following the procedures described in Band et al. (2003). In short, first all reaction times (RTs) for the correct go-trials were rank-ordered. Next, the percentage of failed inhibition was determined. Then, the go-RT corresponding to that percentage was determined. Finally, SSRT was computed as the difference between the go-RT corresponding to the percentage of failed inhibition and the mean SSD.

fMRI Data Analysis

Data were preprocessed using SPM8 (Wellcome Department of Cognitive Neurology, London). Images were corrected for rigid-body motion. Structural and functional volumes were spatially normalized to T1 templates. The normalization algorithm used a 12-parameter affine nonlinear transformation involving cosine basis functions, and then resampled the volumes to 3-mm cubic voxels. Translational movement parameters never exceeded 1 voxel (< 3mm) in any direction for any subject or scan. Templates were based on the MNI305 stereotaxic space (Cocosco, Kollokian, Kwan, & Evans, 1997), an approximation of Talairach space (Talairach & Tournoux, 1988). Functional volumes were spatially smoothed with an 8-mm full-width-at-half-maximum isotropic Gaussian kernel. Statistical analyses were performed on individual participants' data using the general linear model in SPM8. The fMRI time series data were modeled by a series of events convolved with a canonical hemodynamic response function (HRF) and the temporal derivatives. For the marble task, the onset

of marble motion of each trial was modeled as an event of interest. Separate regressors were defined for white nogo (intentional inhibibition), white go (intentional action), green go (stimulus-driven action), and green omissions (omission on the green marble trials). For the stop signal task, the presentation of the arrow of each trial was modeled as an event of interest. Separate regressors were defined for stop-successful, stop-unsuccessful, go-successful, and go-unsuccessful trials. The trial functions were used as covariates in a general linear model, along with a basic set of cosine functions to high-pass filter (120 Hz) the data. The least-squares parameter estimates of the height of the best-fitting canonical HRF for the different conditions were used in pair-wise contrasts. All reported effects consisted of at least 10 contiguous voxels that exceeded a false-discovery-rate (FDR) corrected threshold of $p < .05$, unless otherwise specified.

To examine similarities across contrasts, conjunction analyses were computed using the minimum statistic approach (Nichols, Brett, Andersson, Wager, & Poline, 2005). These analyses identified clusters that were significantly engaged at our threshold in both contrasts that we examined.

Region of interest (ROI) analyses were performed to further characterize the involvement of brain regions in intentional inhibition. ROI analyses were performed with the MarsBaR toolbox in SPM8 (Brett, Anton, Valabregue, & Poline, 2002) (http://marsbar.sourceforge.net).

3.3 Results

Behavior

Marble task. Participants successfully responded to the green marble on 63.22% of the trials. Participants intentionally inhibited responding to the white marble on 53.17% of the trials. Participants more often decided to inhibit responding to the white marble when there were fewer preceding green trials, $F(3, 69) = 18.09$, $p < .001$ (see Figure 2A). That is, intentional inhibition decreased as the previous history of instructed go-responses increased. Planned comparisons showed that participants more often inhibited when there were 0 compared to 1, 2, or 3 preceding green trials (all p's $< .001$) and when there was 1 compared to 3 preceding green trials ($p < .05$). The level of inhibition was comparable for the conditions where there were 1 or 2, and 2 or 3 preceding green trials (respectively $p = .14$, $p = .24$).

To examine the randomness of response selection the RNG2 index was computed. A mean RNG2 index of .807 ($SD = .012$) was observed. To examine the randomness the participants' RNG2 index was compared with a RNG2 index computed over a set of randomly generated sequences of go- and nogo-responses. For the randomly generated set of go- and nogo-response sequences a mean RNG2 index of .801 ($SD = .002$) was observed. Although the RNG2 index for the randomly generated sequences was marginally but significantly smaller compared to the participants' RNG2 index, $F(1, 47) = 5.71$, $p < .05$, these results indicate that the participants' behavior was close to being random and not driven by simple alternation strategies.

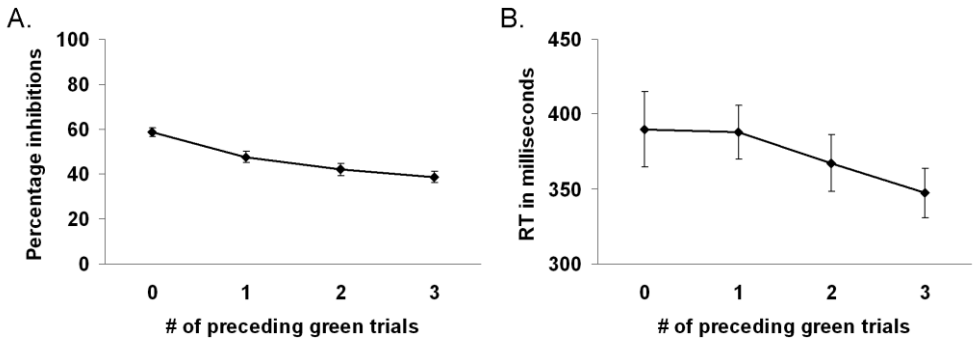

Figure 2: Preceding context effects in the marble task. **A**. Participants inhibited more frequently with less preceding green trials. **B**. Reaction times on the white marble trials were faster with more preceding green trials.

Reaction times were shorter for the green marble trials (M = 301, SD = 39) compared to the white marble trials (M = 372, SD = 89), F (1, 23) = 32.55, p < .001, indicating that the decision process in the white marble trials took more time. However, longer reaction times on the white marble trials might also be partially related to the slower marble speed on those trials. Reaction times on the white marble trials were faster when there were more preceding green trials, F (3, 69) = 5.52, p < .01 (see Figure 2B). Planned comparisons showed that reaction times were faster when there were 3 compared to 0 or 1 preceding green trials (respectively p < .01, p < .001). Reaction times did not differ between the other conditions of preceding green trials (all p's > .05).

Stop-Signal task. Participants successfully responded to the direction of the arrow on 96.46 % of the go-trials. The average reaction time on the successful go-trials was 519 ms (SD = 133). Participants successfully inhibited responding to the direction of the arrow on 46.03 % of the stop-trials. SSRT was 281 ms (SD = 45).

Correlation between intentional and stimulus-driven inhibition. To examine the interrelations between the inhibition tasks, a correlation analysis was performed. Intentional inhibition as measured by the marble task (% intentional inhibition) was not correlated with stimulus-driven inhibition as measured by the stop-signal task (SSRT), r = .181, p = .40.

fMRI results

Marble task. First, to identify the brain regions underlying the intentional inhibition decision process the contrast intentional inhibition > stimulus-driven action (White NoGo > Green Go) was computed. This analysis revealed activation in a widespread neural network (see Figure 3A and Table 1) consisting of bilateral IFG, bilateral middle frontal gyrus (MFG), bilateral superior frontal gyrus (SFG), preSMA/anterior cingulate cortex (ACC), bilateral inferior parietal lobule (IPL), right superior temporal gyrus (STG), and occipital lobe. Second, the brain regions

underlying the intentional action decision process were identified by computing the contrast intentional action > stimulus-driven action (White Go > Green Go). This analysis revealed a similar activation pattern as the previous analysis, namely bilateral IFG, bilateral MFG, bilateral SFG, preSMA/ACC, and bilateral IPL (see Figure 3B and Table 1). To formally compare activation patterns related to the intentional inhibition decision process and the intentional action decision process a conjunction analysis was performed. This analysis confirmed the considerable overlap in brain regions underlying both intentional decision processes by revealing significant overlapping activation in bilateral IFG, bilateral MFG, bilateral SFG, preSMA/ACC, and bilateral IPL (see Figure 3C and Table 1).

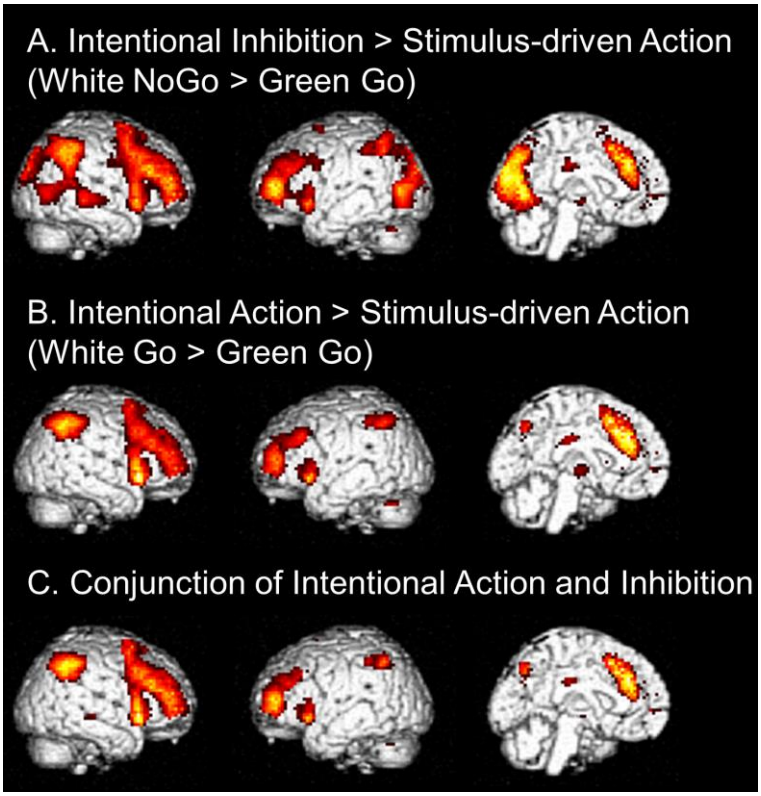

Figure 3: A. Whole brain contrasts showing activation related to intentional inhibition decision process (White NoGo > Green Go) (FDR-corrected $p < .05$, at least 10 contiguous voxels). **B.** Whole brain contrasts showing activation related to intentional action decision process (White Go > Green Go) (FDR-corrected $p < .05$, at least 10 contiguous voxels). **C.** Conjunction analysis showing overlapping activation in intentional inhibition decision processes (White NoGo > Green Go) and intentional action decision processes (White Go > Green Go) (FDR-corrected $p < .05$, at least 10 contiguous voxels).

Table 1. Brain regions revealed by whole brain contrast, focused on decision processes (all FDR corrected, $p < .05$, > 10 voxels).

Anatomical region	L/R	K	Z	MNI coordinates		
				x	y	z
White NoGo > Green Go						
Middle Frontal Gyrus	L/R	4637	5.76	36	45	18
Occipital Lobe	L/R	5484	5.60	12	-69	0
Cerebellum	L	28	3.36	-30	-63	-33
Superior Frontal Gyrus	L	28	3.30	-21	6	69
Middle Cingulate Cortex	L/R	53	3.20	-3	-24	33
Thalamus	L/R	17	2.89	-6	-9	-3
Inferior Frontal Gyrus / Insula	R	11	2.86	36	-12	18
White Go > Green Go						
Middle Frontal Gyrus	L/R	3445	6.25	30	24	0
Inferior Frontal Gyrus / Insula	L	282	5.69	-27	27	0
Inferior Parietal Lobe	R	554	5.69	54	-48	54
Inferior Parietal Lobe	L	184	4.26	-54	-42	51
Precuneus	L/R	124	3.76	6	-66	42
Thalamus	L	35	3.54	-9	-15	0
Middle Cingulate Cortex	L/R	49	3.51	0	-24	33
Cerebellum	L	35	3.41	-33	-60	-33
Conjunction Intentional Action and Inhibition						
Middle Frontal Gyrus	L/R	2625	6.15	9	24	42
Inferior Parietal Lobe	R	521	5.45	51	-45	45
Middle Frontal Gyrus	L	493	5.44	-30	51	12
Inferior Frontal Gyrus / Insula	L	226	5.12	-30	27	0
Inferior Parietal Lobe	L	149	4.28	-54	-42	51
Precuneus	L/R	156	4.23	6	-66	42
Middle Cingulate Cortex	L/R	30	3.34	-3	-24	33
Superior Temporal Gyrus	R	15	2.92	54	-30	-6

The next set of analyses focused on the intentional decision outcome. First, the brain regions underlying the intentional inhibition decision outcome were identified by computing the contrast intentional inhibition > intentional action (White NoGo > White Go). This analysis revealed activation in bilateral IPL, left IFG, left MFG, right medial temporal gyrus (MTG), and occipital lobe (see Figure 4A and Table 2). Next the reversed contrast (White Go > White NoGo) was computed to identify the brain regions underlying the intentional action decision outcome. This analysis did not result in significant activations at a FDR corrected threshold of $p < .05$. However, at an uncorrected threshold of $p < .001$ this analysis revealed activation in cingulate cortex and left postcentral gyrus, consistent with a role for left motor cortex in right-hand responding (see Figure 4B and Table 2).

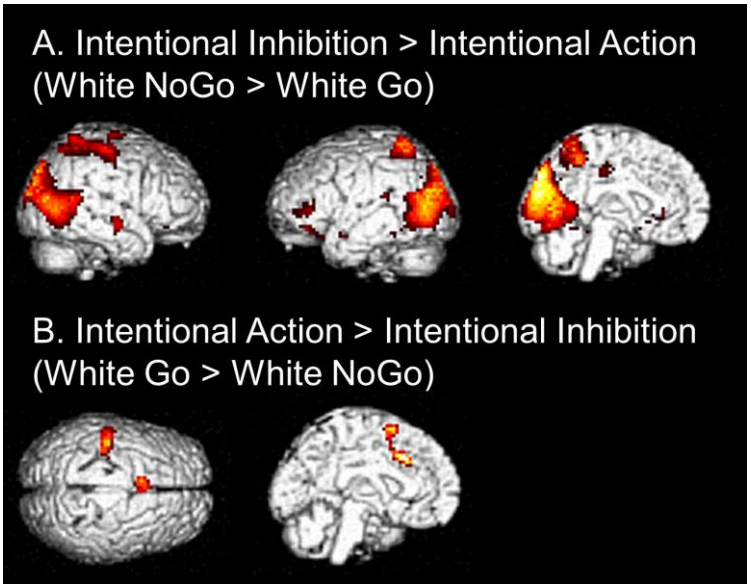

Figure 4: A. Whole brain contrast showing activation related to intentional inhibition decision outcome (White NoGo > White Go) (FDR-corrected $p < .05$, at least 10 contiguous voxels). **B.** Whole brain contrast showing activation related to intentional action decision outcome (White Go > White NoGo) (uncorrected $p < .001$, at least 10 contiguous voxels).

Table 2. Brain regions revealed by whole brain contrast, focused on decision outcomes (FDR corrected, $p < .05$, > 10 voxels, except for White Go > White NoGo which was thresholded $p < .001$ uncorrected, > 10 voxels).

Anatomical region	L/R	K	Z	MNI coordinates		
				x	y	z
White NoGo > White Go						
Occipital Lobe	L/R	5961	5.48	-15	-84	36
Superior Temporal Gyrus	R	51	3.88	60	-9	-9
Insula	L	34	3.59	-33	3	-12
Subgenual Anterior Cingulate Cortex / Caudate	R	113	3.49	6	30	3
Middle Cingulate Cortex	L	22	3.47	-15	-24	39
Inferior Frontal Gyrus	L	42	3.32	-48	42	6
Superior Frontal Gyrus	R	33	3.27	24	-12	72
Orbital Anterior Prefrontal Cortex	R	20	3.24	21	36	-6
Middle Cingulate	R	34	3.16	15	-21	42
Inferior Temporal Gyrus	L	14	3.13	-42	-36	-12
Inferior Frontal Gyrus	L	33	3.08	-30	36	-9
Superior Temporal Gyrus	L	11	2.87	-60	-36	21
White Go > White NoGo						
Anterior Cingulate Cortex / Presupplementary Motor Area	L/R	129	4.00	-6	15	39
Postcentral Gyrus	L	72	3.90	-51	-21	54

3. Intentional versus externally driven inhibition

In order to examine the effect of the number of preceding green trials on intentional inhibition decision outcomes, a parametric analysis of the number of preceding green trials was performed on the contrast intentional inhibition > intentional action (White NoGo > White Go). This analysis revealed stronger activation in dFMC, left IFG pars orbitalis, left IFG pars triangularis, and right SFG when there were fewer preceding green trials ($p < .001$ unc.) (see Figure 5 and Table 3). ROI analysis of dFMC, left IFG pars orbitalis, and left IFG pars triangularis showed increased activation for the contrast intentional inhibition > intentional action when there were 0 or 1 preceding green trials and deactivation when there were 2 or 3 preceding green trials (see Figure 5 and Table 3). For dFMC contrast values were significantly different from zero when there were 0 or 3 preceding green trials (all p's < .05). For left IFG pars orbitalis and pars triangularis contrast values were significantly different from zero when there were 0 preceding green trials (all p's < .05).

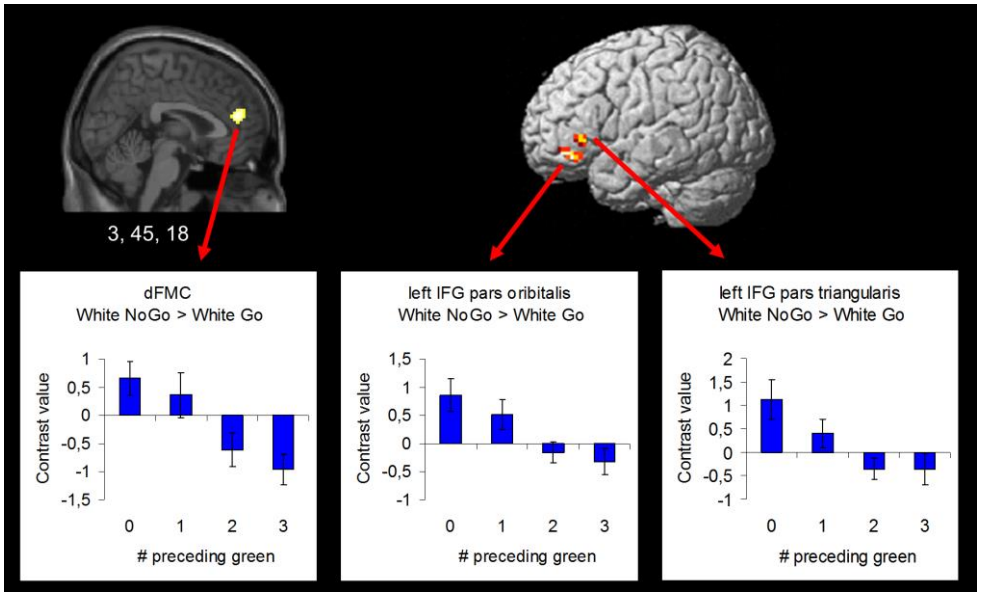

Figure 5: Brain regions showing more intentional inhibition decision outcome related activation when there are less preceding green trials (uncorrected $p < .001$, at least 10 contiguous voxels): dFMC (3, 45, 18), left IFG pars orbitalis (-42, 39, -12), and left IFG pars triangularis (-48, 30, 0).

Table 3. Brain regions revealed by the parametric whole brain analysis on the contrast White NoGo > White Go (thresholded $p < .001$ uncorrected, > 10 voxels).

Anatomical region	L/R	K	Z	MNI coordinates		
				x	y	z
Dorsal Frontomedian Cortex	L/R	79	4.28	3	45	18
Inferior Frontal Gyrus	L	34	3.90	-42	39	-12
Inferior Frontal Gyrus	L	17	3.67	-48	30	0
Superior Frontal Gyrus	R	10	3.51	21	33	54

Stop-Signal task. To identify the brain regions underlying the stimulus-driven inhibition decision process the contrast stop successful > go successful was computed. This analysis revealed activation in a widespread neural network (see Figure 6) consisting of bilateral IFG, bilateral MFG, bilateral SFG, bilateral STG, bilateral IPL, preSMA/ACC, and occipital lobe (see Figure 6A and Table 4).

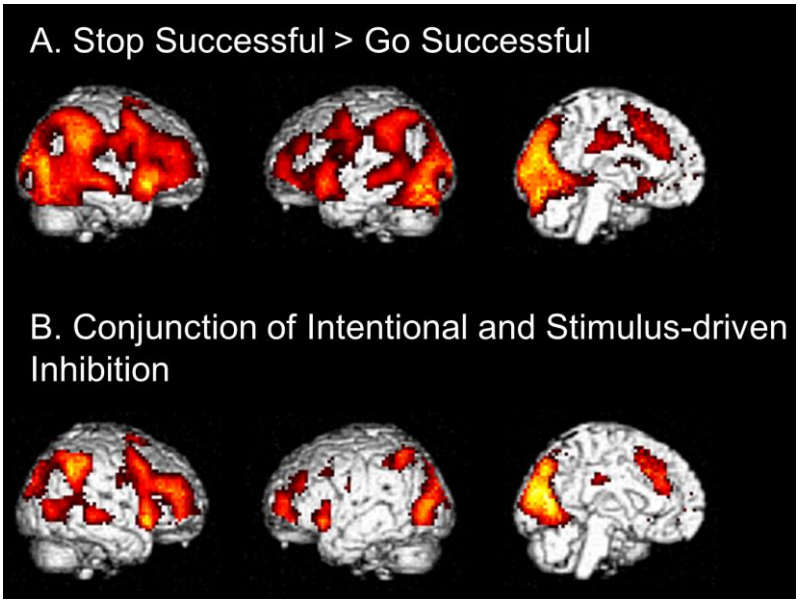

Figure 6: A. Whole brain contrast showing activation related to stimulus-driven inhibition process (Stop Successful > Go Successful) (FDR-corrected $p < .05$, at least 10 contiguous voxels). **B.** Conjunction analysis showing overlapping activation in intentional inhibition process (White NoGo > Green Go) and stimulus driven inhibition process (Stop Successful > Go Successful) (FDR-corrected $p < .05$, at least 10 contiguous voxels).

Comparison between intentional and stimulus-driven inhibition. Visual inspection of the intentional inhibition decision process contrast (Figure 3A) and the stimulus-driven inhibition decision process contrast (Figure 6A) suggested that there is considerable overlap in the neural networks underlying both inhibition decision

processes, although the activation in the stimulus-driven inhibition contrast appears to be more extensive. In order to formally compare the neural networks underlying the intention inhibition decision process and the stimulus-driven inhibition decision process a conjunction analysis was performed. This analysis confirmed the considerable overlap in brain regions underlying both inhibition decision processes by revealing significant overlapping activation in bilateral IFG, bilateral MFG, left SFG, right STG, bilateral IPL, preSMA/ACC, and occipital lobe (see Figure 6B and Table 4).

Table 4. Brain regions revealed by whole brain contrasts taking together intentional and stimulus-driven inhibition (all FDR corrected, $p < .05$, > 10 voxels).

Anatomical region	L/R	K	Z	MNI coordinates		
				x	y	z
Stop Successful > Go Successful						
Lingual Gyrus	L	18667	6.44	-21	-57	-6
Occipital Lobe	R		6.28	27	-72	-12
Insula	R		5.72	30	18	-12
Cuneus	R		5.70	15	-96	15
Occipital Lobe	L		5.67	-30	-66	-9
Insula	R		5.51	42	12	-9
Lingual Gyrus	R		5.42	27	-60	-6
Calcarine Gyrus	L		5.40	-6	-96	3
Inferior Parietal Lobe	R		5.25	48	-42	39
Middle Frontal Gyrus	R		5.17	36	45	21
Superior Temporal Gyrus	R		5.15	54	-24	-3
Caudate	R	22	3.07	12	-3	15
Caudate	L	14	2.55	-12	0	15
Conjunction Intentional and Stimulus-Driven Inhibition						
Occipital Lobe	L/R	4778	5.86	-45	-81	3
Middle Frontal Gyrus	L/R	2519	5.82	36	45	21
Middle Frontal Gyrus	L	311	4.66	-30	60	18
Inferior Frontal Gyrus / Insula	L	221	4.15	-36	18	-9
Middle Cingulate Cortex	L/R	51	3.19	-3	-21	33
Middle Frontal Gyrus	L	19	2.96	-51	18	39
Postcentral Gyrus	L	12	2.90	-63	-6	24

3.4 Discussion

The present study tested the neural correlates of intentional and stimulus-driven inhibition, using the marble task and the stop signal task. The analyses resulted in four main effects: (1) both intentional action and intentional inhibition decisions resulted in a large network of activation including the lateral prefrontal cortex, parietal cortex and preSMA, regions previously referred to as the intentionality network (Lau, et al., 2004; van Eimeren et al., 2006). (2) A parametric analysis of preceding context effects

showed activation in dFMC and left IFG during intentional inhibition to decrease as the number of preceding green (Go) trials increased. (3) Conjunction analysis confirmed that the intentionality network showed large overlap with the stimulus-driven inhibition network. (4) Although the side-by-side comparison shows that intentional inhibition and stimulus-driven inhibition show overlap in networks of activation, intentional inhibition and stimulus-driven inhibition are not directly comparable as shown by behavioral correlation analysis. Participants, who perform well on the intentional inhibition task, do not necessarily perform well on the stimulus-driven inhibition task. Thus, despite the overlap in networks of activation, behavioral performance on the intentional and stimulus-driven inhibition tasks is not predictive of each other. Below, we discuss these findings in relation to our hypotheses.

First, we aimed to replicate prior studies demonstrating that intentional action decisions are associated with increased activation in lateral and medial (ACC/preSMA) prefrontal cortex. Indeed, the contrast intentional action versus stimulus-driven action (white versus green marble Go responses) confirmed that this network was largely engaged, consistent with prior studies in the literature on intention action (Lau, et al., 2004; van Eimeren, et al., 2006). The same network was engaged in intentional inhibition decisions where we compared intention inhibition with stimulus-driven actions, further confirming the notion that this network is important for intentionality, and not for motor planning per se (Lau, et al., 2004). This is in line with previous literature showing overlapping neural regions for inhibition and action, both when inhibition and action are internally driven (Karch et al., 2009) and when inhibition and action are externally driven (Mostofsky & Simmonds, 2008).

Secondly, we tested whether there were brain regions uniquely related to the intentional inhibition decision outcome by contrasting intentional inhibition with intentional action. A network of brain regions was active for intentional inhibition compared to intentional action including bilateral IPL and left IFG, suggesting that the inhibition process cannot be reduced to intentionality per se (Karch, et al., 2009; Kühn & Brass, 2009). We also observed widespread activation in the occipital lobe during intentional inhibition. This is most likely due to differences between conditions with respect to the continued marble movement in the intentional inhibition versus the intentional action trials.

Contrary to prior findings by Kühn et al. (2009), we observed no dFMC activation in this general contrast. We then explored effects of preceding context using parametric analyses. We showed that dFMC activation during intentional inhibition depended strongly on the number of preceding green trials (note that these results are based on an uncorrected threshold of .001, > 10 contiguous voxels). At the behavioral level we also observed an effect of preceding context, such that participants were less likely to intentionally inhibit when there were more preceding green trials. Furthermore, we showed that when participants intentionally decided to act, reaction times were fastest when there were more preceding green trials. Together, these behavioral results are indicative of the formation of a disposition to act rather than inhibit, possibly reflecting an automatic associative mechanism in action generation (Perruchet, Cleeremans, & Destrebecqz, 2006). A run of preceding actions during

green trials may progressively contribute to a predisposition to decide to act, as opposed to inhibit, on intentional white trials. This appears to reflect a positive reinforcement association for the decision to act rather than inhibit (Perruchet, et al., 2006). At the neural level we showed that dFMC does show activation related to intentional inhibition, but only when following a short run of preceding instructed actions (green trials), and not following longer runs of instructed actions. Thus, veto-related activation appears to be stronger when participants are less established in a mode of prepotent responding, or set to act, to external instructive stimuli. This notion is further supported by the observation of not only increased dFMC, but also increased left IFG activation during intentional inhibition following shorter but not longer runs of preceding instructed action trials (green trials). Left IFG, like its right-hemisphere counterpart, may be critically involved in response inhibition (Leung & Cai, 2007; Swick, Ashley, & Turken, 2008).

The results of the parametric analysis shed important light on the role of dFMC in intentional inhibition, and on the significance of intentional inhibition more generally. Briefly, we found dFMC activation was reduced when previous trials had created a prepotent urge to act. Our design differs from the original free-choice whether decision of Brass and Haggard (2007), by including a large proportion of randomly-interleaved instructed action trials. These were included with the express intention of inducing a prepotent urge to act. When the prepotent urge to act is present, we reasoned that intentional inhibition should operate as a late brake on action preparation, rather than simply an early pre-decision not to initiate any action preparation at all. Interestingly, our results suggest that prepotent action also makes intentional inhibition less likely, and reduces the activation in brain areas associated with intentional inhibition. Taken together, these findings suggest that motor drive and intentional inhibition are reciprocal and antagonistic influences, analogous to the competitive interaction thought to occur between alternative response options (Cisek, 2007).

This reciprocal antagonism corresponds to the common intuition that inhibition of action is harder when the drive to act is strong – for example in cases such as craving and addiction. Interestingly, these are exactly the circumstances when intentional inhibition may also be most necessary. It may also explain why we did not find dFMC activation in our main contrast, while previous studies that did not use instructed action trials to enforce a prepotent urge to act did (Brass & Haggard, 2007).

Third, a side-by-side comparison between the intentional and the stimulus driven tasks was made. Stimulus driven inhibition resulted in the expected network of activation, including the right IFG and pre-SMA (Aron, 2011; Aron, et al., 2004; Chikazoe, 2010; Forstmann, van den Wildenberg, & Ridderinkhof, 2008; Jahfari, et al., 2011). This network was highly comparable to the network involved in intentional inhibition, confirming that the two types of inhibition share commonalities. Both intentional and stimulus-driven inhibition require one to refrain from responding, therefore it is likely that the right IFG/pre-SMA network is important for the motoric aspect of inhibition (Chikazoe, 2010). Despite the similarities in underlying neural networks, behavioral performance on the marble and stop-signal tasks was not correlated. However, it is not uncommon that different inhibition tasks correlate

poorly (Huizinga, et al., 2006), but exactly how and when intentional and stimulus-driven inhibition are dissociable on the individual level remains an important avenue for future research.

Some limitations of the present study deserve mention. First, the fact that two different tasks were used to measure intentional and stimulus-driven inhibition pre-empted the possibility to compute a direct contrast between intentional and stimulus-driven inhibition. Future research might benefit from using one single task to measure both forms of inhibition, to allow for such a direct contrast. Second, for the marble task we cannot completely rule out the possibility that participants have pre-decided not to initiate an action on the intentional inhibition trials, instead of deciding in the instant to inhibit an already initiated action. The observed pattern of results showing that intentional inhibition was less likely following a run of instructed action trials, suggests that this was not the case. However, future research could shed more light on this issue, for instance by including electromyography measures to ascertain that the initial action initiation is also present in intentional inhibition trials.

Taken together, this study was the first to test the neural correlates of intentional and stimulus-driven inhibition within the same subjects. The results confirmed the hypothesis that these two types of inhibition rely on the same neural network including lateral PFC and preSMA, regions previously associated with intentionality (Lau, et al., 2004; van Eimeren, et al., 2006). The results also demonstrated additional activation for intentional inhibition compared to intentional action in bilateral IPL and preSMA, suggesting that the inhibition process cannot be reduced the intentionality per se (Karch, et al., 2009; Kühn & Brass, 2009). Finally, the results showed that activation in dFMC, previously observed in other intentional inhibition studies, is dependent on specific task demands, such as prepotency of responding. Several open questions remain for how intentional inhibition relates to individual differences in self-control and self-regulation. For example, Casey et al. (2011) recently showed that individuals who can intentionally inhibit impulses to respond to immediate reward have better response inhibition associated with more lateral prefrontal cortex activation 40 years later. One of the key questions for future research is how motivational tendencies may influence internal drives to veto one's own actions when necessary.

Chapter 4

A medial-lateral distinction for intentional versus externally guided action control: Evidence from a combined heart rate and fMRI study.

This chapter is in preparation as:
Schel, M.A., van der Molen, M.W., & Crone, E.A. (in prep). A medial-lateral distinction for intentional versus externally guided action control: Evidence from a combined heart rate and fMRI study.

4. A medial-lateral disctinction for intentional versus external action control

Abstract

Externally and internally guided action control processes are associated with changes in both central (neural) and autonomic (heart rate) responses, but commonalities between these systems are not well understood. The present study aimed to integrate the study of heart rate and neural changes in one experiment in order to examine the role of a central autonomic network in intentional and externally guided action control. The results showed that heart rate deceleration during externally guided action control was associated with lateral PFC activation, whereas heart rate deceleration during intentional action control was associated with medial frontal cortex activation. The latter was observed for both intentional action and intentional inhibition events. Together, the results indicate that heart rate deceleration during action control is an integral part of the central autonomic network, which shows a medial/lateral distinction for intentional versus externally guided action control.

4.1 Introduction

The ability to exercise control over our actions is an important part of successful functioning in daily life. Action control can be guided both externally, such as when a traffic light turns red, and internally, such as when controlling the urge to scratch an itchy mosquito bite. The latter process is referred to as intentional inhibition, which can be defined as a late veto opportunity (Brass & Haggard, 2007; Filevich, et al., 2012). A host of literature has indicated that externally guided inhibition is associated with heart rate deceleration (e.g. Börger & van der Meere, 2000; van Boxtel, et al., 2001; Van der Veen, et al., 2000). Recently, heart rate deceleration has been shown to also be a sensitive index for intentional inhibition (Schel, Windhorst, van der Molen, & Crone, 2013). Together, these studies suggest the involvement of a central autonomic network in external and intentional action control, but how central and autonomic responses are related in externally and internally guided control is not well understood.

To date, most research on the neural correlates of externally versus internally guided action control has focused on intentional action selection (for a review, see Brass & Haggard, 2008). Within this domain, previous research has suggested a medial-lateral distinction for internally vs. externally guided action control, with internally guided action selection being associated with activation in medial frontal cortex and externally guided action selection being associated with activation in lateral prefrontal cortex (Brass & Haggard, 2008; Goldberg, 1985; Krieghoff, Waszak, Prinz, & Brass, 2011). The evidence for intentional inhibition is less clear. Some studies have found activation in dorsal medial frontal cortex for intentional inhibition (Brass & Haggard, 2007; Kühn, et al., 2009). However, others reported activation during intentional inhibition in lateral prefrontal cortex, in regions similar to those involved in externally guided inhibition (Schel et al., 2014).

The present study aimed to examine the involvement of a central autonomic network in intentional and externally guided action control. For this means, participants performed an action control task in the MRI scanner, while their heart rate was measured continuously. Externally guided action trials were presented intermixed with intentional action control trials, where participants could choose between acting and inhibiting. We expected to observe heart rate deceleration during intentional compared to externally guided action control (Schel, et al., 2013). Furthermore, for intentional action control we expected to find a relation between heart rate responsiveness and activation in medial frontal cortex, and for externally guided action control between heart rate responsiveness and activation in lateral prefrontal cortex (Krieghoff, et al., 2011).

4.2 Method

Participants

Twenty-four healthy right-handed adults between 18-26 years of age participated in the experiment. Eight participants were excluded from all data analysis because of

poor quality heart rate data, caused by scanner artifacts. For these participants, it was not possible to distinguish R-waves from noise. However, when analyzing the fMRI data for the complete sample (N = 24) and for the final sample (N = 16), there were no differences in activation patterns, suggesting that the noisy heart rate measures were not associated with differences in neural activation. The final sample consisted of sixteen adults between 18-26 years of age (8 females, M = 21.82, SD = 2.43). All participants had normal or corrected-to-normal vision, and no neurological or psychiatric impairments according to self-report. Before participating in the experiment, all participants signed informed consent. All anatomical scans were reviewed by a radiologist. No anomalous findings were reported.

To obtain an estimate of cognitive functioning participants completed two subtests of the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1981a); similarities and block design. Estimated IQ scores were within the normal range (M = 112, SD = 7.03).

The behavioral and fMRI results of the complete sample (N = 24) have been published separately in a study comparing intentional and externally guided inhibition (Schel et al., 2014).

Task

The marble task was adapted from Kühn et al. (2009), and optimized for heart rate recording (Schel, et al., 2013). Each trial started with the presentation of a fixation-screen, jittered between 1400 and 2000 ms. Hereafter, a white marble on top of a ramp was shown, which started to roll down and changed color to green after a variable duration of 1400 to 2000 ms. Participants were instructed to respond to the rolling green marble to prevent it from crashing (externally guided action). Intermixed with the green marble trials, trials in which the marble remained white were presented during which participants were free to choose between responding (intentional action) and inhibiting responding (intentional inhibition) to the rolling marble. The experiment consisted of three blocks of 80 (48 green, 32 white) trials each (see Schel, et al., 2014 for further task details (chapter 3)).

fMRI Data Acquisition

Scanning was performed with a standard whole-head coil on a 3.0 Tesla Philips scanner at the Leiden University Medical Center. Functional data were acquired using T2*-weighted echo-planar imaging (EPI). The first 2 volumes of each run were discarded in order to allow for equilibration of T1 saturation effects (TR = 2.2 sec, TE = 30 msec, sequential acquisition, 38 slices of 2.75 mm, field of view 220 mm, 80 x 80 matrix, in-plane resolution 2.75 mm). After the functional runs a high-resolution 3D T1-FFE scan for anatomical reference was obtained (TR = 9.760 ms; TE = 4.59 ms, flip angle = 8 degrees, 140 slices, 0.875 × 0.875 × 1.2 mm^3 voxels, field of view = 224 × 168 × 177 mm^3). Head motion was restricted by using foam inserts between the head and the head coil. Visual stimuli were projected onto a screen in the magnet bore that could be viewed through a mirror attached to the head coil.

Heart Rate Data Acquisition and Analysis

During scanning, the electrocardiogram (ECG) was measured continuously using the MRI-compatible Biopac System at a sample frequency of 5000 Hz. The ECG was recorded from three AgAg/Cl electrodes, attached directly around the heart. Inter Beat Intervals (IBIs) were defined as the length between consecutive R-peaks. The R-peaks were detected with the program Physiospec (developed by Van Beek, Developmental Psychology, UvA). The recorded IBIs were manually screened for physiologically impossible readings and artifacts (i.e. R-peaks not detected or other peaks seen as R-peaks). These were corrected by adjusting specific parameters in the program that extracted the IBIs from the digitized ECGs.

Five consecutive IBIs were selected around the onset of marble motion; the IBI concurrent with the onset of marble motion (IBI 0), two IBIs preceding the onset of marble motion (IBI -2 and IBI -1), and two IBIs following the onset of marble motion (IBI 1 and IBI 2). In order to obtain an index of phasic heart rate change (IBI difference) IBIs were referenced to IBI-2. Thus, we analyzed the differences scores relative to IBI -2 for IBI -1, IBI 0, IBI 1 and IBI 2. Analyses of IBI-2 revealed no significant differences in IBI length between the different test conditions, confirming that there were no a priori differences between these conditions reflected in heart rate. Statistical analyses were performed using repeated measures ANOVA. Huynh-Feldt corrections for violations of the assumption of sphericity were used when necessary (Jennings, 1987; Vasey & Thayer, 1987).

fMRI Data Analysis

Data were preprocessed using SPM8 (Wellcome Department of Cognitive Neurology, London). Images were corrected for rigid-body motion. Structural and functional volumes were spatially normalized to T1 templates. The normalization algorithm used a 12-parameter affine nonlinear transformation involving cosine basis functions, and then resampled the volumes to 3-mm cubic voxels. Translational movement parameters never exceeded 1 voxel (< 3mm) in any direction for any subject or scan. Templates were based on the MNI305 stereotaxic space (Cocosco, et al., 1997), an approximation of Talairach space (Talairach & Tournoux, 1988). Functional volumes were spatially smoothed with an 8-mm full-width-at-half-maximum isotropic Gaussian kernel. Statistical analyses were performed on individual participants' data using the general linear model in SPM8. The fMRI time series data were modeled by a series of events convolved with a canonical hemodynamic response function (HRF) and the temporal derivatives. The onset of marble motion of each trial was modeled as an event of interest. Separate regressors were defined for white nogo (intentional inhibition), white go (intentional action), green go (stimulus-driven action), and green omissions (omission on the green marble trials). The trial functions were used as covariates in a general linear model, along with a basic set of cosine functions to high-pass filter (120 Hz) the data. The least-squares parameter estimates of the height of the best-fitting canonical HRF for the different conditions were used in pair-wise contrasts.

To examine the relationship between heart rate and neural activation, IBI differences scores were added as regressors to the whole-brain regression analyses. All

reported correlations between heart rate and neural activation consisted of at least 10 contiguous voxels at an uncorrected threshold of $p < .001$. The reason for setting this threshold was because we had a priori hypotheses on which brain regions (lateral and medial PFC) were of interest in this study and to avoid Type II errors, because detecting individual correlations requires more power than group analyses (see also Lieberman & Cunningham, 2009). Region of interest (ROI) analyses were performed to visualize the relationship between heart rate and neural activation and to examine the specificity of the relationship between heart rate and neural activation for externally guided versus intentional action control. ROI analyses were performed with the MarsBaR toolbox in SPM8 (Brett, et al., 2002) (http://marsbar.sourceforge.net).

4.3 Results

Behavior

Participants responded in time to the green marble on 65.02 % (*SD* = 6.79) of the trials, and decided to intentionally inhibit responding to the white marble on 44.99 % (*SD* = 8.38) of the trials.

Participants were substantially slower to respond to the white (*M* = 359, *SD* = 68) compared to the green (*M* = 294, *SD* = 21) marble trials, $F(1, 15) = 21.72$, $p < .001$, indicating that the decision process on the white marble trials took longer.

Heart Rate

IBIs were computed separately for the externally guided green go condition and the intentional white go and white nogo conditions. To test for differences in heart rate responses between the three different conditions, a Condition (3: green go, white go, white nogo) x IBI (4: IBI -1 to IBI 2) repeated measures ANOVA was performed. A main effect of IBI was observed, $F(3, 51) = 7.78$, $p < .01$, indicating that heart rate decelerated in anticipation of marble movement (onset during IBI 0), followed by an acceleratory recovery (see Figure 1). A Condition x IBI interaction, $F(6, 102) = 11.13$, $p < .001$, indicated that heart rate responses differed between the different conditions. Follow-up repeated measures ANOVAs on IBI 1 (during which participants decided between acting and inhibiting), showed that heart rate deceleration was less pronounced for the externally guided green go condition compared to both the intentional white go condition, $F(1, 15) = 20.10$, $p < .001$, and the intentional white nogo condition, $F(1, 15) = 25.98$, $p < .001$. Finally, heart rate deceleration was more pronounced for the intentional white nogo compared to the intentional white go condition, $F(1, 15) = 6.37$, $p < .05$.

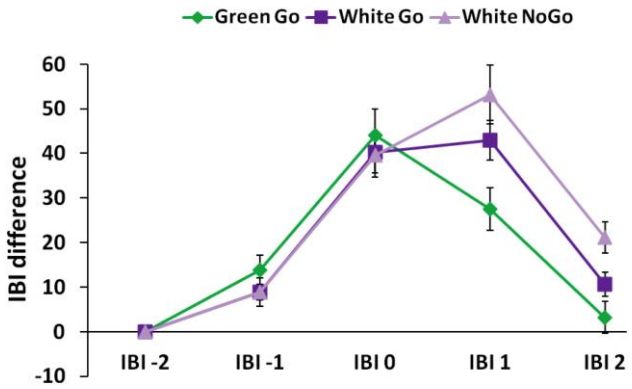

Figure 1: Stimulus-locked heart rate changes associated with externally guided action (Green Go), intentional action (White Go) and intentional inhibition (White NoGo). IBI 0 refers to the IBI during which the marble started to roll down the ramp. An increase in IBI difference scores indicates heart rate deceleration, and a decrease in IBI difference scores indicates heart rate acceleration.

Heart Rate and fMRI correlations

In order to examine the relation between heart rate deceleration and neural activation during action control, whole-brain regression analyses with IBI 1 difference scores as regressors were performed on the three conditions (green go, white go and white nogo) versus fixation baseline (null). The reason for focusing on the conditions versus fixation baseline was because condition versus baseline typically has higher reliability and is not contaminated by individual differences in "control condition" responsiveness (see Ordaz, Foran, Velanova, & Luna, 2013).

For externally guided action (the green go condition), average IBI 1 difference scores were added as a regressor to the contrast green go > null. This analysis revealed activation in right lateral prefrontal cortex (lateral PFC) and right paracentral lobe (see Figure 2A and Table 1). A ROI analysis showed that right lateral prefrontal cortex was more active for individuals who showed stronger heart rate deceleration during externally guided action (see Figure 2D).

For intentional action (the white go condition), average IBI 1 difference scores were added as a regressor to the contrast white go > null. This analysis revealed activation in medial frontal cortex and supplementary motor area (SMA) (Figure 2B, see Table 1 for a full list of active areas). A ROI analysis showed that medial frontal cortex was more active for individuals who showed stronger heart rate deceleration during intentional action (see Figure 2H).

Finally, for intentional inhibition (the white nogo condition) average IBI 1 difference scores were added as a regressor to the contrast white nogo > null. This analysis also revealed activation in medial frontal cortex (Figure 2C, see Table 1 for a full list of areas). A ROI analysis showed that medial frontal cortex was more active for individuals who showed stronger heart rate deceleration during intentional inhibition (see Figure 2L).

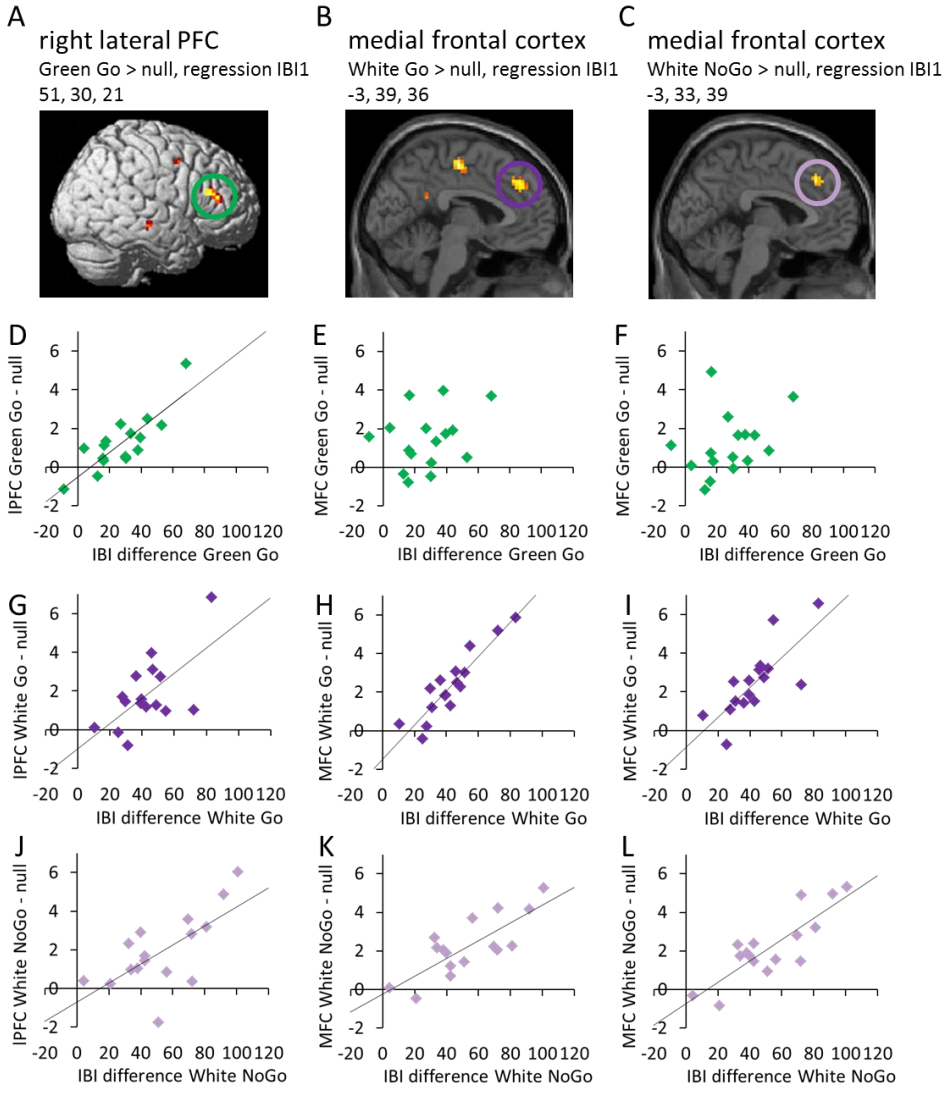

Figure 2: Whole brain regression analyses showing relation between heart rate deceleration and neural activation for: **A.** externally guided action (Green Go), **B.** intentional action (White Go) and **C.** intentional inhibition (White NoGo) (uncorrected $p < .001$, at least 10 contiguous voxels). **D-L.** Associations between heart rate deceleration and neural activation for the different task conditions. Trendlines are added for significant correlations.

Table 1. Brain regions revealed by whole-brain regression analyses (all $p < .001$ uncorrected, > 10 voxels).

Anatomical region	L/R	K	Z	MNI coordinates		
				x	y	z
Green Go > null, regression IBI 1						
Paracentral Lobe	r	14	3.88	9	-27	63
Lateral PFC (IFG)	r	28	3.83	51	30	21
White Go > null, regression IBI 1						
Supplementary Motor Area	l	100	4.80	-3	-18	54
Superior Frontal Gyrus	l	38	4.16	-21	21	39
Para Hippocampal Area	l	22	4.16	-15	-12	-24
Medial Frontal Cortex (SMG)	l	40	4.15	-3	39	36
Anterior Cingulate Cortex	r	29	4.00	9	36	12
Posterior Cingulate Cortex	l	11	3.03	0	-48	27
Inferior Parietal Lobe	l	20	3.83	-48	-33	45
Amygdala	l	17	3.81	-30	3	-18
Hippocampus	l	18	3.73	-18	-24	-12
Superior Frontal Gyrus	l	11	3.73	-18	54	6
Occipital Lobe	l	13	3.66	-48	-72	-9
Supplementary Motor Area	r	15	3.65	9	24	48
Middle Temporal Gyrus	r	10	3.64	45	-36	3
Precentral Gyrus	r	10	3.49	54	3	24
White NoGo > null, regression IBI 1						
Amygdala	l	41	4.43	-30	3	-21
Para Hippocampal Area	r	42	4.41	18	-30	-12
Occipital Lobe	l	11	4.12	-15	-66	39
Medial Frontal Cortex (SMG)	l	34	4.03	-3	33	39
Inferior Parietal Lobule	l	30	3.95	-51	-36	42
Superior Temporal Gyrus	r	10	3.67	66	-15	12

In order to examine the specificity of the relationship between heart rate deceleration and neural activation for externally guided versus intentional action control in lateral and medial prefrontal cortex, we performed additional ROI analyses. For the ROI in right lateral PFC, which was taken from the regression analysis for externally guided action, values for intentional action and intentional inhibition were extracted. Intentional action related activation in this area correlated with IBI 1 difference scores for intentional action ($r = .637$, $p < .01$) (see Figure 2G), and intentional inhibition related activation in this area correlated with IBI difference scores for intentional inhibition ($r = .670$, $p < .01$) (see Figure 2J). For the ROI in medial frontal cortex, which was taken from the regression analysis for intentional action, values for externally guided action and intentional inhibition were extracted. Externally guided action activation in this area did not correlate with IBI 1 difference

scores for externally guided action ($p > .2$) (see Figure 2E), whereas intentional inhibition related activation in this area did correlate with IBI 1 difference scores for intentional inhibition ($r = .778$, $p < .001$) (see Figure 2K). Finally, for the ROI in medial frontal cortex, which was taken from the regression analysis for intentional inhibition, values for externally guided action and intentional action were extracted. Externally guided action activation in this area did not correlate with IBI 1 difference scores for externally guided action ($p > .2$) (see Figure 2F), whereas intentional action related activation in this area did correlate with IBI 1 difference scores for intentional action ($r = .771$, $p < .001$) (see Figure 2I). Taken together, these results show specificity of the relation between heart rate deceleration and neural activation in medial frontal cortex for intentional action control (i.e. both intentional action and intentional inhibition), but not for the relation between heart rate deceleration and neural activation in right lateral PFC for externally guided control.

4.4 Discussion

The present study was the first to examine the role of a central autonomic network in intentional and externally guided action control in a combined neuroimaging and heart rate study. In line with our previous heart rate study outside the scanner (Schel, et al., 2013), the heart rate results showed a pronounced heart rate deceleration during both intentional action and inhibition decisions, indicating that heart rate is sensitive to intentional decisions. Furthermore, the results showed that heart rate deceleration during intentional action control was associated with activation in medial frontal cortex, whereas heart rate deceleration during externally guided action control was associated with activation in right lateral PFC. Here we will discuss these findings vis-à-vis recent hypotheses about the functioning of the central autonomic network and the relation between heart rate responses and neural activation.

In this study both intentional and externally guided action control involved activation of a central autonomic network. However, the implementation of this central autonomic network differed between intentional and externally guided action control. On the autonomic level, the results showed that both intentional and externally guided action control are associated with heart rate deceleration. There was however a difference in the level of autonomic responsiveness, such that heart rate deceleration was more pronounced for intentional compared to externally guided action control. On the central level, the results showed that the association between heart rate deceleration and neural responsiveness differed between intentional and externally guided action control, such that for intentional action control the association was observed in medial frontal cortex and for externally guided action control the association was observed in right lateral PFC. These results are in line with previous research suggesting a medial/lateral distinction for intentional versus externally guided action control (Brass & Haggard, 2008; Goldberg, 1985; Krieghoff, et al., 2011). However, the ROI analyses suggest that this distinction is only partial. That is, for externally guided action control heart rate deceleration is associated with activation in right lateral PFC, whereas for intentional action control (both intentional

action and intentional inhibition) heart rate deceleration is associated with activation in medial frontal cortex, but also in right lateral PFC. These results extent previous findings by showing that regions in lateral PFC are also important for intentional action control (Karch, et al., 2009; Orr & Banich, 2014).

The present study was one of the first to examine the relationship between parasympathetic mediated heart rate deceleration and neural activation during a cognitive task. Previous studies examining the relation between parasympathetic mediated heart rate changes and neural activation have mainly looked at physical tests, such as a handgrip exercise (Norton, Luchyshyn, & Kevin Shoemaker, 2013; Wong, Masse, Kimmerly, Menon, & Shoemaker, 2007). These studies have shown ventromedial PFC (vmPFC) to be important in modulating heart rate (Norton, et al., 2013; Wong, et al., 2007). This vmPFC region is more ventral compared to the medial frontal cortex region, which we have found to be associated with heart rate deceleration during intentional action control. Interestingly, this region in medial frontal cortex is close to the midcingulate cortex region found to be associated with sympathetic regulation in a large meta-analysis on the central processing of autonomic function (Beissner, Meissner, Bar, & Napadow, 2013). In contrast, the lateral PFC region, which was associated with heart rate deceleration during externally guided action control, has not been previously implicated in parasympathetic cardiac control. Besides the medial frontal cortex being important in the central autonomic network for intentional action control, the left amygdala was also found to be associated with heart rate deceleration during intentional action control (both intentional action and intentional inhibition). Previous research has found the amygdala to be one of the key regions via which the prefrontal cortex influences heart rate (Thayer & Lane, 2009), both for sympathetic and parasympathetic regulation (Beissner, et al., 2013). However, the left amygdala was not found to be associated with heart rate deceleration during externally guided action control.

Some limitations of the present study deserve mentioning. First, due to scanner artifacts on the heart rate date, the final sample size of the current study was relatively small. Future studies should replicate these findings in a larger sample. Second, our paradigm did not include an externally guided inhibition condition, only externally guided action. It will be an interesting question for future research to examine the role of the central autonomic network in intentional versus externally guided inhibition.

To conclude, the present study examined the role of the central autonomic network in an action control task in a combined heart rate and neuroimaging study. The results of this study demonstrate a relation between autonomic responsiveness and neural activity in key brain regions for action control, and extent the existing literature by showing that heart rate deceleration during action control is an integrated part of the central autonomic network, dissociating between intentional and externally guided action control on a medial to lateral dimension (Krieghoff, et al., 2011).

Chapter 5
Choosing not to act: Neural bases of the development of intentional inhibition

This chapter is published as:
Schel, M.A., Ridderinkhof, K.R., & Crone, E.A. (2014). Choosing not to act: Neural bases of the development of intentional inhibition. *Developmental Cognitive Neuroscience, 10*, 93-103.

5. Development of intentional inhibition

Abstract
Choosing not to act, or the ability to intentionally inhibit your actions lies at the core of self-control. Even though most research has focused on externally primed inhibition, an important question concerns how intentional inhibition develops. Therefore, in the present study children (aged 10 to 12) and adults (aged 18 to 26) performed the marble task, in which they had to choose between acting on and inhibiting a prepotent response, while fMRI data were collected. Intentional inhibition was associated with activation of the fronto-basal ganglia network. Activation in the subthalamic nucleus and dorsal fronto-median cortex, regions which have previously been associated with intentional inhibition, did not differ between intentional inhibition and intentional action. Even though both children and adults intentionally inhibited their actions to a similar extent, children showed more activation in the fronto-basal ganglia network during intentional inhibition, but not in the subthalamic nucleus and dorsal fronto-median cortex. Furthermore, a positive relation between self-reported impulsivity and intentional inhibition was observed. These findings have important implications for our understanding of disorders of impulsivity, such as ADHD, which are associated with poor self-control abilities.

5.1 Introduction

Self-control abilities are of critical importance for successful functioning across the life span. A classical experiment to test self-control is the marshmallow experiment, a delay of gratification test for preschool children in which children can choose between one marshmallow now or two marshmallows later (Mischel, Shoda, & Rodriguez, 1989). Studies with the marshmallow experiment have shown that during the preschool ages there are large individual differences in the ability to control the immediate impulse to eat the first marshmallow and wait for the second marshmallow (Mischel et al., 1989) and experimental variations of this task have shown a developmental increase in controlling immediate impulses between childhood and adulthood (Christakou, Brammer, & Rubia, 2011; Lee et al., 2013; Scheres et al., 2006). These changes are accompanied by neurodevelopmental changes. Recently, it has been shown that individuals who were less able to delay gratification when they were preschoolers, showed poorer self-control and reduced recruitment of the fronto-basal ganglia network during a response inhibition task in adulthood (Casey et al., 2011).

An important distinction which has been made in tasks that involve self-control, is whether the inhibitory process is externally or internally driven. Externally driven response inhibition involves the ability to interrupt an action when signaled by a cue in the environment, for example, a traffic light which turns red. Neuroscientific studies have shown that the fronto-basal ganglia network, with main nodes in right inferior frontal gyrus (rIFG), striatum, globus pallidus, and subthalamic nucleus (STN), is consistently involved during externally driven response inhibition (e.g. Aron, Behrens, Smith, Frank, & Poldrack, 2007; Aron & Poldrack, 2006; Forstmann et al., 2012; Jahfari et al., 2011; King et al., 2012). Developmental studies have also found evidence for the involvement of the fronto-basal ganglia network in externally driven response inhibition in children (Cohen et al., 2010; Ordaz, Foran, Velanova, & Luna, 2013). So far, most developmental neuroimaging studies have focused on the frontal component of the fronto-basal ganglia network, namely the rIFG (Luna, Padmanabhan, & O'Hearn, 2010). These studies have reported both increases (e.g. Ordaz et al., 2013; Rubia, Smith, Taylor, & Brammer, 2007) and decreases (e.g. Booth et al., 2003; Durston et al., 2002) in inhibition related rIFG activation with age, but an age-related increase in rIFG activation and a decrease in activation in task-unspecific frontal regions appears to be the most common pattern (Crone & Dahl, 2012; Durston et al., 2006; Luna et al., 2010). Overall, these studies show a stabilization of response inhibition performance and its underlying neural correlates during adolescence (Luna et al., 2010).

A second, but understudied component of self-control is intentional inhibition. In daily life often both external cues and internal processes play a role in the decision to inhibit, although sometimes external cues are more important (such as when stopping at a traffic light) and other times internal processes are more prominent (such as when inhibiting yourself from taking another piece of chocolate). However, in contrast to externally driven inhibition, intentional inhibition is not triggered by an external cue. Instead, intentional inhibition has been defined as a late internally driven veto process, a final opportunity to inhibit before action execution

(Brass & Haggard, 2008; Filevich, Kühn, & Haggard, 2012; Haggard, 2008). Since intentional inhibition is not preceded by any external stimulus, and does not result in any overt behavior, intentional inhibition has proven difficult to investigate. Yet, this type of inhibition is involved in many of our day to day activities such as inhibiting yourself from taking another piece of chocolate, inhibiting pressing the send button when being on the verge of sending an angry email, or inhibiting scratching itchy skin caused by eczema. Delay of gratification studies have reported developmental improvements in the ability to intentionally inhibit the impulse to choose an immediate reward (Christakou et al., 2011; Lee et al., 2013; Scheres et al., 2006), but these tasks involve many different processes besides intentional inhibition, such as reward sensitivity and reward discounting. A neuroscience perspective can provide important insights into the development of intentional inhibition, as this provides a covert measure of a process, which occurs without a specific stimulus and without any behavioral outcomes. An important question concerns whether intentional inhibition is guided by the same neural network as externally driven inhibition, or whether intentional inhibition is associated with different underlying neural circuitry, which may develop during child and adolescent development.

In the present study, we used the child-friendly marble paradigm to examine the neural correlates of intentional action and inhibition in children. In this paradigm participants are instructed to freely decide between responding and inhibiting responding to a rolling marble. Children between 10 to 12 years of age were included to allow for comparison of the results to the externally driven response inhibition literature (Booth et al., 2003; Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002; Durston et al., 2002; Rubia et al., 2007). Based on these prior findings, we expect to observe activation in the main nodes of the fronto-basal ganglia network (i.e. rIFG, striatum, globus pallidus, and STN) during intentional inhibition, comparable to what we have observed in adults (Schel et al., 2014). If developmental differences in internally driven inhibition share mechanisms with externally driven response inhibition (Bunge et al., 2002; Durston et al., 2002; Luna et al., 2010), then we may expect inhibition-related activation in the rIFG to be stronger for adults compared to children.

Recently, several studies have suggested that intentional inhibition is associated with increased activation in the dorsal fronto-median cortex (dFMC) (Brass & Haggard, 2007; Kühn, Haggard, & Brass, 2009), a region which was previously found to be more active in early adolescents when inhibiting a selfish impulse in a sharing task (van den Bos, van Dijk, Westenberg, Rombouts, & Crone, 2011). Therefore, we examined whether more activity in the dFMC during intentional inhibition was observed in children compared to adults based on prior studies showing that this region is more active in 10-12-year-olds (Blakemore, 2008; Gunther Moor et al., 2012; van den Bos et al., 2011).

In order to validate our experimental measure of intentional inhibition, participants also completed the Barratt Impulsiveness Scale (Patton, Stanford, & Barratt, 1995) outside of the scanner to obtain an estimate of impulsivity and self-control in daily life. We expect daily life impulsivity to be predictive of intentional action control performance.

5.2 Methods

Participants

Nineteen healthy right-handed children between 10-12 years of age (10 females, M = 11.56, SD = .83) and twenty-four healthy right-handed adults between 18-26 years of age (13 females, M = 21.49, SD = 2.36) participated in the experiment. The results from the adults have previously been published in a larger report on response inhibition (Schel et al., 2014). A chi-square test revealed no significant differences in gender distributions between age groups (p = .92). All participants had normal or corrected-to-normal vision, and no neurological or psychiatric impairments according to self- or parent-report. Informed consent was obtained for all participants and the study was approved by the Internal Review Board at Leiden University Medical Center. In accordance with the guidelines of the Leiden University Medical Center, all anatomical scans were reviewed by a radiologist. No anomalous findings were reported.

To obtain an estimate of cognitive functioning, children and adults completed the subtests similarities and block design of the Wechsler Intelligence Scale for Children (WISC) (Wechsler, 1981b) and the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1981a) respectively. Estimated IQ scores were within the normal range (children: M = 111.32, SD = 9.94, adults: M = 111.33, SD = 6.93) and age groups did not differ in estimated IQ scores, F (1,42) = .00, p = .99, $\eta^2 = 1.04^{-6}$.

Task

The marble task was adapted from Kühn and colleagues (2009). Each trial (see Figure 1) started with the presentation of a fixation screen (white cross against a black background) with duration jittered between 1400 and 2000 ms. The fixation screen was followed by a screen showing a white ramp with a white marble on top presented against black background. After a variable duration of 1400 to 2000 ms the marble started rolling down the ramp and participants could stop the marble from crashing by pressing a button. Finally, a feedback screen, showing trial outcome, was presented for 1000 milliseconds. There were two task conditions: a green marble and a white marble condition.

In the green marble condition, the white marble changed to green as soon as it started rolling. The task was programmed in such a way that participants viewed 16 rapidly presented static pictures showing the marble at successive locations on the ramp, which was experienced as a rolling movement. Participants were instructed to stop the marble from crashing by pressing a response button with their right index finger. When participants were successful at stopping the marble, they were presented with a feedback screen showing the location where they had stopped the marble. When participants were not successful at stopping the marble, they were presented with a feedback screen showing a shattered marble beneath the ramp. The speed of the marble was adjusted by a staircase-tracking procedure. At the start of the experiment, the static pictures were presented for 30 milliseconds each. When participants were successful at stopping the marble the duration was decreased with 10 milliseconds, making the task more difficult. When participants were not successful at

stopping the marble in time the duration was increased with 10 milliseconds, making the task easier. The staircase procedure was allowed to fluctuate between 20 and 80 milliseconds, allowing a response window between 320 and 1280 milliseconds.

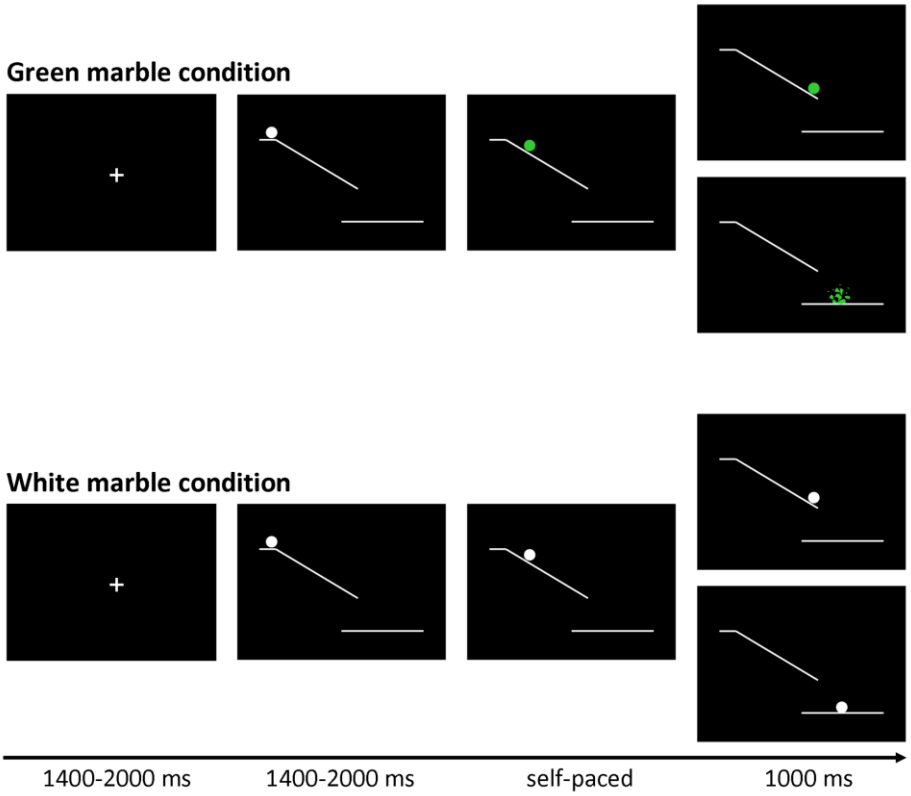

Figure 1. Trial structure of the marble task. Stimuli were presented at a black background. At the beginning of each trial a white marble on top of a ramp was presented. After a variable delay (jittered between 1400 and 2000 ms) the marble started to roll down the ramp, and could change color to green.

In the white marble condition, the marble did not change color and participants were instructed to choose between responding and inhibiting. When participants responded, they were presented with a feedback screen showing the location where they had stopped the marble. When participants inhibited, they were shown a feedback screen showing the white marble at the bottom of the ramp. In order to motivate participants to balance the frequency of responding and inhibiting, they were told that the stopped and non-stopped marbles would fall in different baskets. Participants were instructed to collect an equal amount of marbles in each basket, but were not allowed to count or use a sequencing strategy; therefore participants were instructed to make an independent decision every time the marble stayed white. At the end of each block participants were shown how many marbles they had collected in each basket. As will be described in the results section, the

participants were successful in following the instruction to stop the marble on approximately 50% of the trials.

In order to give participants sufficient time to decide between responding and inhibiting the speed of the white marble rolling down the ramp was set considerably slower. The speed of the sequentially presented static white marble pictures was set to the speed currently reached in the green marble condition plus 30 milliseconds. Consequently the duration of the sequentially presented static white marble pictures was allowed to fluctuate between 50 and 110 milliseconds, allowing a response window between 800 and 1760 milliseconds.

The experiment consisted of three blocks of 80 trials, each block consisting of 48 green and 32 white marble trials. Trials were presented in a pseudo-randomized order so that each white marble trial was preceded by 0, 1, 2, or 3 green marble trials. The large proportion of green trials served two functions. First, the green trials lead to a prepotent tendency for action. Since the green marble trials were rather difficult, participants had to remain focused on the goal of responding quickly to the rolling marble, thus increasing the prepotency of responding. Also, due to the intermixed presentation of green and white trials participants could not predict when a white trial would be presented. Therefore participants had to be prepared to quickly respond to a green marble during the whole duration of the experiment, leaving the prepotency intact. This was desirable, so that intentional inhibition of action would involve a late brake on an already-prepared action, rather than a decision not to initiate action preparation. Second, the randomized interleaving of intentional (white) and instructed (green) trials also discouraged participants from strategically pre-deciding a pattern of intentional action, such as act-inhibit-act-inhibit etc.

Barratt Impulsiveness Scale

Following the scanning session participants completed the Barratt Impulsiveness Scale (BIS-11) (Patton et al., 1995). The BIS-11 is a measure of impulsive traits consisting of three subscales: motor impulsivity ('I act without thinking'), non-planning impulsivity ('I'm not interested in the future, but in today'), and attentional impulsivity ('I have difficulties sitting still during lectures'). For the child participants the questions were rephrased in an age-appropriate style (e.g. 'I have difficulties sitting still in the classroom' instead of 'I have difficulties sitting still during lectures').

Data Acquisition

Scanning was performed with a standard whole-head coil on a 3.0 Tesla Philips scanner at the Leiden University Medical Center. The marble task consisted of 3 event-related runs, each lasting approximately 6 minutes. Functional data were acquired using T2*-weighted echo-planar imaging (EPI). The first 2 volumes of each run were discarded in order to allow for equilibration of T1 saturation effects (TR = 2.2 sec, TE = 30 msec, sequential acquisition, 38 slices of 2.75 mm, field of view 220 mm, 80 x 80 matrix, in-plane resolution 2.75 mm). After the functional runs a high-resolution 3D T1-FFE scan for anatomical reference was obtained (TR = 9.760 ms; TE = 4.59 ms, flip angle = 8 degrees, 140 slices, $0.875 \times 0.875 \times 1.2$ mm^3 voxels, field of view = $224 \times 168 \times 177$ mm^3). Head motion was restricted by using foam inserts

between the head and the head coil. Visual stimuli were projected onto a screen in the magnet bore that could be viewed through a mirror attached to the head coil.

Behavioral Data Analysis

The use of response selection strategies on the marble task was evaluated by computing the Random Number Generation 2 (RNG2) index using Towse and Neil's (1998) RgCalc program. The RNG2 index is an adaptation of the RNG index (Evans, 1978) optimized for two-choice response sequences, which considers the randomness of the sequence (Neuringer, 1986). Scores can range from 0 (no predictability) to 1 (complete predictability).

fMRI Data Analysis

Data were preprocessed using SPM8 (Welcome Department of Cognitive Neurology, London). Images were corrected for rigid-body motion. Translational movement did not exceed 1 voxel (< 3 mm) and mean movement did not differ between age groups, F (1, 42) = .043, p = .84, η^2 = .001. Structural and functional volumes were spatially normalized to T1 templates. The normalization algorithm used a 12-parameter affine nonlinear transformation involving cosine basis functions, and then resampled the volumes to 3-mm cubic voxels. Templates were based on the MNI305 stereotaxic space (Cocosco, Kollokian, Kwan, & Evans, 1997), an approximation of Talairach space (Talairach & Tournoux, 1988). Functional volumes were spatially smoothed with an 8-mm full-width-at-half-maximum isotropic Gaussian kernel. Statistical analyses were performed on individual participants' data using the general linear model in SPM8. The fMRI time series data were modeled by a series of events convolved with a canonical hemodynamic response function (HRF) and the temporal derivatives. The onset of marble motion of each trial was modeled as an event of interest. Separate regressors were defined for white nogo (intentional inhibibition), white go (intentional action), green go (externally guided action), and green omissions (omission on the green marble trials). The trial functions were used as covariates in a general linear model, along with a basic set of cosine functions to high-pass filter (120 Hz) the data. The least-squares parameter estimates of the height of the best-fitting canonical HRF for the different conditions were used in pairwise contrasts. All reported effects consisted of at least 10 contiguous voxels that exceeded a false-discovery-rate (FDR) corrected threshold of $p < .05$, unless otherwise specified.

Region of interest (ROI) analyses were performed to further characterize the involvement of brain regions in the development of intentional inhibition. ROI analyses were performed with the MarsBaR toolbox in SPM8 (Brett, Anton, Valabregue, & Poline, 2002) (http://marsbar.sourceforge.net). ROIs that spanned several anatomical regions were masked with marsbar-aal ROIs. For rSTN, ROI analyses were performed on an anatomical rSTN template derived from a study using ultrahigh 7 Tesla scanning (Forstmann et al., 2010). For dFMC, ROI analyses were performed on a 6 mm radius sphere centered on -7, 42, 21 (Kühn et al., 2009).

4.3 Results

Behavior

The first comparison looked at performance on the instructed green marble trials. The staircase-tracking procedure for green marble trials was overall successful, showing that participants responded in time on 60.63 % of the trials (*SD* = 7.06). However, despite the tracking, adults (*M* = 63.22, *SD* = 7.18) were more successful at responding to the green marble in time compared to children (*M* = 57, 35, *SD* = 5.49), F (1,42) = 8.68, $p < .01$, $\eta^2 = .17$ (see Figure 2A). Second, we examined the choice behavior on the intentional white marble trials. As instructed, participants decided to inhibit responding to the white marble on approximately 50 % of the trials (children: *M* = 40.73, *SD* = 10.03; adults: *M* = 46.83, *SD* = 8.00). However, as can be seen in Figure 2A children more often responded to the white marble compared to adults, F (1,42) = 4.92, $p < .05$, $\eta^2 = .11$.

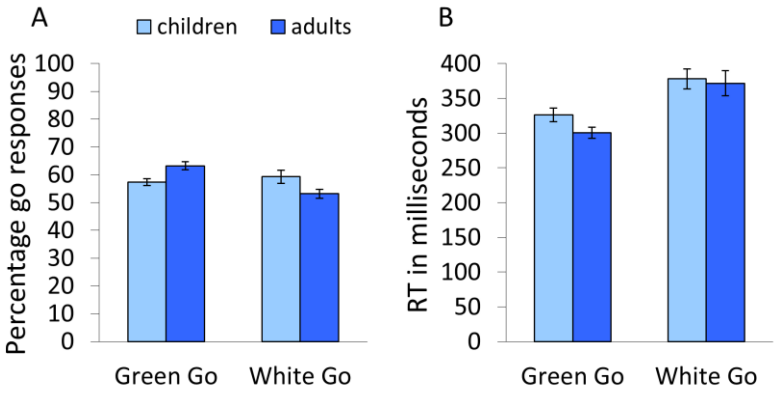

Figure 2. A. Percentage of go responses in the green and white marble conditions for children and adults separately. **B.** Reaction times in the green and white marble conditions for children and adults separately.

To examine the use of response selection strategies the RNG2 index was computed. A mean RNG2 index of .81 (*SD* = .01) was observed. To examine the randomness of the participants' choice behavior, the participants' RNG2 index was compared with a RNG2 index computed over a set of randomly generated sequences of go- and nogo-responses. For the randomly generated set of go- and nogo-response sequences a mean RNG2 index of .801 (*SD* = .002) was observed. Although the RNG2 index for the randomly generated sequences was marginally but significantly smaller compared to the participants' RNG2 index, F (1, 66) = 18.90, $p < .001$, $\eta^2 = .22$, these results indicate that the participants' behavior was close to being random and not driven by simple alternation strategies. Children and adults did not differ in RNG2 index, F (1,42) = 1.20, $p = .28$, $\eta^2 = .03$, indicating that children and adults did not differ in use of strategies for deciding between responding and inhibiting.

Next, we examined whether there were differences in response times to the instructed green and intentional white marble trials. As expected, reaction times on the green trials were shorter compared to the white trials, F (1,41) = 60.79, p < .001, η^2 = .60 (see Figure 2B), indicating that the decision process on the white trials took more time. No main, F (1, 41) = .84, p = .37, η^2 = .02, or interaction, F (1,41) = 1.47, p = .23, η^2 = .04, effects of age group were observed.

No developmental differences in self-reported impulsivity on the BIS-11 were observed (all p's > .1) (see Table 1). However, correlation patterns between self-reported impulsivity and performance on the marble task differed between age groups. First, adults who reported more motor impulsivity, more often chose to inhibit, r = .409, p < .05, but for children this correlation was not significant, r = -.084, p = .73 (see Figure 3A). However, a comparison between the correlations showed that the correlations for adults and children did not differ significantly from each other, z = 1.06, p = .28. Second, adults who reported more non-planning impulsivity, more often chose to inhibit, r = .508, p < .05, but for children this correlation was not significant, r = -.331, p = .17 (see Figure 3B). A comparison between the correlations showed that the correlations for adults and children differed significantly from each other, z = 2.72, p < .01, showing that the correlation was present in adults but not in children. No correlations between self-reported attentional impulsivity and task performance were observed (all p's > .05).

Table 1. Average BIS-11 scores per age group

	BIS-11 Motor	BIS-11 Non-planning	BIS-11 Attentional
Children	2.01 (.28)	2.14 (.43)	2.19 (.47)
Adults	1.87 (.41)	1.96 (.35)	2.06 (.43)

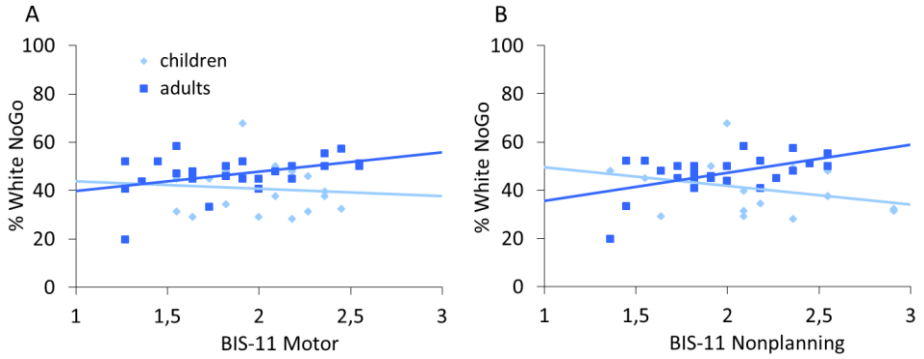

Figure 3. A. Correlation between intentional inhibition and self-reported motor impulsivity for children and adults separately. **B.** Correlation between intentional inhibition and self-reported non-planning impulsivity for children and adults separately.

fMRI

To identify the brain regions involved in intentional inhibition, the contrast intentional inhibition > intentional action (White NoGo > White Go) was computed for the whole group (N=43). This analysis revealed activation in a fronto-basal ganglia network, including bilateral IFG, bilateral striatum, and occipital lobe, but not in the STN and the dFMC (see Figure 4, and Supplementary Table 1 for the MNI coordinates of peak values). A two-sample t-test on the whole brain level revealed no developmental differences on the contrast intentional inhibition > intentional action (White NoGo > White Go). To further examine the involvement of the fronto-basal ganglia network in intentional inhibition across development, ROI analyses were performed for the rIFG, right putamen, right caudate, and right globus pallidus[2]. ROI analyses average across a set of voxels and therefore have more power to detect changes in a priori selected areas.

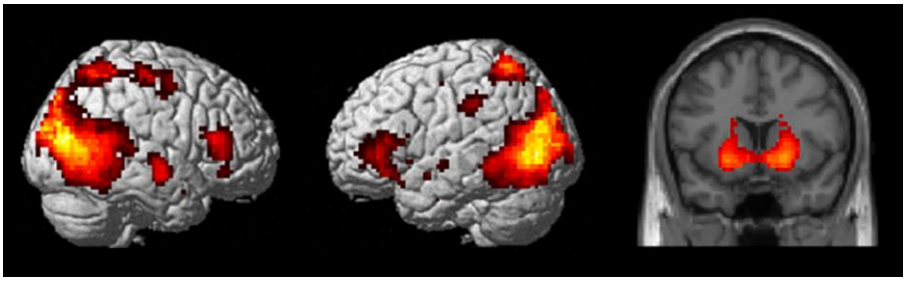

Figure 4. Whole brain contrast showing activation related to intentional inhibition (White NoGo > White Go) for the whole group (N =43) (FDR-corrected $p < .05$, at least 10 contiguous voxels).

For rIFG no main effect of age group was observed F (1, 41) = .29, p = .59, η^2 = .01. However, there was a trend for an age group x condition interaction, F (1,41) = 3.71, p = .061, η^2 = .08, indicating that children showed significantly more rIFG activation for intentional inhibition compared to intentional action, F (1,18) = 25.21, $p < .001$, η^2 = .0=58, whereas adults did not, F (1,23) = 2.05, p = .17, η^2 = .08 (see Figure 5).

In the right putamen no main effect of age group was observed, F (1,41) = .91, p = .35, η^2 = .02. However, an age group x condition interaction, F (1,41) = 6.92, $p < .05$, η^2 = .14, indicated that the activation difference between intentional inhibition and intentional action in right putamen was larger for children, F (1,18) = 29.93, $p < .001$, η^2 = .62, than for adults, F (1,23) = 4.03, p = .057, η^2 = .15 (see Figure 5).

For right caudate there was a main effect of age group, showing that children had more stimulus related deactivation compared to adults, F (1,41) = 18.09, $p < .05$, η^2 = .10 (see Figure 5). However, no age group x condition interaction was observed, F (1,41) = 2.25, p = .14, η^2 = .05.

[2] Here we only report right hemisphere ROIs in line with previous response inhibition literature. However, for the left hemisphere ROIs similar results were found.

For right globus pullidus no main effect of age group was observed, F (1,41) = .38, p = .54, η^2 = .01. However, an age group x condition interaction, F (1,41) =7.28, p < .05, η^2 = .15, indicated that children showed relatively more right globus pallidus activation during intentional inhibition compared to intentional action, F (1,18) = 23.12, p < .001, η^2 = 56, than adults, F (1,23) = 2.86, p = .10, η^2 = .11 (see Figure 5).

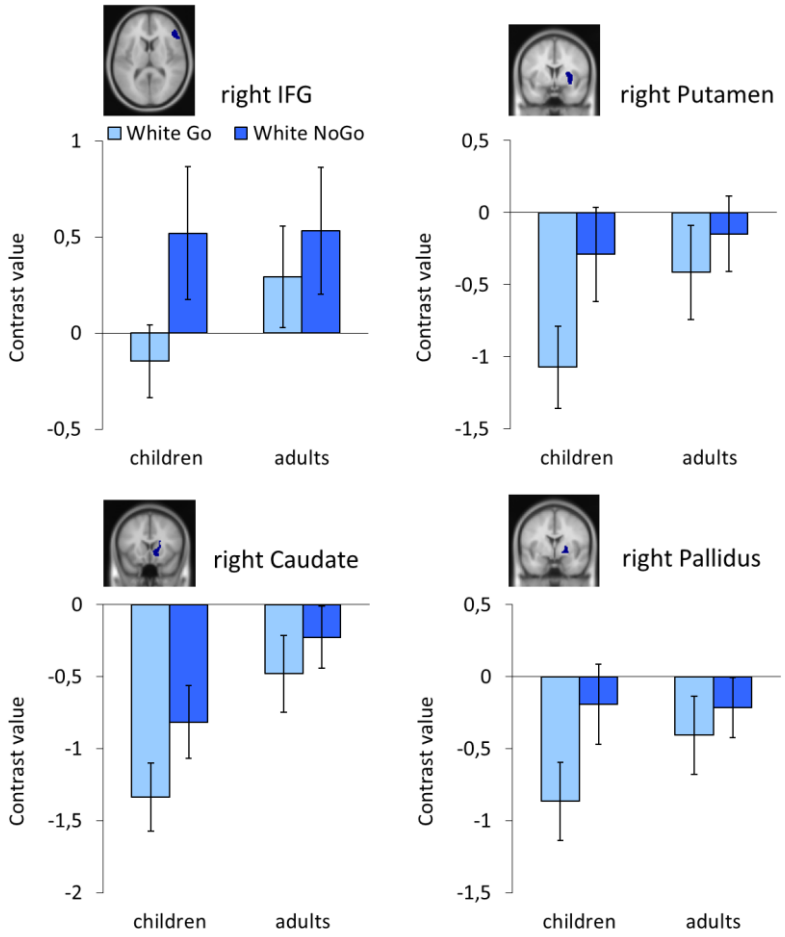

Figure 5. ROI analyses of right IFG, right putamen, right caudate, and right globus pallidus showing activation levels during intentional action (White Go) and intentional inhibition (White NoGo) for children and adults separately.

Role of STN. No STN activation during intentional inhibition was observed in the contrast intentional inhibition > intentional action (White NoGo > White Go). However, when looking at the intentional inhibition decision process (White NoGo > Green Go) and the intentional action decision process (White Go > Green Go) separately, clear bilateral STN activation was observed for both intentional inhibition

and intentional action (see Figure 6, and Supplementary Table 2 for the MNI coordinates of peak values). To further examine the role of the STN in the intentional inhibition and action processes across development a ROI analysis was performed for right STN. STN activation did not differ between intentional inhibition (White NoGo > Green Go) and intentional action (White Go > Green Go), F (1,41) = 2.96, p = .09, η^2 = .07. No main, F (1,41) = .86, p = .36, η^2 = .02, or interaction effects, F (1, 41) = .18, p = .68, η^2 = .004, of age group were observed (see Figure 6).

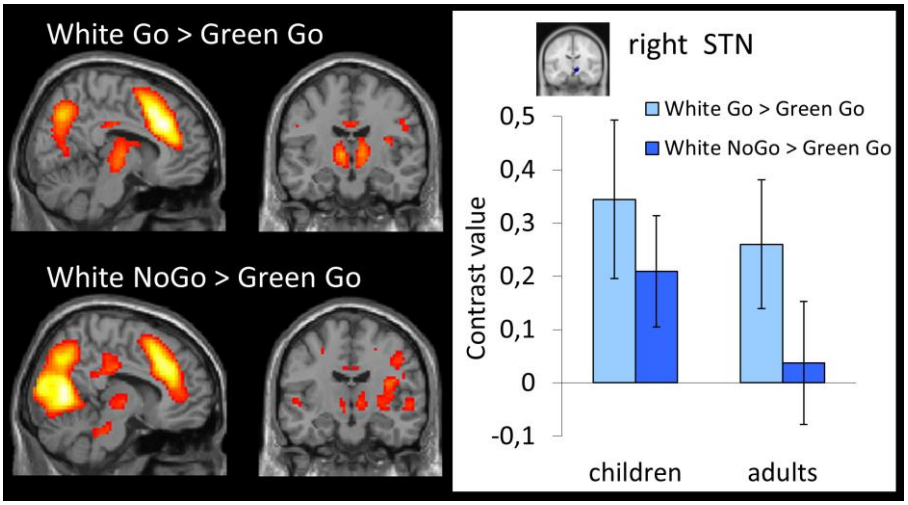

Figure 6. A. Whole brain contrast showing activation related to intentional action decision process (White Go > Green Go) for the whole group (N =43) (FDR-corrected p < .05, at least 10 contiguous voxels). **B.** Whole brain contrast showing activation related to intentional inhibition decision process (White NoGo > Green Go) for the whole group (N =43) (FDR-corrected p < .05, at least 10 contiguous voxels). **C.** ROI analysis of right STN showing activation levels during intentional action decision process (White Go > Green Go) and intentional inhibition decision process (White NoGo > Green Go) for children and adults separately.

Role of dFMC. No dFMC activation during intentional inhibition was observed in the contrast intentional inhibition > intentional action (White NoGo > White Go). To make sure that there indeed were no differences in dFMC activation, a ROI analysis was performed for dFMC. This analysis showed that dFMC activation did not differ between intentional inhibition (White NoGo) and intentional action (White Go), F (1,41) = .43, p = .52, η^2 = .01. Also, no main, F (1,41) = .12, p = .76, η^2 = .003, or interaction effects, F (1, 41) = .01, p = .94, η^2 = .00, of age group were observed.

Brain-behavior correlations. To examine the relation between self-reported impulsivity and intentional inhibition related brain activation, whole brain regression analyses on the contrast White NoGo > White Go with the BIS-11 subscales as regressors were performed on the whole sample (N=43). No effects were observed at the FDR corrected threshold. However, for non-planning impulsivity a significant

relationship with intentional inhibition related brain activation in the left putamen was observed at an uncorrected threshold ($p < .001$, at least 10 contiguous voxels), such that participants who reported more impulsivity showed more activation in left putamen during intentional inhibition (see Figure 7). A ROI analysis of this left putamen region showed a significant positive correlation in adults, $r = .600$, $p < .005$, but for children this correlation was not significant, $r = .368$, $p = .12$. However, the correlations for adults and children did not differ significantly from each other, $z = .93$, $p = .35$. No relationships between motor and attentional impulsivity and intentional inhibition related brain activation were found.

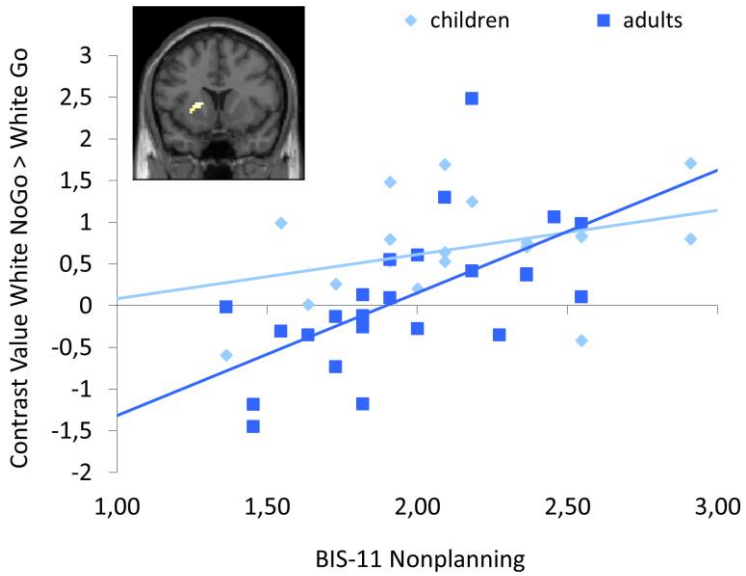

Figure 7. Whole brain regression analysis showing relation between intentional inhibition related neural activation in left putamen and self-reported non-planning impulsivity (uncorrected $p < .001$, at least 10 contiguous voxels). Follow-up ROI analysis showed that this relationship was only significant for adults, not for children.

5.4 Discussion

The present study examined the neural correlates of an important component of self-control; namely intentional inhibition, in children and adults. We used the marble task previously developed by Kühn et al. (2009) to test the neural correlates associated with responding to a rolling marble versus withholding responding to a rolling marble, where the latter process requires intentional inhibition of a prepotent response. As predicted, children and adults showed different recruitment of the fronto-basal ganglia network during intentional inhibition. However, no effects were observed in the dFMC, suggesting that differences are attributable to a similar process as what

previously has been observed for externally guided inhibition (see Luna et al., 2010 for a review).

Prior studies have reported that there is a developmental change in inhibitory performance when the task involves external cues (Luna et al., 2010), but much less is known about developmental differences when inhibition is internally driven. The first question we addressed was therefore whether children were able to withhold responding when they had to freely decide to do so. On a behavioral level we show an early development of intentional inhibition performance. That is to say, children intentionally inhibited responding to the rolling marble on approximately 50 % of the trials. Also, our RNG2 results indicate that children as well as adults did not use strategies to choose between inhibiting and acting. These findings are in line with our previous studies in which we have shown mature performance levels on intentional inhibition tasks in late childhood / early adolescence on similar tasks (Schel & Crone, 2013; Schel, Windhorst, van der Molen, & Crone, 2013).

Even though both children and adults inhibited responding to the marble on approximately 50 % of the trials, it is possible that developmental differences occur in neural responses to intentional inhibition demands, which is potentially a more sensitive index than deciding whether to press the button or not. Therefore, we examined the involvement of the fronto-basal ganglia network in intentional inhibition in children and adults. We show that the fronto-basal ganglia network, which is well known for its involvement in externally driven response inhibition (Aron et al., 2007; Aron & Poldrack, 2006; Jahfari et al., 2011) is activated during both intentional inhibition and intentional action. Although the fronto-basal ganglia network was activated for both intentional inhibition and intentional action, activation in most nodes of the network (i.e. rIFG, right putamen and right globus pallidus) was larger for intentional inhibition. Thus the fronto-basal ganlia network appears to be important for inhibition, irrespective of how inhibition was triggered (externally or internally driven) (see also Schel et al., 2014).

Although there were no developmental differences on the behavioral level, we observed differential recruitment of the fronto-basal ganglia network such that children showed more activation for intentional inhibition compared to intentional action, whereas for adults activation did not differ between intentional inhibition and intentional action. Thus, it appears that children show increased recruitment of the fronto-basal ganglia network during intentional inhibition to reach adult performance levels. The pattern of trend-level increased activation in rIFG and increased activation in putamen during intentional inhibition in children compared to adults is consistent with some studies on externally driven response inhibition (Casey, Thomas, Davidson, Kunz, & Franzen, 2002), but not with others which have reported less recruitment of rIFG and instead compensatory recruitment in dorsolateral prefrontal cortex (Bunge et al., 2002; Durston et al., 2002; Luna et al., 2010). In this study, we do not find compensatory recruitment for children outside the fronto-basal ganglia network. Thus, children already activate the same network as adults, but to a different extent. One explanation for this pattern of results might be that for adults acting and inhibiting are two equal response options, whereas for children acting is the default

response. Therefore, overruling this default response in order to intentionally inhibit, might require increased recruitment of the fronto-basal ganglia network.

One notable finding was that the STN was not more active for intentional inhibition, even though it has been consistently reported as an important region for externally driven inhibition. However, additional analyses showed that the STN, which is conceptualized as a main inhibitory node in the fronto-basal ganglia network for inhibition, was equally activated for intentional inhibition and intentional action. These findings corroborate the conceptualization of response inhibition and response selection as "two sides of the same coin" of Mostofsky and Simmonds (2008). Inhibition and action can be seen as two equal response options, which are supported by a similar neural network (Karch et al., 2009; Mostofsky & Simmonds, 2008).

Finally, we show that individual differences in self-reported impulsivity are predictive of intentional inhibition performance and the underlying neural correlates. Interestingly, the results of our exploratory analyses into the relation between self-reported impulsivity and intentional inhibition show that people who are more impulsive more often chose to inhibit. Also, they showed more activation in the left putamen during intentional inhibition (note that these results are based on an uncorrected threshold of .001, > 10 contiguous voxels). This is opposite to the relation observed between impulsivity and externally driven response inhibition; there more impulsivity is predictive of worse inhibitory performance (Casey et al., 2011). The positive relation between self-reported impulsivity and intentional inhibition could suggest that impulsivity is not always a negative trait. When provided with a choice, impulsive people are well able to choose to inhibit. Thus, acting does not always appear to be the default choice. However, it should be noted that in the current study, the choice between inhibition and action was made in a relatively neutral context (i.e. there were no consequences depending on either choice). In daily life, this is often not the case. There the choice between inhibition and action is almost always influenced by motivational factors like loss, reward or punishment (Leotti & Wager, 2010). How impulsivity influences intentional inhibition in those circumstances remains an important question for future research.

A continuing debate in research on intentional inhibition is the role of the dFMC. Some studies, including the study by Kühn and colleagues (2009), which also used the marble paradigm, have shown that the late veto of a response is associated with more activity in the dFMC. This has been interpreted as a role of this area in the voluntary control of an action (i.e., the "whether" decision in action control) (Brass & Haggard, 2008; Haggard, 2008). Several other studies have confirmed that this region is more active in other paradigms on intentional inhibition, such as choosing not to gamble (Campbell-Meiklejohn, Woolrich, Passingham, & Rogers, 2008) or inhibition of cigarette cravings (Brody et al., 2007). However, not all studies can replicate this effect, for example, in a prior study in adults we observed dFMC activation only under specific preceding context conditions (Schel et al., 2014). In the current study, we found no evidence for dFMC activation in children, suggesting that neural differences are only observed in the network which is also engaged by externally triggered inhibition.

Some limitations of the present study deserve mentioning. First, we only included a selected age-range (10-12 year-olds and 18-26 year-olds) in the present study. Future studies should include participants across the whole age range from early childhood to adulthood, to examine whether there are specific developmental periods during which intentional inhibition is most sensitive to developmental change (see also: Schel & Crone, 2013). Second, we cannot completely rule out the possibility that participants might have pre-decided not to initiate an action, instead of canceling a prepared action at the last moment on the intentional inhibition trials. However, the fast paced and unpredictable nature of the task, made it very difficult to pre-decide. In future research electromyography measures might be included, to make sure that initial action preparation is also present on intentional inhibition trials. Third, since the present study did not have an externally guided inhibition condition, we could not directly compare the development of intentional versus externally driven inhibition. Follow-up studies should include an externally driven inhibition condition to be able to directly compare intentional and externally driven inhibition. Fourth, the present study used the relatively neutral marble task, in which there are no strong internal motivations for action. An interesting avenue for future research might be to include a strong affective or motivational component, such as is the case in the marshmallow paradigm (Mischel et al., 1989). This might be especially interesting for research in adolescence, when there is a sensitivity towards rewards (Somerville, Hare, & Casey, 2011). Fifth, although the role of the rIFG is typically interpreted in terms of response inhibition (for a review, see Ridderinkhof, Forstmann, Wylie, Burle, & van den Wildenberg, 2011), alternative conceptualizations in terms of action selection have also been proposed (Verbruggen, Aron, Stevens, & Chambers, 2010). While the present study does not allow to distinguish the role of rIFG with respect to those alternatives, they may be reconciled by pointing to the role of rIFG in overriding one response alternative (here, to act) in favor of another (here, to inhibit).

To conclude, the present study was the first to examine the neural correlates of intentional inhibition in children and adults. Although children performed at adult level, children showed increased recruitment of the fronto-basal ganglia network during intentional inhibition. Individual differences in impulsivity were predictive of intentional inhibition, more impulsive people were more likely to choose to inhibit. This research has implications for research into disorders of impulsivity, such as ADHD, which are currently associated with poor self-control abilities (Scheres et al., 2006; Scheres, Sumiya, & Thoeny, 2010). Many types of impulsive behaviors, which are typical for children and adults with disorders of impulsivity, require an intentional decision to inhibit, given that external cues are not always available.

5.5 Supplementary material

Table S1. Brain regions revealed by the whole brain contrast intentional inhibition > intentional action (all FDR corrected, $p < .05$, > 10 voxels) for the whole group ($N = 43$).

Anatomical region	L/R	K	Z	MNI coordinates		
				x	y	z
Intentional inhibition > Intentional action (White NoGo > White Go)						
Occipital lobe	L/R	11247	7.12	24	-78	21
Putamen	R		5.17	18	6	-9
Putamen	L		4.69	-21	12	-9
Superior Temporal Gyrus	R	104	4.86	60	-9	-6
Inferior Frontal Gyrus	R	148	3.98	54	33	9
Supramarginal Gyrus	L	47	3.51	-63	-24	36
Superior Temporal Gyrus	L	25	3.08	-45	-9	-6
Precentral Gyrus	L	14	2.96	-30	-12	48

Table S2. Brain regions revealed by whole brain contrast, focused on decision processes (all FDR corrected, $p < .05$, > 10 voxels) for the whole group ($N = 43$).

Anatomical region	L/R	K	Z	MNI coordinates		
				x	y	z
Intentional inhibition > Externally driven action (White NoGo > Green Go)						
Occipital Lobe	L/R	17071	7.65	12	-66	3
Middle Cingulate Cortex	L	320	4.97	-6	-27	-33
Caudate Nucleus	L	79	4.35	-6	9	12
Thalamus (including STN)	R	77	3.56	9	-12	0
Thalamus (including STN)	L	24	3.33	-18	-30	3
Postcentral gyrus	L	15	3.16	-60	-6	24
Intentional action > Externally driven action (White Go > Green Go)						
Middle Cingulate Cortex	L/R	6165	7.58	6	27	33
Supramarginal Gyrus	R	849	5.98	51	-42	42
Precuneus	R	946	5.48	9	-66	42
Inferior Parietal Lobe	L	427	5.32	-54	-42	51
Thalamus (including STN)	L/R	446	4.90	-9	-12	3
Middle Temporal Gyrus	R	119	4.26	54	-27	-3
Cerebellum	L	22	3.58	-30	-66	-27
Insula	R	14	3.39	36	-12	15
Superior Temporal Gyrus	L	36	3.20	-39	-30	12

CHAPTER 6
Development of response inhibition in the context of relevant versus irrelevant emotions

This chapter is published as:
Schel, M.A., & Crone, E.A. (2013). Development of response inhibition in the context of relevant versus irrelevant emotions. *Frontiers in Psychology, 4*, 383.

6. Intentional inhibition in context

Abstract

The present study examined the influence of relevant and irrelevant emotions on response inhibition from childhood to early adulthood. Ninety-four participants between 6 and 25 years of age performed two go/nogo tasks with emotional faces (neutral, happy, and fearful) as stimuli. In one go/nogo task emotion formed a relevant dimension of the task and in the other go/nogo task emotion was irrelevant and participants had to respond to the color of the faces instead. A special feature of the latter task, in which emotion was irrelevant, was the inclusion of free choice trials, in which participants could freely decide between acting and inhibiting. Results showed a linear increase in response inhibition performance with increasing age both in relevant and irrelevant affective contexts. Relevant emotions had a pronounced influence on performance across age, whereas irrelevant emotions did not. Overall, participants made more false alarms on trials with fearful faces than happy faces, and happy faces were associated with better performance on go trials (higher percentage correct and faster RTs) than fearful faces. The latter effect was stronger for young children in terms of accuracy. Finally, during the free choice trials participants did not base their decisions on affective context, confirming that irrelevant emotions do not have a strong impact on inhibition. Together, these findings suggest that across development relevant affective context has a larger influence on response inhibition than irrelevant affective context. When emotions are relevant, a context of positive emotions is associated with better performance compared to a context with negative emotions, especially in young children.

6.1 Introduction

The ability to cognitively control our actions is of critical importance for successful functioning. A well-studied component of cognitive control is response inhibition, which refers to the ability to refrain from a prepotent response (Luna, et al., 2010). Response inhibition has been shown to have a protracted developmental trajectory (Bunge, Dudukovic, et al., 2002; Durston, Thomas, Yang, et al., 2002; van der Molen, 2000), with mature performance levels being reached in mid to late adolescence (Luna, et al., 2010).

In daily life, cognitive control processes seldom stand-alone; one is often required to exercise cognitive control in a social or affective context. Sometimes the context can be relevant, for example when you want to approach friendly people but inhibit from approaching unfriendly people, and sometimes context is irrelevant, for example when you want to approach people belonging to a certain group and inhibit from approaching people belonging to another group, independent of whether they are friendly or unfriendly. To examine the role of affective context on response inhibition, prior studies made use of an emotional go/nogo task (e.g. Tottenham, et al., 2011). In this task, participants are instructed to respond to a certain emotional stimulus and inhibit responding to another emotional stimulus (such as emotional words or emotional facial expressions), thereby making the affective context task-relevant (Reynolds & Jeeves, 1978). Performance on the emotional go/nogo task correlates with performance on the traditional go/nogo task (in which no affective information is presented) thereby validating the emotional go/nogo task as a measure of response inhibition within an affective context (Schulz et al., 2007).

In adults, response inhibition appears to be better for negative compared to positive stimuli (Chiu, Holmes, & Pizzagalli, 2008; Schulz, et al., 2007). This effect goes together with better emotion recognition for negative compared to positive stimuli (Chiu, et al., 2008; Schulz, et al., 2007). Within a large developmental sample (5- to 28-year-olds) worse overall response inhibition performance for negative stimuli was found, and this pattern did not differ with age (Tottenham, et al., 2011). In this study different negative emotions were included, namely sadness, anger, and fear. Importantly, response inhibition performance appeared to be worst for the emotions for which emotion recognition was most difficult (sadness and anger). For fear, emotion recognition was best and response inhibition performance for fearful faces did not differ from response inhibition for positive (i.e. happy) stimuli, consistent with the notion that fearful faces are relatively easy to recognize (Tottenham, et al., 2011).

Recently, studies have examined the influence of irrelevant emotions on response inhibition. In these studies, emotional stimuli were presented in the background and participants were instructed to respond to another dimension of the emotional stimulus (for example, the color or the direction of a stimulus). Importantly, all these tasks share the feature that participants do not have to focus on the emotional aspects of the stimuli for successful task performance. Within adult studies results are mixed, some studies show an effect of irrelevant emotions on response inhibition performance (Albert, Lopez-Martin, & Carretie, 2010; Sagaspe, Schwartz, & Vuilleumier, 2011), and other studies do not show an effect of irrelevant

emotions on performance (Brown et al., 2012).In children and adolescents again mixed results were found, with two studies showing an effect of irrelevant emotions on response inhibition (Cohen-Gilbert & Thomas, 2013; Lamm, White, McDermott, & Fox, 2012), and another study not showing this effect (Todd, Lee, Evans, Lewis, & Taylor, 2012).

Knowing how affective contexts influence response inhibition is of critical importance, since response inhibition is seldom required in a cold situation. Most often response inhibition is needed in hot affective situations, in which emotions play a role. Importantly, these emotions are not always relevant for the task at hand. Currently, it remains unknown whether relevant and irrelevant affective contexts have a similar or different influence on response inhibition. The goal of this study was therefore to examine the influence of relevant and irrelevant affective context on response inhibition in children, adolescents and adults.

The present study is the first to directly compare the influence of both relevant and irrelevant emotions on response inhibition within the same participants of a developmental sample (covering mid-childhood to early adulthood). Participants performed two emotional response inhibition tasks, one in which emotion formed a relevant dimension of the task, and one in which emotion was irrelevant. In the first emotional go/nogo task emotion was a relevant dimension and participants had to respond when a given emotional facial expression was presented and inhibit responding when another emotional facial expression was presented (see Tottenham, et al., 2011). In the second emotional go/nogo task emotion was an irrelevant dimension. In this task the same emotional faces were presented, but now faces were colored and participants had to respond to the color of the faces. A special feature of the latter task was the inclusion of intentional go/nogo trials (Brass & Haggard, 2007, 2008). The task therefore involved three types of trials: go-trials, nogo-trials, and choice-trials (in which participants could freely decide between responding and inhibiting). These choice trials were added to the task to further examine the influence of irrelevant emotions on response inhibition in a free choice situation. Previous research in the field of free choice inhibition has been conducted in a neutral context (e.g. Brass & Haggard, 2007; Kühn, et al., 2009). This research has indicated that free choice inhibition can be distinguished from externally driven inhibition on the basis of underlying neural mechanisms (Filevich, et al., 2012). Here we aimed to examine the influence of affective context on free choice inhibition. In both tasks happy, fearful, and neutral faces were presented, since previous research has shown that within a developmental sample emotion recognition for these emotions is comparable (Tottenham, et al., 2011).

We expected to observe a stronger effect of relevant compared to irrelevant emotions on response inhibition (Brown, et al., 2012; Schulz, et al., 2007; Todd, et al., 2012; Tottenham, et al., 2011). We expected this effect to be present across all age groups. Furthermore, we expected to find a developmental increase in inhibitory performance, and we aimed to examine whether this pattern was different depending on affective context (Tottenham, et al., 2011). Finally, we aimed to test whether we would find a dip in response inhibition performance for happy stimuli in adolescents (Somerville, et al., 2011) when emotion was a relevant or an irrelevant dimension.

6.2 Methods

Participants

Ninety-four participants took part in the study. Participants were divided over 5 age groups; 18 6-7-year olds (M = 7.11, SD = .46, 8 females), 19 8-9-year-olds (M = 9.36, SD = .85, 8 females), 19 10-12-year-olds (M = 11.68, SD = .83, 10 females), 20 13-15-year-olds (M = 14.67, SD = .46, 9 females), and 18 18-25-year-olds (M = 21.04, SD = 2.16, 15 females). A chi-square test revealed no significant differences in gender distributions between age groups (p = .07). Children and adolescents were recruited from a primary and a secondary school in the Netherlands and informed consent was obtained from a primary caregiver. Adult participants were recruited from Leiden University and signed informed consent before participation in the experiment.

Participants completed the Raven Standard Progressive Matrices (Raven SPM) to obtain an estimate of their cognitive functioning (Raven, et al., 1998). For one 6-7-year-old the Raven SPM was not completed. All estimated IQ scores were within the normal range. However, age groups differed in estimated IQ scores, F (4, 92) = 6.00, p < .001. 13-15-year-olds had a significantly lower estimated IQ (M = 107.05, SD = 7.68) compared to the 6-7-year-olds (M = 124.35, SD = 14.77), the 8-9-year-olds (M = 120.84, SD = 11.16), and the 18-25-year-olds (M = 119.17, SD = 9.33) (all p's < .02). 13-15-year-olds' estimated IQ did not differ significantly from the 10-12-year-olds (M = 116.53, SD = 14.17) (p = .09). Therefore, all analyses were performed twice, once without estimated IQ score and once with estimated IQ score added as a covariate. Since all results remained the same with estimated IQ score added as a covariate we here report only the results of the analyses without estimated IQ score as a covariate.

Stimuli

Face stimuli were selected from the Radboud Faces Database (Langner et al., 2010). The selected set consisted of four adult males, four adult females, four child males, and four child females, all posing three different expressions (happy, fearful, and neutral), resulting in 48 stimuli in total. For the standard emotional go/nogo task face stimuli were transformed to grayscale images. For the colored emotional go/nogo task blue, purple, and orange color filters were placed over the grayscale images, resulting in blue, purple, and orange colored face images.

Tasks

Participants performed two tasks; a standard emotional go/nogo task, in which emotion was a relevant dimension of the task, and a colored emotional go/nogo task in which emotion was an irrelevant dimension of the task.

Standard emotional go/nogo task. The standard emotional go/nogo task was adapted from Tottenham et al. (2011). In this task participants had to respond by pressing a button when a given facial expression (e.g. happy) was presented and inhibit responding when another facial expression (e.g. neutral) was presented (see Figure 1A). In each task block emotional facial expressions (happy or fearful) were coupled

with neutral facial expression, resulting in four different go/nogo blocks (happy/neutral, neutral/happy, fearful/neutral, and neutral/fearful, with the first emotion as the go-, and the second emotion as the nogo-stimulus). Participants were not instructed about the valence of the nogo-stimulus, but instead were instructed to inhibit responding when another facial expression than the go-stimulus was presented. Face stimuli were presented for a maximum duration of 1000 ms, and participants had to respond within that time window. When participants responded within the time window, the face stimulus disappeared from the screen and the remaining time was added to the presentation time of the fixation cross as a filler to keep the task duration equal across participants. The subsequent jitter (fixation cross) was presented for 750 ms.

Face stimuli were presented on a black background. Each task block consisted of 60 trials; 42 go-trials (to create a prepotency for responding) and 18 nogo-trials. Trials were presented in a pseudo-randomized order, such that there were never more than two consecutive nogo-trials. Task blocks were presented in a random order and before each task block participants were instructed which facial expression formed the go-stimulus.

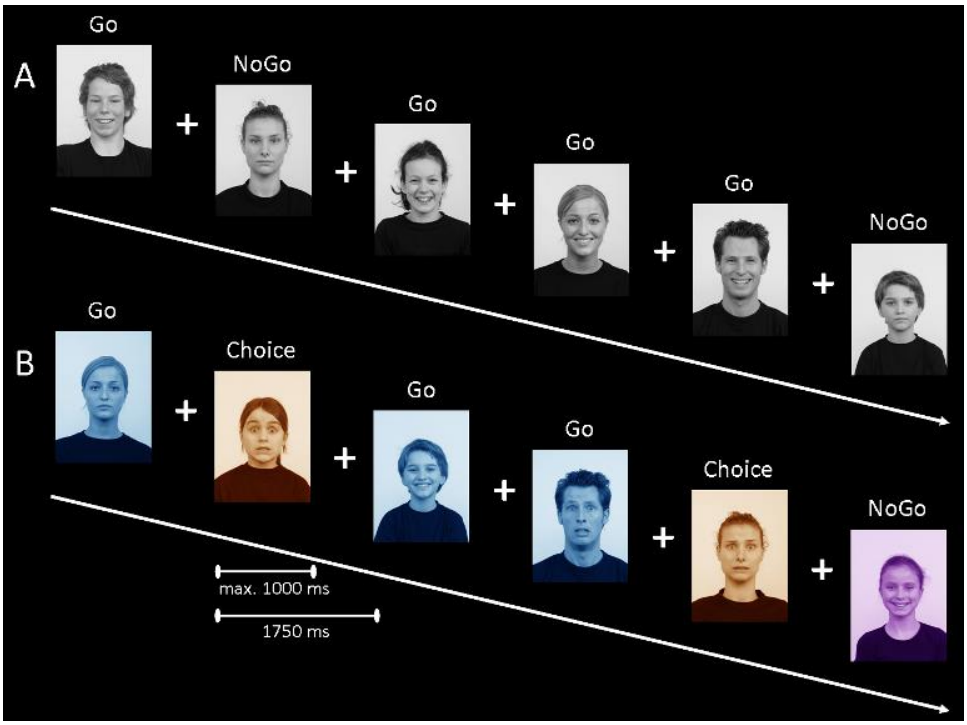

Figure 1. A. Outline of the standard emotional go/nogo task. **B.** Outline of the colored emotional go/nogo task. See text for details about the tasks.

Colored emotional go/nogo task. In the colored emotional go/nogo task emotion was an irrelevant dimension and participants were instructed to respond to the color of the faces (see Figure 1B). In this task there were three types of trials: go-trials,

nogo-trials, and choice-trials. In the choice trial condition, participants could freely decide between responding and inhibiting. The task was explained to the participants as a catching game, in which they had to catch and inhibit catching members of colored teams. Participants were instructed that they had to catch the members of the blue team by pressing a button and had to inhibit catching members of the purple team. Participants were explained that people in the orange team were in disguise. 50% of the orange team members actually belonged to the blue team and therefore had to be caught, and the other 50% of the orange team members actually belonged to the purple team and therefore should not be caught. Participants were instructed to freely decide and not use a strategy to decide when to respond or inhibit in the choice condition. The meaning (i.e. go, nogo, choice) of the colors was counterbalanced across participants, to control for possible a priori color preferences.

The temporal properties of the task were similar to the standard emotional go/nogo task; face stimuli were presented for a maximum duration of 1000 ms, and participants had to respond within that time window. When participants responded within the time window, the face stimulus disappeared from the screen and the remaining time was added to the presentation time of the fixation cross as a filler to keep the task duration equal across participants. The subsequent jitter (fixation cross) was presented for 750 ms.

Face stimuli were presented on a black background. In total there were 270 trials; 180 go-trials (to create a prepotency for responding), 30 nogo-trials, and 60 choice trials. Emotions (happy, fearful, and neutral) were equally distributed across conditions. Trials were presented in a pseudo-randomized order, such that there were never more than two consecutive nogo-trials or more than two consecutive choice-trials. The task was divided in two task blocks of 135 trials each.

Procedure

All participants were tested in a laboratory or an empty classroom. Tasks were performed in a fixed order. First the colored emotional go/nogo task was performed, to ensure that emotion would be an irrelevant dimension in that task. Before each task participants were given instructions and performed a short practice block (18 trials for the colored task and 15 trials for the standard task). It was stressed that participants were not supposed to use a specific strategy to decide whether to act or inhibit in the choice condition of the colored task. Care was taken that all participants understood the instructions and were able to perform the tasks. Including instructions, the tasks took approximately 25 minutes to complete. After completion of the tasks participants were asked whether they had used a specific strategy in the choice condition of the colored task. Finally, participants completed the Raven SPM.

Data analysis plan

For both the standard and the colored emotional go/nogo task, the main variable of interest was the percentage of false alarms (i.e. failed inhibitions). Furthermore we were interested in the percentage of correct responses on the go-trials and the reaction times for the correct go-trials to examine overall task performance. For the colored emotional go/nogo task an additional variable of interest was the percentage of nogo

choices. These variables were added to repeated measures ANOVAs with Age group as a between subjects factor, and Emotion as within subjects factor, to examine task performance in the context of happy and fearful faces across development. For the standard emotional go/nogo task, Type (i.e. emotion as the go-stimulus vs. emotion as the nogo-stimulus) was added as an additional factor to the repeated measures ANOVAs to examine whether performance in the context of happy and fearful faces was the same independent of the emotional face being the go- or nogo-stimulus.

6.3 Results

Standard emotional go/nogo task

Four participants (one 6-7-year-old, two 8-9-year-olds, and one 13-15-year-old) were excluded from all analysis of this task because of misunderstanding of task instructions (i.e. reversal of go and nogo stimuli). Therefore the final sample for this task consisted of 17 6-7-year olds (M = 7.09, SD = .46, 8 females), 17 8-9-year-olds (M = 9.37, SD = .88, 7 females), 19 10-12-year-olds (M = 11.68, SD = .83, 10 females), 19 13-15-year-olds (M = 14.71, SD = .41, 9 females), and 18 18-25-year-olds (M = 21.04, SD = 2.16, 15 females).

False alarms. To examine differences in the percentage of false alarms (i.e. failed inhibitions), an Age group (5) x Emotion (2: happy and fearful) x Type (2: emotion as go- or nogo-stimulus) repeated measures ANOVA was performed. A main effect of Emotion, F (1, 85) = 50.89, p < .001, indicated that overall participants made more false alarms in blocks with fearful faces compared to blocks with happy faces (see Figure 2A). No main or interaction effects of Type were observed (all p's > .08), indicating that performance did not differ based on the emotional face being the go- or nogo-stimulus.

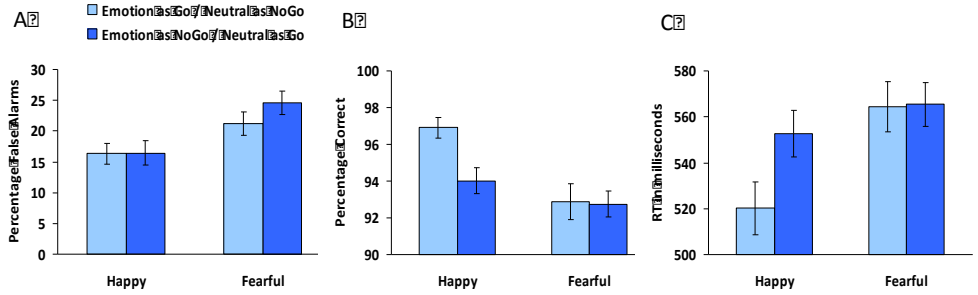

Figure 2. Overall results of the standard emotional go/nogo task: **A.** Percentage of false alarms for the blocks with happy and fearful faces. **B.** Percentage of correct responses for the blocks with happy and fearful faces **C.** RTs in milliseconds for the blocks with happy and fearful faces. Note that happy and fearful faces were presented in separate blocks, paired with neutral faces (see text for explanation).

A main effect of Age group, F (4, 85) = 14.72, p < .001, indicated that overall the percentage of false alarms decreased with age (see Figure 3A). Post-hoc Tukey tests showed that the 6-7-year-olds (M = 34.72, SD = 16.01) did not differ from the 8-9-year-olds (M = 28.35, SD = 16.76) (p = .58), but made significantly more false alarms compared to the other age groups (all p's < .005). 8-9-year-olds did not differ from the 10-12-year-olds (M = 18.71, SD = 14.59) (p = .16), but made significantly more false alarms compared to the two oldest age groups (both p's < .005). 10-12-year-olds, 13-15-year-olds (M = 10.60, SD = 5.28), and 18-25-year-olds (M = 7.64, SD = 5.54) did not differ significantly from each other (all p's > .05). No interactions between Age group and Emotion or Type were observed (all p's > .1)

Percentage correct go-trials. To test for differences in the percentage of correct responses on the go-trials, an Age group (5) x Emotion (2: happy and fearful) x Type (2: emotion as go- or nogo-stimulus) repeated measures ANOVA was performed. A main effect of Emotion, F (1, 85) = 23.22, p < .001, indicated that percentage correct go-trials was higher in blocks with happy faces compared to blocks with fearful faces. A main effect of Type, F (1, 85) = 9.03, p < .005, indicated that percentage correct go-trials was higher in blocks in which the emotional face was the go-stimulus compared to blocks in which the neutral face was the go-stimulus. Finally as can be seen in Figure 2B, an Emotion x Type interaction, F (1, 85) = 8.60, p < .005, indicated that better performance for blocks where the emotional face was the go-stimulus to relative to the nogo-stimulus, was driven by the blocks with happy faces. For the blocks with fearful faces it did not matter whether the emotional face was a go- or a nogo-stimulus (p = .84).

Overall, the percentage correct on the go-stimulus increased with age, F (4, 85) = 18.91, p < .001 (see Figure 3B). Post-hoc Tukey tests showed that the 6-7-year-olds (M = 87.43, SD = 6.45) made fewer correct responses compared to all other age groups (all p's < .03). 8-9-year-olds (M = 91.84, SD = 4.40) did not differ significantly from the 10-12-year-olds (M = 95.68, SD = 2.91) (p = .058), but made significantly fewer correct responses compared to the two oldest age groups (both p's < .01). 10-12-year-olds, 13-15-year-olds (M = 96.68, SD = 4.28), and 18-25-year-olds (M = 98.35, SD = 1.70) did not differ significantly from each other (all p's > .3). An Emotion x Age group interaction, F (4, 85) = 3.90, p < .01, showed that the difference between percentage correct for the blocks with happy faces compared to the blocks with fearful faces (independent of whether these were go- or nogo-stimuli) was larger for the youngest age groups (see Figure 3B).

Reaction times. Differences in reaction times to the go-stimuli were examined by performing an Age group (5) x Emotion (2: happy and fearful) x Type (2: emotion as go- or nogo-stimulus) repeated measures ANOVA. A main effect of Emotion, F (1, 85) = 51.02, p < .001, showed that reaction times were faster for the blocks with happy faces compared to the blocks with fearful faces. A main effect of Type, F (1, 85) = 12.30, p < .005, showed that reaction times were faster for the blocks in which the emotional face was the go-stimulus compared to block in which the neutral face was the go-stimulus. As can be seen in Figure 2C an Emotion x Type interaction, F (1,

85) = 11.86, $p < .005$, indicated that the effect of faster reaction times when the emotional face was the go-stimulus was driven by the block with happy faces, for the blocks with fearful faces conditions did not differ ($p = .61$).

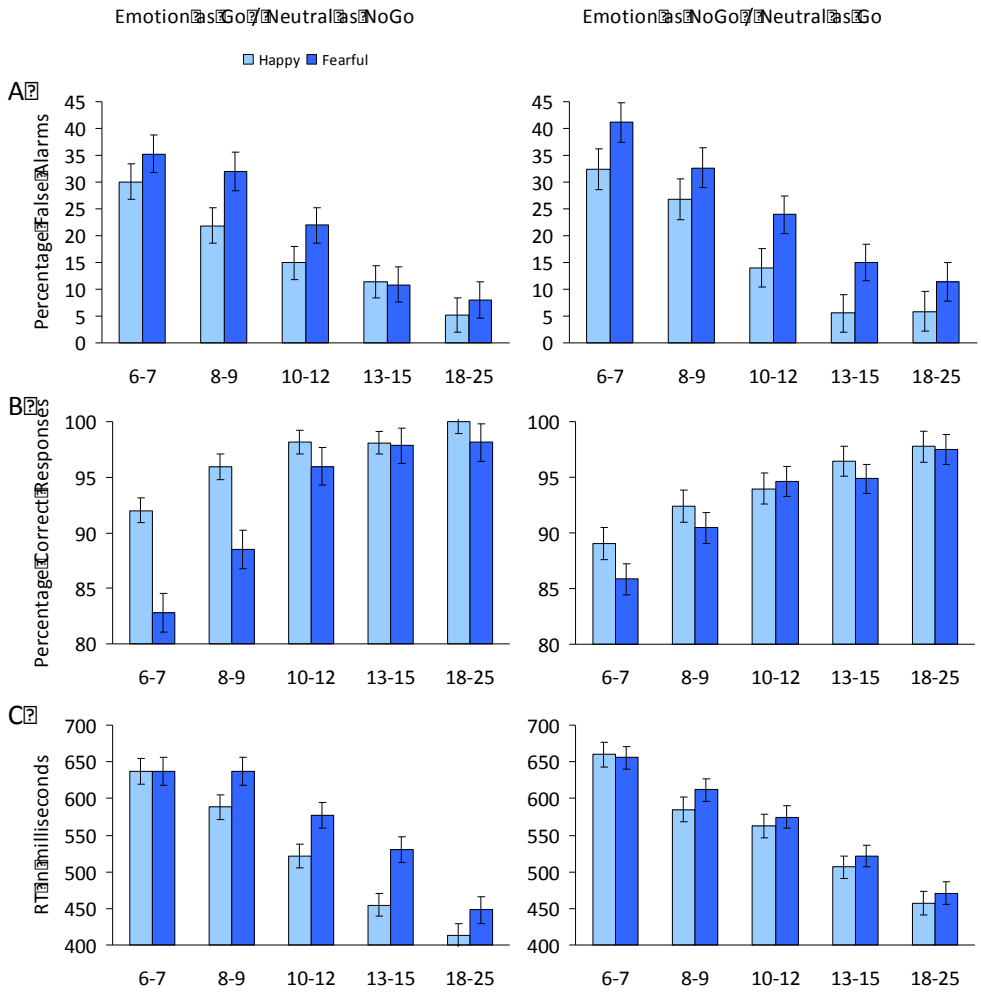

Figure 3. Developmental differences on the standard emotional go/nogo task: **A.** Developmental decrease in the percentage false alarms for happy and fearful faces plotted separately for the blocks in which the emotional face was the go- versus the nogo-stimulus. **B.** Developmental increase in the percentage correct responses for happy and fearful faces plotted separately for the blocks in which the emotional face was the go- versus the nogo-stimulus. **C.** Developmental decrease in RTs to happy and fearful faces plotted separately for the blocks in which the emotional face was the go- versus the nogo-stimulus. Note that happy and fearful faces were presented in separate blocks, paired with neutral faces (see text for explanation).

Overall, reaction times to the go-stimuli decreased with age, F (4, 85) = 29.28, p < .001 (see Figure 3C). Post-hoc Tukey tests showed that the 6-7-year-olds (M = 647, SD = 56) did not differ from the 8-9-year-olds (M = 605, SD = 70) (p = .28), but were significantly slower compared to the other age groups (all p's < .001). 8-9-year-olds did not differ from the 10-12-year-olds (M = 559, SD = 52) (p = .17), but were significantly slower compared to the two oldest age groups (both p's < .001). 10-12-year-olds were slower compared to both the 13-15-year-olds (M = 504, SD = 65) (p < .05) and the 18-25-year-olds (M = 447, SD = 63) (p < .001). The 13-15-year-olds were also significantly slower compared to the 18-25-year-olds (p < .05). An Emotion x Age group interaction, F (4, 85) = 4.40, p < .005, indicated that the emotion effect of faster response times for blocks with happy faces than for blocks with fearful faces was driven by the four oldest age groups, whereas the youngest age groups did not differ in reaction times to emotions (see Figure 3C). A Type x Age group interaction, F (4, 85) = 2.88, p < .05, indicated that the type effect of faster reaction times for the blocks in which the emotional face was the go-stimulus was reversed for the 8-9-year-olds (see Figure 3C).

Together, these results indicate that task relevant emotions influence task performance such that participants are more accurate and faster for happy faces than for fearful faces, and that this effect is strongest for the younger age groups. Overall, the results suggest that the blocks with fearful faces were more difficult compared to the blocks with happy faces.

Colored emotional go/nogo task

False alarms. In order to examine the influence of irrelevant emotions on false alarms, an Age group (5) x Emotion (3: neutral, happy, and fearful) repeated measures ANOVA was performed for the nogo-trials. No main effect of Emotion was observed (p > .4). Overall, the percentage of false alarms decreased with age, F (4, 89) = 7.26, p < .001 (see Figure 4). Post-hoc Tukey tests showed that the 6-7-year-olds (M = 25.56, SD = 12.68) did not differ from the 8-9-year-olds (M = 28.25, SD = 20.07) (p = .96) and both groups made more false alarms compared to the two oldest groups (13-15-year-olds: M = 12.83, SD = 9.44, 18-25-year-olds: M = 9.44, SD = 9.85) (all p's < .05). The 10-12-year-olds (M = 21.05, SD = 10.89) did not differ significantly from any group (all p's > .06).

Percentage correct go-trials. To examine whether the irrelevant emotion of the go-stimulus influenced correct responding, an Age group (5) x Emotion (3: neutral, happy, and fearful) repeated measures ANOVA was performed. No main effect of Emotion was observed (p > .7). Overall, correct responding to the go-trials increased with age, F (4, 89) = 7.58, p < .001 (see Figure 5). Post-hoc Tukey tests showed that the 6-7-year-olds (M = 95.74, SD = 3.59) made fewer correct responses to the go-stimuli compared to all other age groups (8-9-year-olds: M = 98.10, SD = 2.79, 10-12-year-olds: M = 98.51, SD = 1.57, 13-15-year-olds: M = 99.06, SD = 1.33, 18-25-year-olds: M = 99.41, SD = .75) (all p's < .05). The other age groups did not differ significantly from each other (all p's > .3).

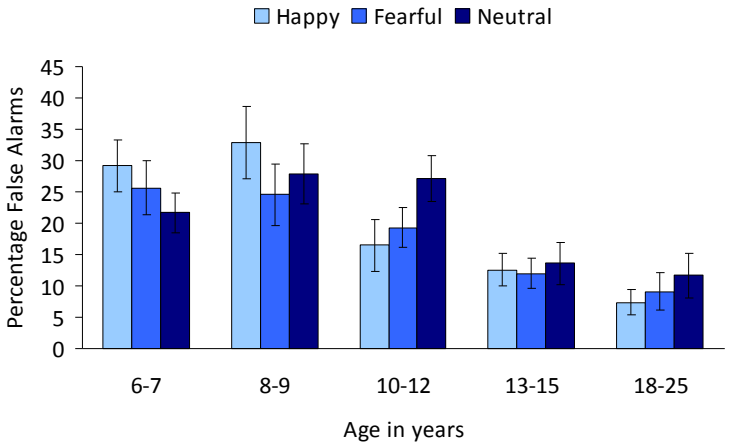

Figure 4. Percentage false alarms on the colored emotional go/nogo task. Participants were instructed to respond to colors and emotion was an irrelevant dimension.

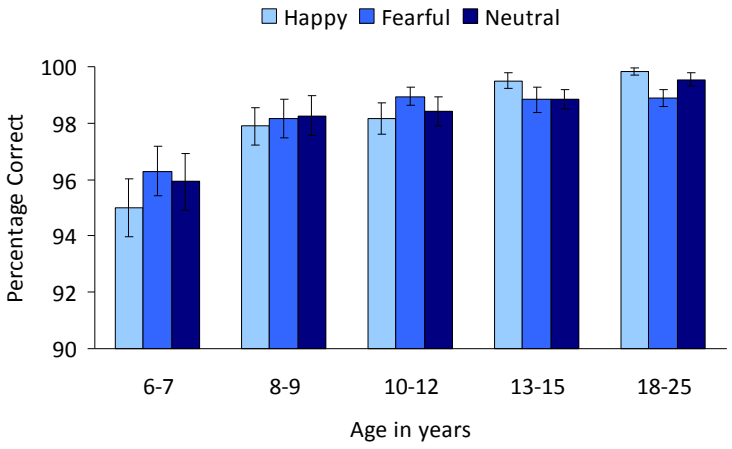

Figure 5. Percentage correct on the colored emotional go/nogo task. Participants were instructed to respond to colors and emotion was an irrelevant dimension.

Nogo choices. To further examine the influence of irrelevant emotions on action and inhibition, an Age group (5) x Emotion (3: neutral, happy, and fearful) repeated measures ANOVA for the choice trials was performed. No main effect of Emotion was observed ($p > .2$). Overall, the percentage of nogo-choices for choice trials increased with age, F (4, 84) = 4.64, $p < .005$ (see Figure 6). Post-hoc Tukey tests showed that the 6-7-year-olds (M = 32.31, SD = 20.10) did not differ significantly from the 8-9-year-olds (M = 43.07, SD = 19.70) (p = .16), but made significantly fewer nogo-choices compared to the oldest three age groups (10-12-year-olds: M =

48.86, *SD* = 14.84, 13-15-year-olds: *M* = 49.75, *SD* = 7.24, 18-25-year-olds: *M* = 49.44, *SD* = 8.71) (all *p*'s < .01). The oldest four age groups did not significantly differ in the percentage of nogo-choices (all *p*'s > .5).

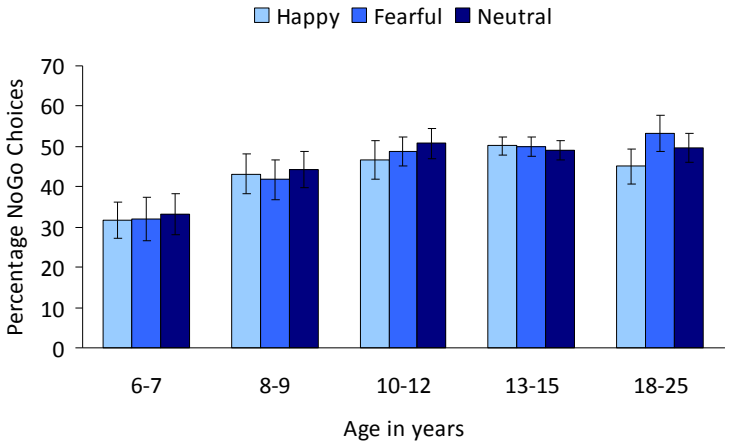

Figure 6. Percentage nogo choices on the colored emotional go/nogo task. Participants were instructed to respond to colors and emotion was an irrelevant dimension.

Reaction times. To examine whether irrelevant emotions influenced reaction times differently depending on condition (go versus choice), an Age group (5) x Condition (2: go and choice) x Emotion (3: neutral, happy, and fearful) repeated measures ANOVA was performed. A main effect of Condition, F (1, 89) = 220.41, p < .001, indicated that making an intentional decision to act took more time compared to acting in response to an external go-stimulus.

Overall, reaction times decreased with age, F (4, 89) = 5.04, p < .005 (see Figure 7). Post-hoc Tukey tests showed that the 6-7-year-olds were significantly slower compared to the two oldest age groups (both *p*'s < .05). The other age-groups did not differ significantly from each other (all *p*'s > .08).

As indicated by a Condition x Age group interaction, F (4, 89) = 4.25, p < .005, developmental differences in reaction times were more pronounced in the choice compared to go condition (see Figure 7).

Together, these results show an increase in performance with age. Irrelevant emotions had no effect on performance. Also in the choice condition, decisions to act or inhibit were not influenced by irrelevant emotions.

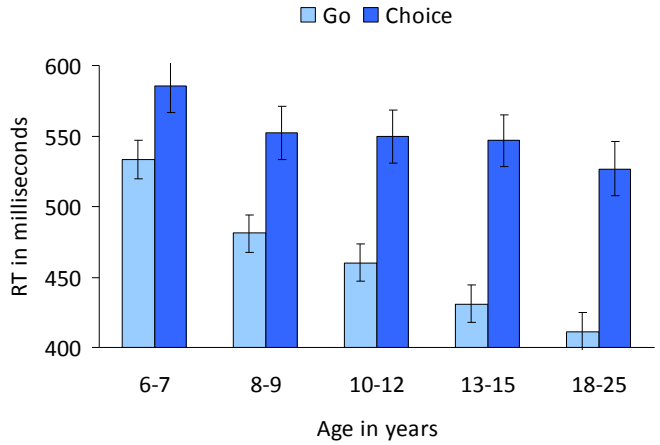

Figure 7. Developmental differences in RTs for the go- and choice-conditions. Participants were instructed to respond to colors and emotion was an irrelevant dimension.

6.4 Discussion

The present study examined the influence of relevant and irrelevant emotions on response inhibition across child and adolescent development. For this means participants performed two emotional go/nogo tasks, one in which emotion formed a relevant dimension and one in which emotion was an irrelevant dimension. The latter task also involved a condition in which participants could make free choices between responding and inhibiting. Here we will discuss the findings of the present study related to (1) the main effects of emotion on response inhibition, (2) the linear age-related increase in response inhibition performance within an affective context, and (3) the influence of irrelevant affective context in a free-choice situation.

Emotion effects

In the standard emotional go/nogo task relevant emotions influenced response inhibition. Overall, the blocks with fearful faces were more difficult compared to the blocks with happy faces. This finding could indicate that emotion recognition was easier in blocks with happy compared to fearful faces. Previous studies with the emotional go/nogo task have shown better performance (i.e. fewer false alarms) for negative compared to positive emotions (Chiu, et al., 2008; Schulz, et al., 2007). It should be noted that this reversed effect of better performance for negative emotions was found in the context of sad or anger facial expressions (Schulz, et al., 2007) and in the context of generally negative words (Chiu, et al., 2008). The one study also including fearful faces did not show a difference in performance between fearful and happy faces (Tottenham, et al., 2011). Thus, we reasoned based on prior studies that fearful faces and happy faces should not differ in demands on emotional recognition. Yet, the finding that performance was *worse* for fearful faces than for happy faces contrasts with these earlier studies.

Our observation of decreased performance in the blocks with fearful faces could be explained by literature showing negative effects of threatening stimuli on cognitive control in general (Lindstrom & Bohlin, 2012) and response inhibition in particular (Hartikainen, Siiskonen, & Ogawa, 2012; Lindstrom & Bohlin, 2012). Fearful faces are an indicator of possible threat and therefore might have a similar negative effect on response inhibition as threatening stimuli. Future studies should examine this effect of emotion valence vis a vis demands on emotion recognition in more detail.

One of the specific questions we aimed to study was whether the effect of emotions on inhibition was different for relevant and irrelevant affective contexts. In line with our expectations we found strong effects of relevant emotions on response inhibition, but no effects of irrelevant emotions on response inhibition. This is in agreement with prior studies showing small or no effects of irrelevant emotions on response inhibition (Albert, et al., 2010; Brown, et al., 2012; Lamm, et al., 2012; Sagaspe, et al., 2011; Todd, et al., 2012). This strengthens the hypothesis that differences in demands on emotion recognition may be a stronger indicator of inhibition performance than the presence of an emotion per se. Future studies should unravel whether it is truly the effect of an emotion that influences inhibition, or if other stimuli which differ in recognition demands would also result in inhibitory differences.

Developmental effects

Previous research has reported two interesting effects with respect to the development of response inhibition. First, several studies have reported a developmental increase in inhibitory control (Cohen-Gilbert & Thomas, 2013; Durston, Thomas, Yang, et al., 2002; Tottenham, et al., 2011; van der Molen, 2000), a finding which was supported in this study. Second, a prior study showed a dip in response inhibition performance for happy faces during mid-adolescence (Somerville, et al., 2011). This dip has been interpreted as an increased tendency to approach appetitive stimuli within adolescence, which is supported by the observation of increased activation in striatal reward areas when seeing those positive stimuli (Somerville, et al., 2011). We aimed to test this hypothesis in more detail in a large sample, but we could not replicate this finding, neither when emotion was a relevant dimension, nor when emotion was an irrelevant dimension of the task. Instead, we observed a linear increase in task performance independent of the influence of relevant and irrelevant emotions. This is in line with the findings of Tottenham et al. (2011) who also did not find an adolescent dip in performance on the standard emotional go/nogo task and findings of Cohen-Gilbert and Thomas (2013) who did not find an adolescent dip in performance on an emotional go/nogo task with irrelevant emotions. One possibility is that this effect is dependent on specific faces which were used or task instructions. The nonlinear development of sensitivity to emotions should be studied in more detail in future experiments.

In agreement with Tottenham et al. (2011) we showed a stable effect of emotions on response inhibition across development, such that inhibition was more difficult for fearful faces than for happy faces, especially when emotions were relevant

for the task. When emotions were irrelevant, we showed a small enhancement of happy faces on response inhibition, but response inhibition for fearful faces was comparable to response inhibition for neutral faces. In contrast, Cohen-Gilbert and Thomas (2013) showed decreased performance in the context of negative compared to neutral and positive irrelevant emotions across development. However, in this study pictures from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 2008) were used as irrelevant background stimuli. Negative pictures from the IAPS might be more salient in capturing attention compared to the fearful faces used in the present study, which could explain why we did not find a negative effect of irrelevant fearful faces in the present study (see also Hartikainen, et al., 2012; Lindstrom & Bohlin, 2012). Previous research has suggested that seeing emotional faces involves more emotion recognition, whereas seeing IAPS stimuli involves more emotion evocation (Britton, Taylor, Sudheimer, & Liberzon, 2006), resulting in more arousal. Therefore, arousal instead of valence per se might be the driving factor through which affective stimuli influence response inhibition.

Free choice

In the colored emotional go/nogo task free choice-trials were added to further examine the effect of irrelevant emotions on response inhibition. One could expect to observe a stronger effect of irrelevant emotions in a free choice situation, given that participants can use the affective context to base their decisions on (M Brass, Lynn, Demanet, & Rigoni, 2013). However, decisions to act or inhibit were not made on the basis of affective context. Brass et al. (2013) argued that in free choice situation social context can be an important motivator for behavior. Moreover, free choice experiments with an affective, social, or motivational context are more ecologically valid compared to the standard free choice experiments in which participants can choose between arbitrary response options (M Brass, et al., 2013). Here, however, we did not show an effect of irrelevant affective context on choice behavior. Future studies should address whether a more salient affective, social, or motivational context has a stronger effect on behavior.

There were also developmental differences in deciding between acting and inhibiting on the choice-trials. Young children in general chose to inhibit on a fewer percentage of trials than adults, which can reflect the same underlying mechanism as standard stimulus-driven inhibition (Bunge, Dudukovic, et al., 2002; Durston, Thomas, Yang, et al., 2002; Luna, et al., 2010; van der Molen, 2000). Thus, even in a choice context it was more difficult for them to choose to inhibit. Second, all participants were slower on choice trials than on go trials, consistent with prior studies on free choice (Kühn, et al., 2009). However, there was no developmental difference in reaction times on free choice trials, whereas there was a steep developmental decrease in reaction time to standard go trials. The latter finding is consistently reported in the developmental literature (Tamnes, et al., 2012), but the absence of age differences in choice trials suggests that the deliberation time of choice versus no choice puts additional demands on reaction time in adolescents and adults. But most importantly, this deliberation time was not dependent on irrelevant affective context.

An interesting question for future research will be to add a free choice condition to the task where affective context is relevant.

Limitations

The present study has a number of limitations. First, the standard and the colored emotional go/nogo tasks were explained in a slightly different manner. The colored emotional go/nogo task was explained in a game-framework, whereas the standard emotional go/nogo task was explained with standard instructions. This might have influenced how participants have experienced the tasks. If the colored emotional go/nogo task was experienced more as a game, this might have been more engaging for the younger participants. However, it is not very likely that this difference in framing had an effect on how emotion influenced task performance.

Second, the free choice condition was only presented in the emotional go/nogo task with irrelevant emotions. Therefore, we could not examine whether relevant affective contexts, in contrast to irrelevant affective contexts, would have an effect on choices to act or inhibit. A fruitful direction for future research would be to add such a free choice condition to an emotional go/nogo task with relevant emotions, to further unravel the effects of relevant affective context on response inhibition.

Third, the color of the emotional faces differed between tasks. In the standard emotional go/nogo task emotional faces were presented in grayscale, whereas in the colored emotional go/nogo task emotional faces were presented in color. Therefore, the relevance of emotion is confounded with the absence or presence of color. Future studies should examine whether the different influence of relevant versus irrelevant emotion remains present, when color remains constant.

Fourth, the present study was a behavioral study. Therefore, we could not examine the underlying mechanisms of the influence of relevant and irrelevant emotions on response inhibition. Future studies comparing the influence of relevant and irrelevant emotions on response inhibition should include psychophysiological measures to examine these mechanisms. Previous studies focusing on the effect of irrelevant emotions on response inhibition did not all observe effects on the behavioral level (e.g. Brown, et al., 2012). However, all studies showed an effect of irrelevant emotions on the neural level, indicative of increased effort when applying response inhibition within an affective context (Albert, et al., 2010; Brown, et al., 2012). One open question is whether this effect is equally strong for relevant and irrelevant emotions.

Summary and conclusion

Affective or social contexts can interact with cognitive control, especially during childhood and adolescence (Blakemore & Robbins, 2012). The present study set out to directly compare the influence of relevant and irrelevant emotions on response inhibition across development. We show that with increasing age there is a linear increase in response inhibition performance within affective contexts. In this large cross-sectional sample we have found no evidence of a previously observed mid-pubertal dip in affective response inhibition (Somerville, et al., 2011).

Furthermore, our results indicate that across development relevant emotions have a stronger effect on response inhibition compared to irrelevant emotions, and this effect was stronger in young children. In a free choice situation people did not base their decisions on irrelevant affective context. An interesting question for future research would be to incorporate a free choice condition in a response inhibition task with relevant affective context to further elucidate the influence of affective context on cognitive control.

Chapter 7
Summary and General discussion

This chapter is based on:
Schel, M.A., Scheres, A., & Crone E.A. (in press) New perspectives on self-control development: Highlighting the role of intentional inhibition. *Neuropsychologia*

7.1 Summary

The primary goal of this thesis was to gain insight in the development of intentional inhibition. In the first four empirical chapters the marble task was employed in combination with heart rate and/or neuroimaging measures to gain insight in the covert processes underlying intentional inhibition. The marble paradigm is a valuable paradigm for studying the dynamics of intentional inhibition, in which participants are instructed to freely choose between acting and inhibiting to a rolling marble. Since the free choice trials are presented intermixed with instructed action trials, responding to the rolling marble is the prepotent response in the marble paradigm. Given that responding is prepotent, intentional inhibition in the marble paradigm taxes the late veto-mechanism.

In chapter 2 the marble paradigm was combined with the study of phasic heart rate changes in a cross-sectional experiment comparing 3 age groups (8-10, 11-12, and 18-26). In this chapter it was shown that heart rate deceleration was a sensitive index of intentional action control. Both intentional inhibition and intentional action were associated with pronounced heart rate deceleration compared to externally guided action. Heart rate deceleration was most pronounced during intentional inhibition, indicative of the involvement of a central autonomic network in intentional inhibition. With regard to development, this study showed that children as young as 8-years-old are well able to intentional inhibit a prepotent response. Both on the behavioral and on the heart rate level, there were no differences between age groups in intentional inhibition.

Chapter 3 examined the differences and similarities between intentionally and externally guided inhibition at the neural level in a group of young adults (18-26). So far, dissociations between intentional and externally guided inhibition were mainly based on conceptual ideas regarding both forms of inhibition, but the differences and similarities were never directly tested. The study described in chapter 3 aimed to test this in an experiment in which participants performed two experimental tasks: the marble task as a measure of intentional inhibition and the stop-signal task as a measure of externally guided inhibition. The results of this study showed that intentional and externally guided inhibition were supported by a common neural network. However, dFMC was found to be specifically activated for intentional inhibition, not for externally guided inhibition. Importantly, results showed that dFMC activation was context specific, such that dFMC activation during intentional inhibition was reduced when there was a strong prepotency for acting (i.e. when the intentional inhibition trial was preceded by a larger number of green action trials).

The study described in chapter 4 examined the role of the central autonomic network involved in intentional action control in a combined fMRI and heart rate study. For this study heart rate was measured continuously, while participants lay inside the scanner. The heart rate results showed a replication of the heart rate results presented in chapter 2, with pronounced heart rate deceleration for intentional compared to externally guided action control. Furthermore, the results showed that for intentional action control heart rate deceleration was related to activation in medial frontal cortex (in a region posterior to the dFMC region found in chapter 3) and for

externally guided action control heart rate deceleration was related to activation in lateral PFC. These results are consistent with an often suggested medial/lateral distinction for intentionally versus externally guided action control, and indicate that heart rate deceleration is an integrated part of the central autonomic network involved in intentional action control.

The development of intentional inhibition was further examined in the study presented in chapter 5. This study examined the neural correlates of intentional inhibition in a group of children (10-12) and a group of young adults (18-26). Even though both age groups were well able to intentionally inhibit a prepotent response on about 50% of the choice trials, the results showed that children recruited the fronto-basal ganglia network to a different extent during intentional inhibition compared to adults. That is, compared to adults, children showed more activation during intentional inhibition relative to intentional action in the core regions of the fronto-basal ganglia network. Correlations between intentional inhibition and self-reported impulsivity also differed with age. Adults who reported more impulsivity, more often choose to intentionally inhibit and showed more activation in the left putamen during intentional inhibition, but for children these correlations were not significant.

The final empirical chapter described in this thesis (chapter 6), examined the development of inhibition within an affective context. In this study, participants performed two tasks: an externally guided inhibition task in which emotion formed a relevant dimension, and a combined externally and intentionally guide inhibition task in which emotion formed an irrelevant dimension. The results showed that across development emotion only influenced inhibition performance when it formed a relevant dimension of the task. With regard to the development of intentional inhibition this study showed that also children younger than 8-years-old (the youngest age tested with the marble task) are able to intentionally inhibit. The youngest participants in this study were 6-years-old and although they intentionally inhibited less frequently than the participants who were 8 years of age and older (until 26), they were able to intentionally inhibit a prepotent response.

In the following section the main results of the empirical chapters described in this thesis will be discussed and directions for future research will be presented.

7.2 General conclusions and future directions

At a conceptual level there are clear reasons to dissociate intentional and externally guided inhibition (Filevich, et al., 2012). However, most studies have looked at either intentional or externally guided inhibition and no studies have yet directly compared both forms of inhibition. Based on previous studies examining either intentional or externally guided inhibition, a different underlying neural architecture was proposed, with intentional inhibition being associated with dFMC activation and externally guided inhibition being associated with activation in the fronto-basal ganglia network. The studies described in this thesis were the first to examine both forms of inhibition within the same participants. Below, the general conclusions based on these studies for the development of intentional inhibition will be given.

Development of intentional inhibition

On the behavioral level, the developmental studies presented in this thesis have indicated that, in contrast to stimulus-driven inhibition, intentional inhibition as measured with the marble paradigm appears to have a relatively early developmental trajectory (chapters 2 and 5). This idea was reinforced by the absence of covert heart rate differences in response to intentional inhibition demands (chapter 2). However, the underlying neural correlates differed between children and adults, such that children compared to adults showed relatively more activation in the main nodes of the fronto-basal ganglia network during intentional inhibition compared to intentional action (chapter 5).

Thus, although in a neutral context, intentional inhibition performance appears to be mature in childhood, the underlying neural network is differently activated for children compared to adults, indicating that the network is still immature. Therefore, the neural network in children may be more vulnerable in motivationally and/or affectively relevant contexts. It remains an interesting question for future research to examine whether the developmental pathway of intentional inhibition is the same when faced with motivationally and/or affectively attractive options (see also the section: Self-control in context).

Neural networks for intentional inhibition

An important step in gaining insight in the development of intentional inhibition is gaining a better understanding of the neural network involved in intentional inhibition. The study presented in chapter 4 aimed to acquire this by examining the associations between heart rate deceleration and neural activation during intentional and externally guided action control. In this study it was shown that for intentional action control heart rate deceleration was related to activation in medial frontal cortex and for externally guided action control heart rate deceleration was related to activation in lateral PFC, consistent with an often-suggested medial/lateral distinction for intentional versus externally guided action control.

This study however, could not give insight in the dynamics of the neural network involved in intentional inhibition. That is, it does not help to understand how the different regions in the fronto-basal ganglia network and the dFMC interact to produce intentional inhibition. This will be an important question for future research, which could be examined with functional connectivity analyses, such as psycho-physiological interactions (PPI) or dynamic causal modeling (DCM). The studies employing the marble task, which are presented in this thesis, were not very well suited for these kinds of functional connectivity analyses, given the fast-paced version of the marble task that was employed in this study. Therefore, future studies examining the dynamics of the neural network involved in intentional inhibition would benefit from a slower-paced intentional inhibition task.

Another approach to gain a better understanding of the neural network involved in intentional inhibition is by examining the relationship between intentional inhibition and structural connectivity. Diffusion tensor imaging (DTI) can be used to examine fractional anisotropy (FA), a measure of white matter integrity, of the tracts connecting different brain regions in a neural network. Preliminary results based on

additional data collected as part of the studies presented in this thesis show that there are developmental differences in the relation between FA in the white matter tract connecting right IFG and right SMA/preSMA and measures of self-control between children and adults (see Figure 1) (Schel, Peper, & Crone, in prep). That is, for self-reported impulsivity both children and adults show a negative relationship with white-matter integrity, indicating that individuals who are more impulsive have lower white matter connectivity between regions important for self-control. However, for intentional inhibition related activation in the right IFG the relation with white matter integrity changes with age. For children there is no relation between neural activation and structural connectivity, but for adults, individuals who have better structural connectivity also show more activation during intentional inhibition in right IFG (one of the key inhibitory regions). Taken together, these preliminary results suggest that the fronto-basal ganglia network continues to mature from childhood to adulthood. Whereas the network may appear mature for some components of self-control (i.e. self-reported impulsivity), there appears to be continued development related to intentional inhibition. Thus, even though behaviorally children are able to perform well on the task, the underlying neural architecture remains immature, both on the functional (see chapter 5) and on the structural level.

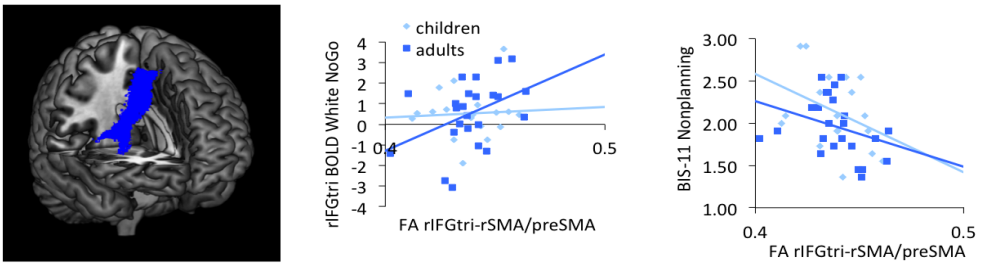

Figure 1. Associations between white matter integrity in the rIFG-rSMA/preSMA tract and self-control across development (Schel, et al., in prep).

Self-control in context

As mentioned before, intentional inhibition rarely happens in an affectively neutral situation. When this affective information is irrelevant, intentional inhibition performance appears not to be influenced by the affective context (chapter 6). However, when faced with motivationally and/or affectively attractive options intentional inhibition might be influenced, especially during adolescence, a time during which appetitive cues might be experienced more strongly (Somerville, et al., 2010).

An important motivator for self-control concerns determining the balance between preferring small immediate rewards over larger delayed rewards, a process also referred to as delay of gratification (Mischel, et al., 1989), or delay discounting (Ainslie, 2005; Green, Fry, & Myerson, 1994). Paradigms tapping into these processes are highly applicable to understanding intentional components of self-control, because in such paradigms, participants have control over whether to act and receive the

immediate reward, or to control the tendency to act by inhibiting and waiting for the delayed reward. A classic developmental paradigm in which these motivational forces are clearly present is the delay of gratification paradigm, also referred to as the marshmallow test. This delay of gratification paradigm for preschoolers presents children with one pair of two options: one marshmallow now, or two marshmallows after an unspecified delay (Mischel, et al., 1989). Studies using this paradigm have shown that there are individual differences in the ability to inhibit the impulse to choose the immediately gratifying option of one marshmallow during the preschool ages (Mischel, et al., 1989), which appear to be predictive for self-control abilities later in life (Casey, et al., 2011; Eigsti et al., 2006). In addition, Casey and colleagues found that individuals who were less able to delay gratification when they were preschoolers, showed poorer self-control and differential recruitment of the fronto-basal ganglia network during an emotional go/nogo paradigm 40 years later (Casey, et al., 2011), suggesting that these early individual differences reflect temperament characteristics with long term effects.

In addition to these individual differences, several studies have reported that preferences for small immediate rewards tend to decrease as a function of age, suggesting that self-control increases with age (Christakou, et al., 2011; de Water, Cillessen, & Scheres, in press; Lee, et al., 2013; Olson, Hooper, Collins, & Luciana, 2007; Prencipe et al., 2011; Scheres, et al., 2006; Steinberg et al., 2009). This has been observed both in real-time delay discounting task, in which participants really have to wait during the delay, and in hypothetical delay discounting tasks, in which participants not have to experience the delay. When hypothetical delay tasks are combined with brain imaging, it was found that in adults a network of brain regions, including medial prefrontal cortex (mPFC), ventral striatum, and posterior cingulate cortex (PCC), regions involved in the valuation of immediate rewards, and posterior parietal cortex (PPC), dorsolateral prefrontal cortex (dlPFC), and ventrolateral prefrontal cortex (vlPFC) regions involved in the valuation of immediate and delayed rewards, is associated with hypothetical delay discounting (for a review, see Scheres, de Water, & Mies, 2013).

To date, no study has yet examined the neural correlates of actual waiting for delayed rewards during real delay discounting tasks across development, which entails the intentional inhibition of an (tempting) action. The prediction would be that waiting for the delayed reward will be associated with increased activity in the dFMC, a region which partly overlaps with the mPFC region associated with hypothetical discounting. Currently, only a few studies have focused on the inhibition of tempting actions and these studies were all based on adults. These studies have shown that in adults, inhibiting the temptation to continue gambling (Campbell-Meiklejohn, et al., 2008), and inhibiting a craving for cigarettes (Brody, et al., 2007) both activate the dFMC, the same region implicated in intentional inhibition of motoric actions (Brass & Haggard, 2007; Kühn, et al., 2009; Schel, et al., 2014). Given that developmental differences seem present mostly when there is a strong motivation to act, an important model for future research will be to test the interplay between activity in brain regions which drive emotions and brain regions which 'veto' our motives to act, which will allow us to understand self-control from a broader perspective, integrating

knowledge from externally-guided response control, motivation, and internal self-control.

Implications for developmental disorders

There are several childhood/adolescence disorders, which are associated with problems with self-control, such as Attention Deficit Hyperactivity Disorder (ADHD) (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005), oppositional defiant disorder/conduct disorder (ODD/CD) (Nigg, 2003), and substance abuse (Wills & Stoolmiller, 2002). Traditionally, these disorders have been examined from a self-control perspective using externally driven inhibition tasks, with mixed results. For example, meta-analyses of studies using externally driven inhibition tasks have shown that there are clear inhibition problems in children and adults with ADHD (Lijffijt, Kenemans, Verbaten, & van Engeland, 2005; Willcutt, et al., 2005). However, effect sizes are small to moderate, and not all children with ADHD have problems with externally driven inhibition (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005). In terms of neurobiological correlates, the results of prior studies have shown that children and adults with ADHD show decreased recruitment of the fronto-basal ganglia network (including rIFG) during externally driven response inhibition compared to healthy controls (for meta-analyses, see: Cortese et al., 2012; Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013).

One interesting direction for future research on self-control in ADHD, will be to examine the role of intentional inhibition, given that in many daily life situations, children need to control impulses such as wanting to get up of their chair and walk around in the classroom. These types of behavior, which are typical or children with ADHD or conduct disorder, often require an internal decision to inhibit, or veto, actions. The behavioral paradigms and neurobiological model proposed in this thesis provide a promising starting point for examining intentional inhibition in these disorders. Additionally, as children grow up, adults expect an increasing ability to intentionally inhibit actions. Specifically, when still in their childhood, individuals with ADHD will more often than not have adults in their proximity who serve as external drivers of self-controlled behaviors. However, as individuals with ADHD get older, the demands on internally driven inhibition will only increase. For example, in high school and beyond, it is expected that students demonstrate self-controlled behaviors with less and less assistance from others. Therefore, an intriguing hypothesis, which could be addressed in future research, is that the development of intentional inhibition may play a role in the remission versus persistence of ADHD symptoms over time.

A promising start for studying intentional inhibition in motivationally relevant contexts in individuals with ADHD has been made in research employing delay discounting tasks (Barkley, Edwards, Laneri, Fletcher, & Metevia, 2001; Demurie, Roeyers, Baeyens, & Sonuga-Barke, 2012; Hurst, Kepley, McCalla, & Livermore, 2011; Paloyelis, Asherson, Mehta, Faraone, & Kuntsi, 2010; Plichta et al., 2009; Scheres, et al., 2006; Scheres, Tontsch, Thoeny, & Kaczkurkin, 2010; Wilson, Mitchell, Musser, Schmitt, & Nigg, 2011) or choice delay tasks (Solanto et al., 2001; Sonuga-Barke, Taylor, Sembi, & Smith, 1992; for a review, see: Luman, Oosterlaan, & Sergeant, 2005). These tasks are relevant here, because participants have control over whether

or not to control the tendency to act by inhibiting and waiting for the delayed reward. If these tasks are viewed as measures of intentional inhibition, a preliminary conclusion would be that those with ADHD have relatively weak intentional inhibition, since the majority of studies has demonstrated that individuals with ADHD chose not to control the tendency to act and prefer the immediate reward. However, it should be noted that additional processes are involved in delay discounting tasks such as delay aversion and sensitivity to reward magnitude and reward immediacy (Marco et al., 2009; Scheres, Tontsch, et al., 2010). Additionally, a substantial portion of these studies made use of hypothetical tasks, reducing the demand on intentional inhibition to resist a temptation. Therefore, other paradigms may be more suitable for measuring intentional inhibition in individuals with ADHD, both in cool contexts, such as the marble paradigm (Kühn, et al., 2009), and in hot contexts, such as the marshmallow paradigm (Mischel, et al., 1989).

A better understanding of the typical development of the underlying mechanisms of the ability to intentionally inhibit tempting actions, might help to better understand developmental disorders of impulsivity such as ADHD. Currently, many children with ADHD receive cognitive behavioral therapy focused on the use of external reinforcers in order to stimulate positive behavior (Serrano-Troncoso, Guidi, & Alda-Diez, 2013). However, an important direction for future research will be to examine whether shifting the focus to motivations and drives from within (internal processes) may help children, adolescents, and adults with ADHD to better regulate their own behavior.

7.3 Conclusion

To conclude, examining self-control development from the perspective of intentional inhibition is a valid and important road for future research. The studies presented in this thesis have shown that intentional inhibition can at least be partially dissociated from externally guided inhibition based on underlying neural networks. Furthermore, on the behavioral level intentional inhibition appears to have a relatively early development compared to externally guided inhibition. However, the underlying neural network is still immature in childhood, leaving the network potentially vulnerable under motivationally and/or affectively taxing circumstances. Therefore, it remains an important avenue for future research to examine whether this early development also holds up under motivationally and/or affectively taxing circumstances.

Nederlandse samenvatting

8.1 Inleiding

Zelfcontrole is de vaardigheid om zelf de controle te hebben over je eigen acties, gedachten en emoties (Casey & Caudle, 2013). Deze zelfcontrole vaardigheden zijn zeer belangrijk voor succesvol functioneren in het dagelijks leven (bijvoorbeeld in sociale situaties en in school- en werk-omgevingen). De ontwikkeling van zelfcontrole is daarom een belangrijk aspect van de cognitieve ontwikkeling van kinderen en adolescenten (Diamond, 2013).

De vaardigheid om zelf je acties te stoppen (intentionele inhibitie) vormt de kern van zelfcontrole. Intentionele inhibitie is gedefinieerd als een laat 'veto' mechanisme (Filevich et al., 2012) waarmee men er zelf voor kan kiezen om een alreeds geïnitieerde actie op het allerlaatste moment te stoppen (Filevich et al., 2012; Haggard, 2008). Dit proces verschilt van stimulus- of extern gedreven inhibitie, waarbij het niet iemands eigen gedachtenproces, maar een extern signaal is, dat aangeeft dat je met je actie moet stoppen.

Zover, heeft het meeste onderzoek naar de ontwikkeling van zelfcontrole gebruik gemaakt extern gedreven inhibitie taken. Echter, intentionele inhibitie is zeer belangrijk tijdens de ontwikkeling en problemen met intentionele inhibitie vormen ook een belangrijke component in psychologische stoornissen zoals Attention Deficit Hyperactivity Disorder (ADHD) (Moffit et al., 2011). Daarom is het doel van de studies beschreven in dit proefschrift om meer inzicht te krijgen in de ontwikkeling van intentionele inhibitie.

8.2 Intentionele inhibitie

In het dagelijks leven moeten we vaak zelf beslissen om onze acties te stoppen, aangezien er niet altijd expliciete signalen zijn die aangeven dat je moet stoppen. Ondanks dat intentionele inhibitie zo belangrijk is in het dagelijks leven, heeft voorgaand onderzoek zich voornamelijk gericht op de ontwikkeling van extern gedreven inhibitie. Uit dit onderzoek hebben we geleerd dat extern gedreven inhibitie een langzame ontwikkeling heeft. Jonge kinderen kunnen wel inhiberen, maar zij doen dit nog niet zo efficiënt als volwassenen (Luna et al., 2010). Ook laten kinderen een ander patroon van hersenactiviteit zien tijdens extern gedreven inhibitie dan volwassenen (e.g. Durston et al., 2002).

Een belangrijke reden waarom onderzoek naar de ontwikkeling van inhibitie voornamelijk naar extern gedreven inhibitie heeft gekeken, is dat intentionele inhibitie moeilijk te onderzoeken is. Bij het onderzoeken van de ontwikkeling van intentionele inhibitie hebben we te maken met drie belangrijke struikelblokken. Allereest resulteert intentionele inhibitie in geen gedragsoutput. Dit betekent dat wanneer we enkel naar gedrag kijken, we enkel kunnen zeggen of iemand heeft geïnhibeerd of niet. Echter, op basis van enkel geen gedrag is het moeilijk om te concluderen dat men daadwerkelijk een actie heeft geïnhibeerd (zie ook het derde struikelblok). Daarom zijn psychofysiologische en neuroimaging maten erg belangrijk in het onderzoek naar intentionele inhibitie, aangezien ze kunnen helpen om inzicht te krijgen in de aan

intentionele inhibitie ten grondslag liggende processen. Ten tweede, is intentionele inhibitie een intern proces, wat niet vooraf wordt gegaan door een extern signaal. Dit maakt dat intentionele inhibitie lastig is te manipuleren in een experimentele taak. Ten derde, om te kunnen spreken van intentionele inhibitie moet er ook daadwerkelijk een actie worden geïnhibeerd. Echter, op gedragsniveau kunnen we geen onderscheid maken tussen een actie die op het allerlaatste moment is geïnhibeerd en een actie die nooit was geïnitieerd. De vroege keuze om een actie niet te initiëren komt vaker voor in experimentele taken waarin er geen sterkte motivatie om een actie uit te voeren is (Filevich et al, 2012). Daarom is het belangrijk dat taken om intentionele inhibitie te onderzoeken een sterke motivatie of prepotentie voor actie bevatten.

In de experimenten beschreven in dit proefschrift is gebruik gemaakt van het knikkerspel om intentionele inhibitie te meten. In dit spel rolt er steeds een witte knikker van een helling naar beneden. Zodra de knikker begint te rollen, verandert de knikker van kleur en wordt hij groen. Deelnemers is gevraagd om zo snel mogelijk op een knop te drukken om de knikker te stoppen en er zo voor te zorgen dat de knikker niet van de helling afrolt en breekt. Deze groene knikker conditie creëert een prepotentie voor actie. Dat wil zeggen, zodra deelnemers een knikker bovenaan de helling zien liggen, zitten ze klaar om op de knop te druk zodra de knikker begint te rollen. Tijdens een gedeelte van de trials verandert de rollende knikker niet van kleur (hij blijft wit) en mogen de deelnemers zelf kiezen of ze willen reageren of inhiberen. Aangezien reageren de prepotente actie is in dit spel, heeft men het late 'veto' mechanisme voor intentionele inhibitie nodig in dit spel. De eerste 4 empirische hoofdstukken van dit proefschrift (hoofdstuk 2 t/m 5) maken gebruik van het knikkerspel in combinatie met hartslag en neuroimaging maten om meer inzicht te krijgen in processen betrokken bij intentionele inhibitie.

Hartslag

Een belangrijke maat om de aan intentionele inhibitie ten grondslag liggende processen te bestuderen is de studie van fasische hartslag veranderingen. Veranderingen van hartslag naar hartslag staan onder de controle van zowel het sympathisch als het parasympathisch zenuwstelsel (Berntson et al., 2007). Het sympathisch systeem heeft relatieve lange termijn effecten, het kost het sympathisch systeem enkele seconden om de hartslag te beïnvloeden. Het parasympathisch systeem daarentegen, heeft een meer direct effect op het hart en kan de hartslag snel vertragen. Deze snelle parasympathische hartslag vertraging wordt geïnterpreteerd als een oriëntatie reflex (Bradley, 2009).

Parasympathische hartslag veranderingen zijn een gevoelige index van cognitieve controle processen in het algemeen (Crone et al., 2003, 2004; Jennings et al., 2003) en van actie en inhibitie in het bijzonder (Jennings & Van der Molen, 2002; Van der Veen et al., 2000). Gedurende de voorbereiding voor een snelle reactie, treedt er gewoonlijke een voorbereidende hartslag vertraging op (Jennings & Van der Molen, 2002, 2005). Wanneer er een reactie wordt gegeven of een actie wordt uitgevoerd, wordt deze voorbereidende hartslag vertraging gevolgd door een hartslag versnelling, waardoor de hartslag weer herstelt naar zijn basissnelheid (Jennings & Van der Molen, 2005). Echter, wanneer men een actie inhibeerd, wordt deze hartslag

versnelling uitgesteld en vertraagd de hartslag verder (Jennings & Van der Molen, 2005, Van der Veen et al., 2000).

In dit proefschrift worden fasische hartslag veranderingen bestudeerd om meer inzicht te krijgen in de ontwikkeling van intentionele inhibitie (hoofstuk 2). In hoofdstuk 4 wordt deze maat gebruikt in combinatie met neuroimaging om meer inzicht the krijgen in het aan intentionele inhibitie ten grondslag liggende netwerk.

fMRI

Functionele MRI (fMRI) is een neuroimaging techniek die inzicht geeft in welke hersengebieden betrokken zijn bij cognitieve processen. Hierbij wordt gebruik gemaakt van de zogenaamde Blood Oxygenation Level Dependent (BOLD) response.

Deze techniek is veel gebruikt om de neurale correlaten van extern gedreven inhibitie te onderzoeken. Deze studies hebben laten zien dat er tijdens extern gedreven inhibitie een specifiek netwerk van hersengebieden actief is, waaronder de rechter inferior frontal gyrus, de pre-supplementary motor area en de subthalamic nucleus (Aron & Poldrack, 2006; Verbruggen & Logan, 2008). Recent, zijn er ook enkele fMRI studies naar intentionele inhibitie gedaan. Deze studies hebben laten zien dat voor volwassenen intentionele inhibitie, in tegenstelling tot extern gedreven inhibitie, is geassocieerd met activatie in een specifiek gebied in de frontale cortex, namelijk in de dorsal fronto-median cortex (Brass & Haggard, 2007; Kühn et al., 2009).

In dit proefschrift is fMRI gebruikt om te onderzoeken of intentionele inhibitie en extern gedreven inhibitie inderdaad op basis van het onderliggende neurale netwerk van elkaar onderscheiden kunnen worden (hoofdstuk 3). In hoofdstuk 5 is fMRI daarnaast gebruikt om de ontwikkeling van het aan intentionele inhibitie ten grondslag liggende neurale netwerk te onderzoeken.

8.3 Samenvatting van de studies

In de studie beschreven in hoofdstuk 2 speelden deelnemers het knikkerspel terwijl hun hartslag continue werd gemeten. In deze cross-sectionele studie werden 3 leeftijdsgroepen (8-10, 11-12, en 18-26) met elkaar vergeleken. De resultaten van deze studie laten zien dat fasische hartslag veranderingen een goede index zijn voor intentionele actie controle. Zowel intentionele inhibitie als intentionele actie waren geassocieerd met een sterkere hartslagvertraging dan extern gedreven actie. Tijdens intentionele inhibitie was de hartslagvertraging bovendien het sterkst. Daarnaast laten de resultaten zien dat jonge kinderen (8-jarigen) al zeer goed in staat zijn om intentioneel te inhiberen. Zij deden dit op hetzelfde niveau als de volwassenen in deze studie en ook op het gebied van fasische hartslag veranderingen waren er geen verschillen tussen de leeftijdsgroepen.

In hoofdstuk 3 zijn de verschillen en overeenkomsten tussen intentionele en extern gedreven inhibitie onderzocht in een groep jong-volwassenen (18-26 jaar). Tot nog toe, werden intentionele en extern gedreven inhibitie vooral van elkaar onderscheiden op basis van conceptuele ideeën ten aanzien van beide vormen van

inhibitie. Voorgaand fMRI onderzoek heeft weliswaar gesuggereerd dat intentionele en extern gedreven inhibitie zijn geassocieerd met verschillende neurale netwerken, maar dit is nog nooit direct getest is dezelfde proefpersonen. De studie beschreven in hoofdstuk 3 was de eerste om beide vormen van inhibitie direct te vergelijken. Hiervoor hebben de deelnemers twee taken uitgevoerd terwijl ze in de scanner lagen: het knikkerspel als een maat van intentionele inhibitie en een stop-signaal taak als maat van extern gedreven inhibitie. In de stop-signaal taak moesten de deelnemers zo snel mogelijk aangeven in welke richting een pijl wees. Echter, als de pijl onverwacht rood werd, was dit een extern signaal dat ze hun reactie moesten inhiberen. De resultaten van deze studie hebben laten zien dat intentionele en extern gedreven inhibitie in dezelfde proefpersonen worden ondersteund door eenzelfde neuraal netwerk. Echter, daarnaast was er ook activatie specifiek voor intentionele inhibitie in de dorsal fronto-median cortex, het hersengebied dat eerder met intentionele inhibitie was geassocieerd. De resultaten van deze studie laten echter zien dat de activatie van dit hersengebied context specifiek is. Dat wil zeggen, dit gebied was minder actief wanneer er een sterke prepotentie voor actie was.

Het netwerk geassocieerd met intentionele actie controle is verder onderzocht in hoofdstuk 4. Voor deze studie werd de hartslag continue gemeten terwijl de deelnemers in de MRI scanner het knikkerspel speelden. De hartslag resultaten waren een replicatie van de studie beschreven in hoofdstuk 2: hartslag vertraagde meer tijdens intentionele dan extern gedreven actie controle. Bovendien was hartslagvertraging geassocieerd met hersenactiviteit tijdens het knikkerspel. Tijdens intentionele actie controle was hartslagvertraging geassocieerd met activatie in de mediale frontale cortex (in een gebied iets achter het dorsal fronto-median cortex gebied uit hoofdstuk 3). Hartslagvertraging tijdens extern gedreven actie controle was geassocieerd met activatie in laterale frontale cortex. Deze resultaten zijn consistent met een vaak gesuggereerde mediaal/lateraal distinctie voor intentioneel versus extern gedreven actie controle. Ook laten ze zien dat hartslag vertraging een integraal onderdeel is van het centraal autonoom netwerk voor intentionele actie controle.

De ontwikkeling van intentionele inhibitie is verder bekeken in de studie beschreven in hoofdstuk 5. Deze studie focuste op de neurale netwerken die ten grondslag liggen aan intentionele inhibitie in een groep kinderen (10-12) en een groep jong-volwassenen (18-26). Zowel de kinderen als de jong-volwassenen waren in staat om hun prepotente reactie in ongeveer 50% van de tijd intentioneel te inhiberen. Ondanks hetzelfde gedragspatroon, verschilden de groepen in onderliggende neurale activiteit. Beiden groepen activeerden hetzelfde frontal-basal ganglia hersennetwerk, maar kinderen activeerden dit netwerk sterker tijdens intentionele inhibitie dan intentionele actie in vergelijking met volwassenen. Daarnaast waren er ook verschillen in correlaties tussen zelf-gerapporteerde impulsiviteit en intentionele inhibitie tussen de leeftijdsgroepen. Dat is, volwassenen die meer impulsiviteit rapporteerden, kozen er vaker voor om intentioneel te inhiberen en zij lieten ook meer activiteit in het putamen zien tijdens intentionele inhibitie. Voor kinderen waren deze correlaties niet significant. Dus ondanks het feit dat kinderen en volwassenen hetzelfde gedrag laten zien, blijkt het onderliggende netwerk voor intentionele inhibitie in kinderen nog niet volledig ontwikkeld.

In het laatste empirische hoofdstuk van dit proefschrift (hoofdstuk 6) is de ontwikkeling van intentionele inhibitie in een affectieve context onderzocht. Tot zover hebben alle studies gebruik gemaakt van het knikkerspel, waarmee de ontwikkeling van intentionele inhibitie in een neutrale context onderzocht kan worden. Echter in het dagelijks leven moet de beslissing om intentioneel te inhiberen vaak in een affectieve context gemaakt worden. Daarom zijn in deze studie twee inhibitie taken met een affectieve context gebruikt. De eerste taak was een extern gedreven inhibitie taak waarin emotie een relevante dimensie vormde. In deze taak moesten de deelnemers zo snel mogelijk reageren als ze een bepaald emotioneel gezicht zagen (bijvoorbeeld blij) en inhiberen als ze een ander emotioneel gezicht zagen (bijvoorbeeld neutraal). De tweede taak was een gecombineerde intentioneel en extern gedreven inhibitie taak waarin emotie een aanwezige, maar irrelevante dimensie vormde. In deze taak werden verschillende emotionele gezichten in verschillende kleuren getoond en de kleuren gaven aan of de deelnemer moest reageren, inhiberen of dat hij zelf mocht kiezen om te reageren of inhiberen (de intentionele inhibitie conditie). De resultaten van deze studie laten zien dat gedurende de ontwikkeling emotie alleen een effect heeft op inhibitie gedrag wanneer het een relevante dimensie van de taak vormt. Ten aanzien van de ontwikkeling van intentionele inhibitie, laten de resultaten zien dat ook kinderen jonger dan 8 jaar (de jongste deelnemers aan deze studie waren 6 jaar) in staat zijn om intentioneel te inhiberen. De 6-jarigen deden dit echter wel minder frequent dan de deelnemers van 8 jaar en ouder.

8.4 Algemene conclusies en richtingen voor vervolgonderzoek

De studies beschreven in dit proefschrift hebben laten zien dat intentionele inhibitie een relatief vroeg ontwikkelingstraject heeft in vergelijking met extern gedreven inhibitie. Dit werd onder andere ondersteund door het feit dat kinderen dezelfde hartslag responsen lieten zien als volwassenen tijdens intentionele inhibitie. Echter, het onderliggende neurale netwerk werd door kinderen sterker geactiveerd om tot hetzelfde gedrag als volwassenen te komen. Dit wijst erop dat het onderliggende netwerk voor kinderen nog niet volledig ontwikkeld is. Hierdoor kan het netwerk kwetsbaarder zijn in motivationele en affectieve contexten.

Om de mogelijke kwetsbaarheid van het onderliggende neurale netwerk in kinderen beter te begrijpen is het belangrijk om een beter inzicht in de dynamiek van dit netwerk te krijgen. De studies beschreven in dit proefschrift hebben laten zien welke hersengebieden bij dit netwerk betrokken zijn. De volgende stap is om te onderzoeken hoe deze hersengebieden met elkaar samenwerken om intentionele inhibitie te ondersteunen. Een veelbelovende aanpak hiervoor is om te kijken naar de connecties tussen de betrokken hersengebieden. Dit kan met behulp van diffusion tensor imaging, waarmee men de witte stof connecties tussen hersengebieden in kaart kan brengen. Voorlopige resultaten, verkregen uit additionele date verzameld als onderdeel van de studies in dit proefschrift, laten zien dat er ontwikkelingsverschillen zijn in de relatie tussen witte stof connecties en gedrag (Schel et al., in prep). Voor de ene component van zelfcontrole (impulsiviteit) is de relatie tussen witte stof

connecties en gedrag al vroeg op een volwassen niveau, terwijl voor de andere component van zelfcontrole (intentionele inhibitie) de relatie verschilt tussen kinderen en volwassenen.

Dit onvolwassen netwerk maakt intentionele inhibitie in kinderen kwetsbaar voor de mogelijke invloed van motivationele of affectieve contexten. De studie gepresenteerd in hoofdstuk 6 heeft laten zien dat affectieve context geen invloed heeft op intentionele inhibitie gedurende de ontwikkeling, wanneer deze affectieve context irrelevant is. Echter in het dagelijks leven is een motivationele of affectieve context vaak zeer relevant en kan dus een effect hebben op intentionele inhibitie. Dit effect zou bovendien extra sterk kunnen zijn gedurende de adolescentie, wanneer affectieve cues sterker worden ervaren (Somerville et al., 2010). Een belangrijke richting voor vervolgonderzoek is daarom om de ontwikkeling van intentionele inhibitie in een sterk relevante motivationele of affectieve context te onderzoeken.

Uiteindelijk kan een beter begrip van de aan intentionele inhibitie ten grondslag liggende mechanismen ook helpen om een beter begrip te krijgen van ontwikkelingsstoornissen waarin zelfcontrole een belangrijke rol speelt, zoals ADHD. Een belangrijke richting voor vervolgonderzoek is om te onderzoeken of een focus op intentionele inhibitie bij kinderen met ADHD kan helpen om hen te leren om hun gedrag beter te reguleren.

8.5 Conclusie

Samenvattend kan men concluderen dat het belangrijk is om zelfcontrole vanuit het perspectief van intentionele inhibitie te onderzoeken. Intentionele inhibitie kan op basis van zijn onderliggende neurale netwerk deels van extern gedreven inhibitie worden onderscheiden. Daarnaast heeft intentionele inhibitie een relatief vroeg ontwikkelingstraject in vergelijking met extern gedreven inhibitie. Echter het onderliggende neurale netwerk is nog niet volgroeid, waardoor het kwetsbaarder is in motivationele en affectieve contexten.

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Curriculum Vitae

Margot Schel was born on November 8th 1986 in Uden, the Netherlands. She graduated from the Udens College in 2005. In 2010 she received her Research Master's degree (cum laude) in developmental psychology from Leiden University. During her studies Margot has worked on several research projects in the Brain and Development Lab, which she joined as an Honours bachelor student in 2007. In October 2012, Margot started her PhD research in the Brain and Development Lab on the neurobiological bases of the development of intentional inhibition, which was supervised by Prof. Dr. Eveline Crone. This research project was part of a European Collaborative Research Project focused on intentional inhibition of human action. In September 2014, Margot started as a postdoctoral researcher in Prof. Dr. Torkel Klingberg's Developmental Cognitive Neuroscience Lab at the Karolinska Institute in Stockholm, Sweden.

Dankwoord

De weg van het begin van mijn promotietraject tot het schrijven en verdedigen van mijn proefschrift heb ik gelukkig niet alleen af hoeven leggen. Onderweg zijn er veel mensen geweest die mij hebben geholpen en geïnspireerd en daar wil ik hen graag voor bedanken.

Allereerst wil ik graag mijn promotor bedanken. Eveline, bedankt dat je me 7 jaar geleden als Honours bachelor student in het Brain & Develoment Lab hebt verwelkomd en mij een kijkje in de keuken van het developmental cognitieve neurosciene onderzoek hebt gegeven. Hiermee werd mijn passie voor het wetenschappelijk onderzoek gevoed en was de basis voor onze samenwerking gelegd. Ik ben heel blij dat ik de afgelopen jaren met jou heb mogen samen werken en zoveel van jou heb mogen leren. Ik wil je graag bedanken voor het vertrouwen dat je altijd in me stelt en de vele kansen die je me hebt geboden. Ik hoop van harte dat we in de toekomst blijven samenwerken.

Richard, bedankt voor alle interessante discussies over intentionele inhibitie. Ook bedankt dat je me liet aanschuiven bij de ACACIA meetings waar ik extra inspiratie voor mijn onderzoek kon opdoen.
Maurits, bedankt voor de samenwerking bij de hartslagstudies. Jouw kennis van de hartslagliteratuur heeft mij ontzettend geholpen om deze studies tot een succes te maken.
Anouk, bedankt voor de fijne samenwerking bij het schrijven van het reviewpaper.

I also want to thank the researchers involved in the Euroveto project. Patrick, Marcel, and Alex thank you for the all the inspiring project meetings. It was a great opportunity to work on this European Collaborative Research Project.

Ik had al het werk voor deze studies niet kunnen doen zonder de hulp van mijn bachelor en researchmaster studenten. In het bijzonder wil ik Dafna en Anita bedanken voor hun fantastische inzet voor de verschillende onderzoeken.

Daarnaast wil ik natuurlijk alle leden en oud-leden van het Brain & Development Lab bedanken voor de samenwerking en support. Jullie waren de beste collega's die ik kon wensen.

Natuurlijk wil ik ook mijn paranimfen bedanken. Geert-Jan, je was de beste kamergenoot die ik kon hebben tijdens mijn promotie. Bedankt voor alle gesprekken over onderzoek, alle gezelligheid en natuurlijk ook voor je steun tijdens mijn promotie. Carina, bedankt voor de vele Skype-gesprekken over onze promoties en natuurlijk ook voor je steun tijdens mijn promotie.

Lieve familie, natuurlijk wil ik ook jullie bedanken. Opa, bedankt voor alle steun en vertrouwen. Papa en Mama, zonder jullie had ik hier niet gestaan. Ontzettend bedankt voor jullie geloof in mijn kunnen en jullie grote betrokkenheid.

Lieve Bart, jij bent de allerbeste. Bedankt dat je er altijd voor mij bent. Het maakt niet uit of je dichtbij bent, zoals tijdens mijn promotie, of ver weg, zoals nu tijdens mijn Zweedse avontuur. Jij bent er altijd.