Free won't : neurobiological bases of the development of intentional inhibition

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Chapter 1
General introduction

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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).

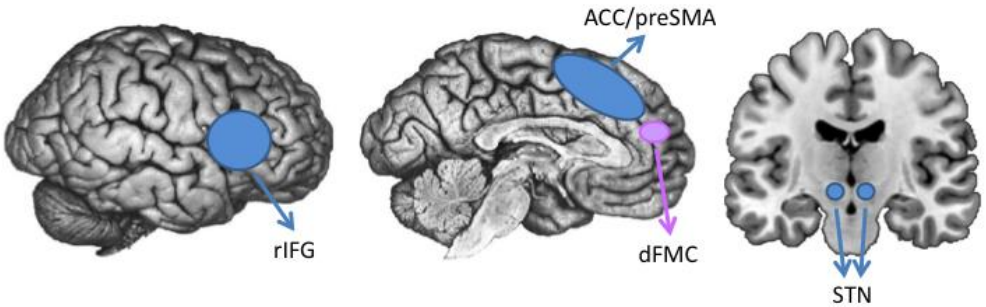

Figure 1. Brain regions associated with externally guided inhibition (in blue) and internally guided inhibition (in purple).
Note. rIFG = right inferior frontal gyrus, ACC/preSMA = anterior cingulate cortex/presupplementary motor area, dFMC = dorsal fronto-median cortex, STN = subthalamic nucleus.

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.