Neuromodulation of cognitive-behavioral control

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Introduction

Without even realizing, human beings perform extraordinary feats on a daily basis. We navigate an increasingly complicated and demanding world by using our sophisticated ability to override habitual tendencies. Furthermore, we can meticulously plan, carry out and adapt actions in order to achieve goals that we set for ourselves. This capacity for goal-directed behavior—often considered a hallmark of human excellence over other animals—is commonly referred to as 'cognitive control' or 'executive function'. These are rather vague, typically synonymous concepts that serve more as an umbrella term for many different processes rather than referring to a single, unitary function. Decades of neuropsychological research have been devoted to understanding cognitive control and its component processes, the way it is implemented in the brain, and how we can alter—and possibly improve—its efficacy. These issues have driven the work included in this dissertation. In particular, the research presented in this dissertation concerns itself with the overarching questions of how chemical processes in the brain enable and affect cognitive control, and how we might non-invasively measure and manipulate these biological underpinnings of goal-directed behavior.

Cognitive control

When it comes to defining and operationalizing cognitive control, this dissertation has been inspired by two influential and certainly not mutually-exclusive theoretical frameworks. The first framework is represented in the seminal work by Miyake et al. (2000), who focused on identifying three major executive functions and determining their separability. They postulate that cognitive control consists of three major functions, including *inhibition* (i.e., the ability to withhold prepotent / dominant responses), *updating* (i.e., the ability to maintain and update working memory representations), and *shifting* (i.e., the ability to switch between goals or task-sets). A key finding by Miyake et al. is that these functions are (only) moderately correlated with each other,

implying that these are separable processes that might be sensitive to different manipulations. Consistent with this idea, cognitive training studies have shown that training one of these functions rarely produces transfer effects to the others. However, the moderate correlation of these functions also highlights that executive functions may have a common underpinning—which will be elaborated upon momentarily—and that their efficacy may rely on each other (see Diamond, 2013).

The second theoretical framework concerns itself less with specific cognitive functions and instead proposes that there are different cognitive control 'modes' or 'states' that determine the way in which the aforementioned functions might operate. In particular, control mode is thought to vary from (i) a more stable setting that supports maintenance of task goals and shields them from distraction, to (ii) a more flexible setting that promotes disengagement from and switching between goals (Cools & D'Esposito, 2011; Goschke, 2003; Hommel, 2015). Each control mode is advantageous in different situations, but also has its own notable disadvantages. Whereas a stable control mode allows for the pursuit of a particular goal, it also carries the risk of rendering one too rigid to adapt to a change in environmental demands. In contrast, a flexible control mode allows for efficient switching between goals or task-sets, but can render one distractible when this switching is not done selectively. As such, adaptive cognitive control requires a balance between the opposing demands of cognitive stability and flexibility, which is also known as the *cognitive control paradox* or the *paradox of the flexible mind*.

There is great compatibility between these two theoretical frameworks of cognitive control. For example, Miyake et al. (2000) report considerable individual differences in performance on tasks that tap into the three postulated executive functions, and these differences might stem from individual variability in cognitive control mode. That is, those with a more stable control mode would plausibly be better at the inhibition of responses triggered by distracting, task-irrelevant stimuli, whereas those with a flexible control mode would have an easier time updating their working memory representations and switching between goals or task-sets. This idea has been supported by a variety

of studies (for example, Colzato, Ozturk, & Hommel, 2012; Colzato, Sellaro, Samara, & Hommel, 2015; Colzato, Szapora, Lippelt, & Hommel, 2017; Fischer & Hommel, 2012; Fröber & Dreisbach, 2017). The question of *why* some individuals demonstrate superior inhibitory control or cognitive flexibility addresses another commonality between these theoretical frameworks and the shared biological underpinning of executive functions that was alluded to earlier: dopamine activity in the brain.

Dopamine

The neurotransmitter dopamine is thought to be a major determinant of individual differences in cognitive control mode and efficiency of the three major executive functions. Dopamine is commonly referred to as a neuro*modulator* because of its widespread, complex effects on neural activity (Nieoullon, 2002; Seamans & Yang, 2004). Rather than following a 'more is better' rule, the relationship between dopamine activity and cognitive performance typically follows a characteristic inverted-U-curved relationship (Cools & D'Esposito, 2011; Cools, 2006; Goldman-Rakic, Muly, & Williams, 2000). That is, a moderate level of dopaminergic activity is generally associated with optimal performance, whereas both lower and higher dopamine activity are associated with suboptimal performance.

Although dopamine is perhaps most well-known to the general public for its role in reward, the experience of pleasure, and addiction, its significance to cognitive control is difficult to overstate. To understand this significance, it is important to distinguish between two dopaminergic pathways in the brain that contribute differentially to cognitive control. These are (i) the mesocortical pathway that projects to cingulate and prefrontal cortices, and (ii) the nigrostriatal pathway that projects to the subcortical basal ganglia. In brief, dopaminergic activity in the former pathway is thought to support cognitive stability whereas activity in the latter pathway promotes cognitive flexibility (Cools & D'Esposito, 2011; Cools, 2006).

In more detail, within the prefrontal cortex (PFC) dopamine modulates cognitive control via two distinct receptor families: the D1-like and D2-like

receptors. As outlined in the dual-state theory of PFC function (Durstewitz & Seamans, 2008), dopaminergic stimulation of prefrontal D1-like receptors inhibits firing of neurons in a low, spontaneous firing state while enhancing the firing of neurons in a high, persistent activity state. This increases the cortical signal-to-noise ratio and facilitates the stability of mental representations maintained in PFC. On the other hand, activation of D2-like receptors leads to an overall decrease in inhibition of PFC neurons, which facilitates their spontaneous firing and thereby promotes flexible but also interference-prone representations (Robbins, 2005; Seamans, Gorelova, Durstewitz, & Yang, 2001; Seamans & Yang, 2004; Trantham-Davidson, Neely, Lavin, & Seamans, 2004). As such, dopamine in the PFC is assumed to impact the balance between a stable and flexible control mode through the ratio of D1 and D2-like receptor activation.

Within the basal ganglia, dopamine promotes flexible control via an input-gating mechanism that determines whether the PFC is open to new information. The *prefrontal-cortex basal-ganglia working memory model* (Frank, Loughry, & O'Reilly, 2001; Hazy, Frank, & O'Reilly, 2006; O'Reilly, 2006) proposes that phasic dopamine release in the basal ganglia opens a proverbial gate to the PFC, which renders cortical representations susceptible to updating and interference, whereas a lack of dopamine activity in basal ganglia keeps the gate closed and thereby shields cortical representations from distraction (see also Braver & Cohen, 2000). Notably, dopaminergic stimulation of D1-like receptors in the basal ganglia facilitates gating whereas D2-like receptors hinder it, and increased tonic dopamine level in the basal ganglia leads to preferential D1 over D2 stimulation (Hazy et al., 2006; O'Reilly & Frank, 2006; van Schouwenburg, Aarts, & Cools, 2010). Consequently, higher dopamine levels in the basal ganglia promote flexibility by facilitating access of information to PFC. At the same time, however, this also increases the risk that task-irrelevant information interferes with maintenance in PFC, thereby increasing not only flexibility but distractibility as well.

In sum, dopamine is of great importance to understanding cognitive control. Via regionally-specific effects in cortical and subcortical networks, it can bias cognitive processing to be either more stable or flexible, thereby impacting the efficacy of inhibition, updating and shifting. However, it would be remiss to imply that dopamine is the only neurotransmitter with relevance to cognitive-behavioral control. Other neurotransmitters are also known to play critical roles, such as noradrenalin (Robbins, 2005), serotonin (Cools, Roberts, & Robbins, 2008), and glutamate and GABA (de la Vega et al., 2014; Munakata et al., 2011). Accordingly, the final chapters of this dissertation shift the focus toward the latter two neurotransmitters, glutamate and GABA, and aim to investigate how manipulation of these neurotransmitter systems impacts control.

Glutamate and GABA

As the primary excitatory and inhibitory neurotransmitters, respectively, glutamate and GABA play an important role in the control over actions. In brief, it is thought that glutamate and GABA (and particularly the ratio between them) determine the level of intracortical inhibition, which in turn affects the ability to select one particular representation or action among alternatives (de la Vega et al., 2014; Munakata et al., 2011). This may affect common daily life situations, such as deciding which word to use in a sentence and making a decision when there is no clear best option.

In brief, higher levels of glutamate (and conversely, lower GABA levels) suppress the competition between representations in PFC, making it more likely that alternative, perhaps even task-irrelevant competitors become active. This can result in choosing an incorrect action, or slowing down the process of choosing the appropriate one. In contrast, greater inhibition (due to lower glutamate and/or higher GABA levels) has the opposite effect by suppressing activation of competing responses (de la Vega et al., 2014; Jocham, Hunt, Near, & Behrens, 2012). Several studies have confirmed this model of action selection within the brain, for example by showing that higher GABA concentration in certain regions predict faster (Dharmadhikari et al.,

2015) and more accurate (Haag et al., 2015) responses in the Simon task, a classical response-interference paradigm (Hommel, 2011).

In light of this model of action selection and inhibition in the brain, the final three chapters in this dissertation investigate how a presumed increase or decrease in neural inhibition affects response selection. This is examined by making use of the serial reaction time (SRT) paradigm (Abrahamse & Noordzij, 2011), in which one needs to carry out a sequence of button presses in rapid succession. This sequence can be either random, or contain an embedded second-order conditional (SOC) sequence. Whereas a random response sequence requires a strongly stimulus-based, reactive mode of control, in a SOC sequence it is possible to use knowledge about the previous two responses to anticipate which response is required next. As such, SOC sequences allow for a shift toward a more plan-based, proactive mode of control (Tubau, Hommel, & López-Moliner, 2007) that allows for increasingly faster and more accurate responses. As such, the SRT task allows us to investigate response selection, inhibition of non-target responses and the implicit formation of response sequence structures, each of which are assumed to be sensitive to a change in neural inhibition.

Overview

This dissertation can be divided into three overarching topics. The first section (Chapters 1-2) presents one literature review and one empirical study that focus on non-invasive markers of individual differences in dopamine function and whether it is possible to predict cognitive control performance based on these differences. The second section (Chapters 3-7) shifts away from this correlational approach and toward mild experimental manipulations of the dopaminergic system and their associated changes in cognitive control, as discussed in two literature reviews and two empirical studies. Lastly, the third section (Chapters 8-10) covers three empirical studies that used different methods of manipulating neural inhibition in order to examine the corresponding effects on action selection.

Chapter One presents a comprehensive review of literature that has used the spontaneous eye blink rate (EBR) as an indirect marker of dopaminergic activity. As covered in this chapter, there is a large body of literature showing a positive correlation between EBR and dopaminergic activity. In brief, pharmacological studies have shown that dopamine agonists and antagonists respectively increase and decrease EBR, and clinical populations with hypoactive dopamine activity exhibit lower EBR whereas those with hyperactive dopamine activity demonstrate higher EBR. Particularly interesting is the finding that EBR in healthy individuals can predict cognitive performance on a wide variety of experimental paradigms. Consistent with the idea that EBR is primarily associated with dopaminergic activity in the basal ganglia, higher EBR predicts greater cognitive flexibility as measured, for example, by task-switching and divergent thinking paradigms.

Considering the already extensive literature on EBR as marker of dopaminergic activity, **Chapter Two** presents a study that focuses on a different aspect of our eyes that may predict dopaminergic activity. Specifically, it appears that color vision, i.e., the ability to discriminate between colors, can predict individual differences in dopamine and associated cognitive functioning. This was investigated by assessing both color vision and performance on an action cascading (also referred to as multitasking or task-switching) paradigm. Action cascading refers to the ability to chain together and switch efficiently between different task goals. This can be done in a more serial, step-by-step manner in which the next task goal is activated only when the previous goal has fully finished, or in a more parallel, overlapping manner in which different task goals are activated simultaneously. Action cascading is known to be related to dopamine function, as a previous study demonstrated that individuals who are genetically predisposed to greater dopamine D2 receptor function (which is particularly prevalent in the basal ganglia) tend to process goals in a parallel manner. The results in Chapter Two demonstrate that, similarly, individuals with good color vision demonstrate performance that is consistent with a more parallel rather than serial processing mode. This

tentatively suggests that good color vision is particularly predictive of the dopamine D2 receptor and cognitive flexibility. A discussion of this interpretation, and an alternative perspective, will be elaborated upon in the Discussion section of this dissertation.

Although markers such as EBR and color vision can allow us to investigate presumed individual differences in dopamine function, this approach is correlational in nature and therefore does not confirm a causal role for dopamine in the reported findings. That is why the following chapters focus instead on a mild but effective method of manipulating dopaminergic activity. In **Chapter Three** a comprehensive review is presented regarding the cognitive-behavioral effects of administering the food supplement L-tyrosine, which is also the biochemical precursor of dopamine. Given that tyrosine can be converted into dopamine in the brain, many studies have investigated whether tyrosine supplementation can benefit cognitive processes that are modulated by dopamine. Indeed, tyrosine has been shown to enhance the three executive functions outlined by Miyake et al. (2000), that is inhibition (Colzato, Jongkees, Sellaro, van den Wildenberg, & Hommel, 2014), task-switching (Steenbergen, Sellaro, Hommel, & Colzato, 2015), and in particular working memory (Colzato, Jongkees, Sellaro, & Hommel, 2013; Jongkees, Sellaro, et al., 2017; Thomas, Lockwood, Singh, & Deuster, 1999). Notably, the effects of tyrosine appear to be reliable only when one is exposed to an external stressor such as heat, cold or noise, or an internal stressor such as high cognitive load. Therefore, tyrosine is proposed to be a 'depletion reverser', being effective only in circumstances where performance would normally be degraded by the depletion of cognitive resources, motivation, or dopamine levels.

Chapter Four serves as an extension of the previous chapter, by highlighting that the effects of tyrosine supplementation are likely to depend on individual differences in dopamine function. Indeed, it is often observed that the effect of dopaminergic manipulations are state-dependent and differ for those with low or high baseline dopamine levels. Typically, those with lower dopamine levels are shifted upward on the inverted-U-curve relating

dopamine and cognitive performance when provided with an increase in dopamine activity. In contrast, those with higher dopamine levels would subsequently shift downward to the right side of curve. For low and high baseline dopamine individuals this would respectively lead to an observed increase and decrease in cognitive performance relative to baseline[1]. That is why the brief review in Chapter Four proposes several possible markers of individual differences in dopamine function that might predict the efficacy of tyrosine supplementation. These markers include EBR and color vision as discussed in earlier chapters, as well as genetic markers of dopamine function in PFC or basal ganglia. A recent study has confirmed one of these hypotheses by demonstrating that tyrosine supplementation was most effective in individuals with a genetic predisposition toward lower dopamine activity in the basal ganglia (Colzato et al., 2016), who presumably have the most room for shifting upward on the curve relating dopamine activity and performance.

Chapter Five presents one of the empirical studies on tyrosine supplementation that is included in the review in Chapter Three. In particular, this chapter investigates the efficacy of tyrosine supplementation in enhancing inhibitory control, which is known to be dependent on dopamine activity. This is investigated by means of the stop-signal paradigm, in which participants must carry out a simple forced-choice reaction time task as fast as possible unless a stop signal indicates they should withhold their response. By varying the onset delay of the stop signal, it is then possible to estimate how much time someone needs to successfully inhibit their response. As expected, the results revealed that participants were faster in withholding their responses after tyrosine supplementation as compared to a placebo. In contrast, response execution remained unaffected, highlighting that tyrosine supplementation is only effective in enhancing performance on particularly demanding tasks.

In **Chapter Six** a different approach to dopaminergic manipulation is taken, by making use of transcranial direct current stimulation (tDCS). This is

[1] However, it should be noted that such a pattern of results can also be accounted for by regression to the mean (see Barnett, van der Pols, & Dobson, 2005). Future studies need to consider and address this alternative explanation, which is often not done in the existing literature.

a noninvasive method of brain stimulation that is known to alter cortical excitability and neural plasticity. It is thought that tDCS can affect dopamine not directly but indirectly by acting on GABA, which in turn has a modulatory influence on dopaminergic signaling. Although there are many studies showing that tDCS can affect cognitive performance, there is also considerable doubt about the reliability of its effects as results have varied across studies. This is likely related in part to methodological differences between studies, but it has been suggested that individual differences in dopamine can also contribute to variability in response to tDCS (Wiegand, Nieratschker, & Plewnia, 2016). There are some studies that support this notion. In light of the aforementioned inverted-U-curve relating dopamine activity and cognitive performance, previous studies indicate that applying excitatory (anodal) stimulation to individuals with already high dopaminergic signaling leads to an impairment in performance. Conversely, applying inhibitory (cathodal) stimulation to those with already low dopaminergic signaling also leads to impaired cognitive control. This pattern of results has been observed by distinguishing between individuals with a genetic predisposition toward higher or lower dopamine activity in the PFC. However, it is important to acknowledge that genetics studies can only offer correlation evidence and do not speak to the causal role of dopamine in the effects of tDCS. That is why the study presented in Chapter Six sought to take a more experimental approach by combining tDCS with tyrosine supplementation and assessing the effects on working memory, which is the most often investigated cognitive function in tDCS studies. As in the majority of previous studies, tDCS was applied to the dorsolateral PFC, which is a region important for cognitive control and in particular working memory. Consistent with the aforementioned findings on genetics, the results demonstrated that the combination of tyrosine and excitatory stimulation produced an impairment in working memory performance. This finding supports the notion that tDCS can affect dopamine in the brain and lead to a detrimental increase in dopaminergic signaling when combined with a manipulation that also augments dopamine activity.

In light of the evidence supporting a role for dopamine in the effects of tDCS, **Chapter Seven** investigated whether the pattern of results in the previous chapter can be mirrored by pre-existing individual differences in dopamine activity rather than an experimental manipulation thereof. If this were the case, then this and the previous chapter would have the important implications that (i) dopamine plays a role in the effects of tDCS and (ii) individual differences in dopamine activity might contribute to variability in the effects of tDCS. To investigate the latter hypothesis, this chapter presents a study using the same experimental set-up as in Chapter Six. Instead of a tyrosine manipulation, this time participants were genotyped for the COMT Val^{158}Met polymorphism, which determines the level of dopaminergic signaling in the PFC. Similar to the pattern of results observed in Chapter Six, it was hypothesized that applying excitatory stimulation to those with a predisposition toward higher dopamine activity would demonstrate worse working memory performance. Curiously enough, however, the study yielded only null-findings. That is, different COMT polymorphisms were not associated with different responses to the tDCS. Combined with the findings from the previous chapter, this implies that results from studies including pharmacological manipulation (e.g., tyrosine) should be generalized only with caution to findings of inter-individual differences (e.g., the COMT polymorphism). In this particular case, state (i.e., a manipulation of) and trait (i.e., baseline) differences in dopamine appear to exert different effects on tDCS

Chapter Eight marks the transition away from dopamine and toward the topic of neural inhibition and response selection. The next following chapters, each in their own way, investigate how a presumed increase or decrease in neural inhibition affects the ability to select the right response from several alternatives. In Chapter Eight the first study related to this topic is presented, which focused on the food supplement glutamine. Similar to how tyrosine is the precursor to dopamine, so is glutamine the precursor to glutamate and GABA. These are the main excitatory and inhibitory neurotransmitters, respectively, and therefore supplementation of glutamine

could potentially affect the level of neural inhibition. Despite glutamine being a popular supplement used often by bodybuilders, its cognitive-behavioral effects have been little examined so far. To investigate if and how glutamine affects response selection, participants were supplemented with glutamine or placebo and then performed the SRT task, which taps into both sensorimotor (i.e., stimulus-based) control and implicit sequential learning. The results revealed no effect of glutamine on motor learning, but those who received glutamine did demonstrate an overall increase in response errors, particularly when the task required them to switch responding from one hand to the other. This finding implies that glutamine enhanced the level of glutamate over GABA, thereby increasing cortical excitability and the response competition between different alternatives. This impairment appeared to be reliable only when switching between hands during the task, indicating that the increased cortical excitability allowed the laterality of the previous response to interfere with the current one. This is the first demonstration that glutamine can impair response selection via a presumed decrease in neural inhibition.

In **Chapter Nine** it was investigated whether the opposite can also be demonstrated. That is, whether an increase in neural inhibition could enhance response selection. Correlational evidence for this idea already exists, as studies have shown that individuals with greater GABA levels in striatal and thalamic regions are better at selecting a correct response from several competing options. In order to obtain causal evidence for this idea, the study in Chapter Nine made use of transcutaneous (through the skin) vagus nerve stimulation (tVNS), a non-invasive method of brain stimulation that can effectively enhance GABA level in the brain. This manipulation was again combined with the SRT task, to determine whether tVNS benefits response selection processes. Similar to the previous chapter, there were no differences in implicit sequence learning between those who received active (real) or sham (placebo) stimulation. However, as expected tVNS did enhance response selection. In particular, active tVNS eliminated a phenomenon similar to 'inhibition of return', in which participants are slower when the currently-required response is the same as the response on two trials earlier. In other

words, whereas those receiving sham tVNS did demonstrate this inhibition of return, also referred to as a reversal effect, those receiving active tVNS did not demonstrate such slowing of response speed. This finding converges on reports from previous studies that suggest tVNS, via a presumed enhancement of GABA, can be an effective tool to enhance cognitive-behavioral control.

Lastly, in **Chapter Ten** neural inhibition was manipulated with tDCS. However, whereas previously mentioned tDCS studies typically directly targeted PFC regions, in this chapter tDCS was instead applied to the cerebellum. This area is notable for the fact that it contains up to 80% of all neurons in the entire brain, and it is known to play an important role in the planning, initiation and coordination of movement. Few studies have yet investigated if cerebellar tDCS can affect response selection, but evidence in favor of this possibility comes from a study demonstrating that cerebellar tDCS can modulate a phenomenon called 'cerebello-brain inhibition' (CBI). This refers to the fact that the cerebellum exerts an inhibitory tone over the primary motor cortex, and this inhibition can be strengthened by excitatory and weakened by inhibitory stimulation of the cerebellum. This in turn can affect whether it is more difficult or easier to initiate movement. To investigate whether this modulation of CBI can indeed translate to a change in response selection ability, in Chapter Ten participants received either excitatory (anodal), inhibitory (cathodal) or sham (placebo) stimulation to the cerebellum while performing the SRT task. As in previous chapters, this manipulation did not appear to immediately affect implicit motor sequence learning, but the excitatory stimulation as compared to inhibitory and sham stimulation did impact response selection as evidenced by an overall increase in reaction time. This finding is consistent with the idea that excitatory stimulation of the cerebellum strengthens CBI and thereby hinders the ability to initiate movement. Notably, this study also included a 24 hour follow-up session without any tDCS, in order to investigate how stimulation during the task might have affected consolidation processes after the task had finished. This follow-up revealed that the pattern of results on the previous day persisted: those who had received excitatory stimulation still demonstrated increased

reaction times, but only when they were presented with two different response sequences in the same SRT block. Possibly, this indicates that excitatory stimulation of the cerebellum did affect how robustly participants acquired the motor sequence, which became apparent only when an untrained sequence on day two interfered with the trained sequence. These results are among the first to establish cerebellar tDCS as a potential tool for modulating response selection, and they suggest that its effects are mediated by a change in the inhibitory tone of the cerebellum over primary motor cortex.

Concluding this overview, the chapters in this dissertation provide further insight into if and how it is possible to measure individual differences in the neural chemistry underlying cognitive-behavioral control. Furthermore, it explores various methods for noninvasive manipulation of these biological underpinnings and provides evidence that some of these methods are promising tools for the purpose of cognitive-behavioral enhancement.