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Chapter 7
Summary and General discussion

This chapter is based on:
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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 psychophysiological 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
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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 (vIPFC) 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
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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.