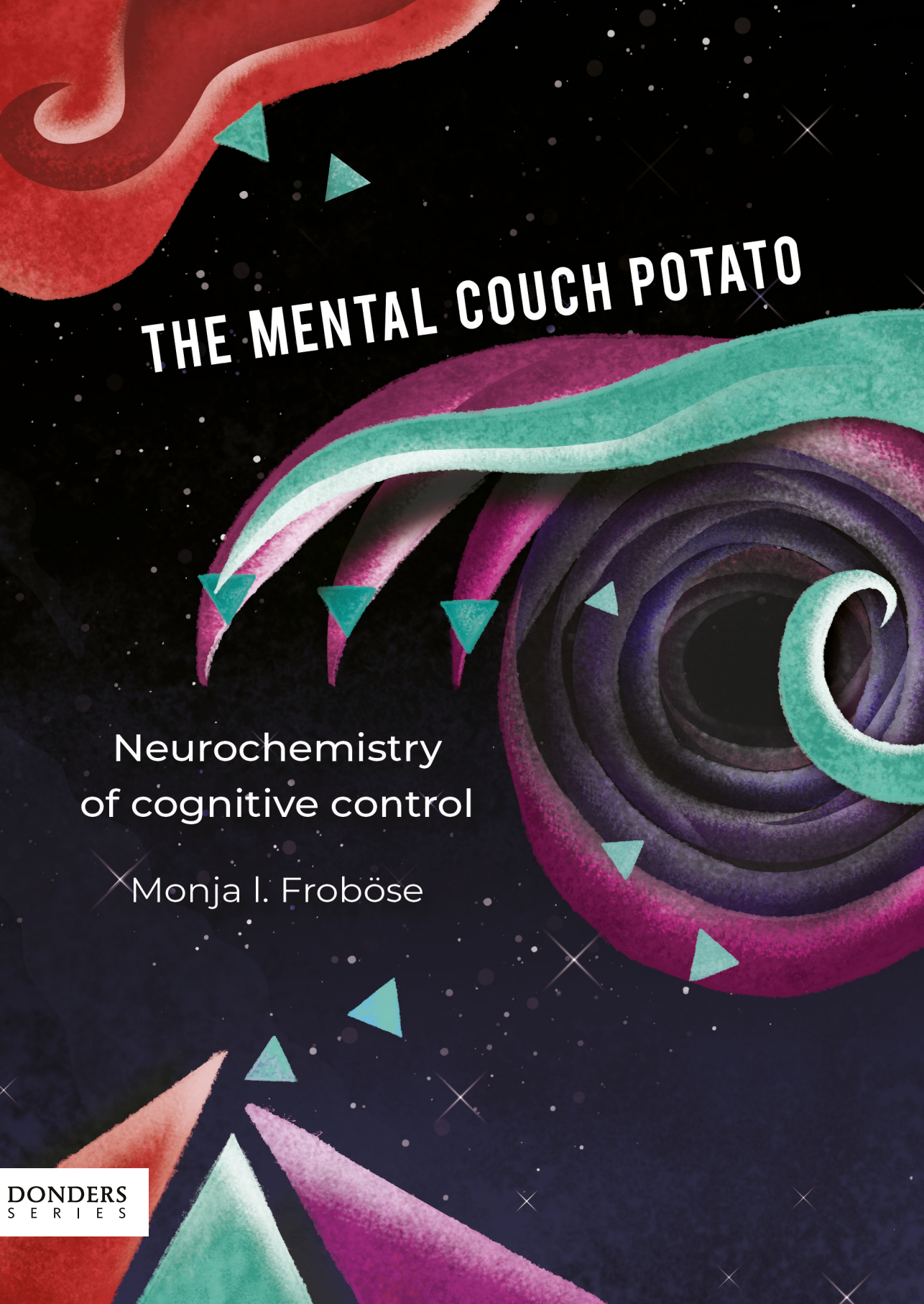
THE MENTAL COUCH POTATO
Neurochemistry
of cognitive control
Monja I. Froböse
DONDERS
SERIES

The mental couch potato

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Monja I. Froböse

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Neurochemistry of cognitive control

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Promotor	Prof. dr. R. Cools
Copromotoren	Dr. B. Zandbelt Dr. E. Aarts
Manuscript comissie	Prof. dr. R. Kessels Prof. dr. G. Dreisbach *University of Regensburg* Dr. M. Altgassen

CONTENT

for my grandfather

who would be proud

CHAPTER 1

General Introduction

AIM OF THIS THESIS

When I ask you to think of a couch potato, I am sure that you can come up with at least one person in your surrounding who deserves that title. Probably that person is lazy, wears jogging pants and enjoys to eat crisps while binge-watching series on Netflix. However, this thesis is not about the couch potato in its classical terms, but about the mental couch potato. Unlike aversion with regard to physical exercise, the mental couch potato enjoys to put his brain on a couch. However, every mental couch potato is unique: some are particularly averse to focusing on long demanding movies and can't handle any extra input, such as incoming WhatsApp messages; Others suffer mainly from fast, ever-changing, flexible mental activities, such as playing my favorite game Halli-Galli.

To begin with, I find it interesting to observe that individuals differ in their willingness to engage in cognitively demanding tasks and I wonder why this is the case. For physical effort, there are several advantages to being averse to activity (Hull, 1943): muscle tension requires the limited resource glucose, muscle aches are painful, risk of injury, etc. However, I have never met a person who reported injuries or muscle ache-like pain in his brain after a long day of thesis-writing. So, the question that inspired me and this thesis is what kind of cognitive demands are particularly aversive to which people? And, more importantly, by understanding mechanisms of cognitive demand avoidance, is there a way of promoting motivation to engage in effortful cognition on the long term? To begin to address these questions, in this thesis I aim to

- quantify the willingness (i.e. motivation) to conduct cognitively effortful tasks and assess how the motivation is affected by pharmacological interventions that challenge the catecholamine system,

- develop a novel paradigm that allows to quantify the motivation to engage in flexible versus stable cognition, and

- study how a catecholamine challenge alters performance on a task probing flexible versus stable cognition.

In this chapter, I will introduce the key concepts that will help the reader navigate through the subsequent chapters. This thesis builds on classical work on cognitive control functions and the role of motivation in the willingness to recruit cognitive control, introduced in 1.2 and 1.3. Next, I will introduce the neural structures and neurochemical factors that have been implicated in cognitive control and its avoidance in the healthy young population (1.4), before describing how

these factors are altered in healthy aging (1.5). Finally, I will introduce the pharmacological interventions that we employ (1.6) and outline specific research projects presented in this thesis (1.7).

COGNITIVE CONTROL

Cognitive control is a broad term which can be defined as the capacity to guide behavior in the service of internally represented goals (Braver, 2012; Braver and Barch, 2006; Miller, 2000; Miller and Cohen, 2001; Montague et al., 2004). As such, it is an umbrella term that refers to the set of cognitive functions that enable us to stabilize our goals by resisting impulses, temptation and distraction. Cognitive control generally includes three core executive functions: working memory, inhibition and cognitive flexibility (Diamond, 2013).

In this thesis, I study cognitive control from two perspectives: the willingness to engage in broad cognitive control functions (further introduced in 1.3) and the neural and behavioral mechanisms of cognitive stability and cognitive flexibility, which I will further outline here. The need for flexible and stable cognition can be illustrated easily by means of our office life: When you share an office with multiple people, it requires you to inhibit incoming distractors, such as office mates running in and out or conversations with students. However, when the fire alarm in the building goes off or your office mate offers chocolate, you should be able to integrate the signal and act on it. The relevance of an optimal balance becomes also evident when looking at different neuropsychiatric diseases that affect cognitive control. Attention-deficit hyperactivity disorder (ADHD) for example is characterized by excessive distractibility, reduced working memory (Castellanos et al., 2006; Martinussen et al., 2001), but perhaps better flexibility and creativity (Boot et al., 2017; Healey and Rucklidge, 2005). Patients suffering from Parkinson's disease or obsessive compulsive disorder (OCD) in contrast suffer from rigid, compulsive cognition with trouble switching to new things (Cools et al., 1984, 2001; Gu et al., 2008; Lees and Smith, 1983; Meiran et al., 2011). Many working memory paradigms, such as the N-back task, but also many situations in everyday life rely on a mixture of these processes: keeping online in working memory recently presented stimuli (i.e. cognitive stability), but also integrating new stimuli in the stream while letting go of initially relevant ones (i.e. cognitive flexibility). Thus, performance impairments can be a consequence of reduced stability or increased flexibility. In chapter 5 & 6, we study the opposing functions by administering an adapted delayed match-to-sample task. Like in delayed match-to-sample tasks, participants need to encode stimuli and judge after a delay whether a probe is a 'match' or 'non-match'. However, during the

delay period, we either present distracting stimuli that need to be ignored (i.e. the office mates), or stimuli that need to be updated (i.e. the fire alarm). By analyzing performance on the two task conditions, we can independently assess cognitive flexibility and stability.

MOTIVATED COGNITION

When we assess cognitive control in the lab or grade exams, we often assume that the performance or grade reflects a person's true and maximal capacity. This implies that we always perform at our best. However, there is a rich body of evidence suggesting that, unfortunately, this is not the case.

One clear example is the often observed incentivization effect: When employees expect to receive a bonus for their work, they tend to improve their output (Gielen et al., 2010; Weibel et al., 2009). The same is observed in the lab: Participants who can receive a bonus or monetary incentive for good performance, tend to improve it (Botvinick and Braver, 2015). This has been shown on a variety of tests, including task-switching, working memory, conflict tasks, etc (Aarts et al., 2011; Chib et al., 2012, 2014; Manohar et al., 2015; Padmala and Pessoa, 2011). Such a performance benefit due to incentives has commonly been ascribed to an effect of motivation, where motivation is defined as energizing of behavior in pursuit of a goal (Simpson and Balsam, 2015). Thus, it seems that we do not always perform at our best and that cognitive control performance is a mixture of (at least) our capacity to perform a certain task and our motivation, or choice, to do so (Cools, 2015, 2016). Remember the classical couch potato who is lying on the couch watching Netflix instead of doing sports in the gym. We can evaluate his behavior as an inability to stand up or move, but I think it is obvious that in principle he is able to run and even do sports and it's a matter of motivation. Likewise, a mental couch potato might not be incapable of reading a book or solve difficult puzzles, but just doesn't feel like it. The problem is that often we cannot distinguish one from the other when we only assess performance. Therefore, in this thesis, I aim to quantify the motivation to engage in cognitive effortful tasks and I want to introduce next how this is generally obtained.

The motivation to 'work' for a certain goal has already been studied for ages, albeit primarily in the motor domain (Salamone, 2009). How willing is a rat to invest physical effort (i.e. climb a certain barrier) for varying levels of reward? Effort is defined as the intensification of either mental or physical activity in the service of meeting some goal (Inzlicht et al., 2018). Thus, effort is the mean by which motivation is translated into goal-directed actions. When quantifying

motivation, usually a harder option is contrasted with an easier, lower-effort option, in which a rat does not need to climb any barrier, but receives a smaller reward. The general unsurprising finding is that higher amounts of reward, such as sucrose or pellets, increase the likelihood of rats to choose the harder option, interpreted again as increased motivation. This work has been translated to study motivation for physical effort in humans, both in the healthy and diseased population (Chong et al., 2015; Treadway et al., 2012; Wardle et al., 2011). Even though motivation for cognitive control has been a hot topic for ages already (Kahneman, 1973), there is a recent interest in quantifying human motivation with choice paradigms.

In 2007, a paradigm was published that was designed to assess the implicit engagement versus avoidance of cognitively demanding process, namely task-switching (Botvinick, 2007). In a later version of this task (Kool et al., 2010), participants repeatedly choose between two stimuli that vary in their demand for task-switching and, following every choice, execute the chosen demand right away (task-repeat versus task-switch). Cognitive demand avoidance can be measured in terms of the overall proportion of low versus high demand choices. Unlike many rodent and human versions of physical effort avoidance, in this paradigm there is no benefit or reward offered for engaging in the high-demand trials. Thus, choices are believed to be driven exclusively by participants' internal desire to avoid or engage in cognitive demand, sometimes even unconsciously (Kool et al., 2010). Importantly, there is also no feedback presented on how participants execute the task-switching task, such that performance (feedback) should not alter choices. I employ this paradigm, the demand selection task, in chapter 3 to assess avoidance of task-switching in a young healthy population.

An alternative way of quantifying motivation for cognitive control is to employ discounting paradigms formally known from the intertemporal choice literature (Berns et al., 2007). A common procedure in intertemporal choice paradigms is to let participants choose between receiving a certain amount of money today or a higher amount of money at a later point in time. Based on the choices, researchers extract an indifference point: the indifference point indicates that a participant is equally likely (i.e. indifferent) to choose one option (e.g. Eur 1 today) or the other (e.g. Eur 10 in 10 days). In intertemporal choice, indifference points are used to derive an index for impulsivity, as it reflects the tendency to forego money to obtain a sooner reward. Westbrook and colleagues adapted such a paradigm in order to obtain an index of motivation for cognitive control (Westbrook et al., 2013). Participants can choose to earn or forego monetary rewards for conducting different levels of a working memory N-back task. The N-back task is well-suited

as the load on the working memory is manipulated parametrically: in the 1-back task, participants need to remember 1 stimulus, in the 2-back task 2 stimuli, etc. On every trial of this paradigm participants choose between a smaller monetary reward for conducting an easy task (1-back) and a larger reward for conducting one of the harder tasks (higher N-back levels). Depending on participants' choices, the amount offered for the easy task is adapted in a staircase procedure (i.e. increased or decreased) until participants become indifferent between two choices. Based on the indifference point, the subjective value of conducting the N-back task can be calculated per participant per demand level. Subjective value scores range from 0 to 1, where a high value means that a participant prefers to obtain higher monetary rewards in exchange for investing more cognitive effort, and a low value reflects the tendency to forego monetary rewards for the sake of avoiding cognitive effort. Obviously, participants need to know what it feels like to conduct the different levels, which is achieved by having them perform the N-back task preceding the choices. In chapter 4, I employ this cognitive effort discounting (COGED) paradigm to quantify the subjective value that healthy older adults perceive when conducting the N-back task.

So far, I have described that we do not always perform at our best and that different factors, such as enhancing the motivation, can improve it. The obvious next question is *why* we are not always performing at our maximum? Based on earlier studies employing above choice paradigms, it seems that the short answer is that investing cognitive control can be aversive and we tend to avoid it (Botvinick, 2007). On average, healthy young students select to avoid task-switching (Kool et al., 2010), and prefer to sacrifice money to avoid performing difficult N-back levels (Westbrook et al., 2013) or backward compared to forward word-typing (Massar et al., 2015). This suggests that cognitive control is costly. Therefore, I chose the title mental couch potato. Despite a recent hype in studying the cost of cognitive control, there is no agreement yet on the nature of the cost (Kurzban, 2016). In short, according to some reports, the cost is energetic and reflects blood glucose metabolism (Gailliot et al., 2007). When people engage in self-control (tasks), glucose is progressively depleted yielding people unable to engage in additional control. However, this account has received robust criticism and replications failed (Carter and Mccullough, 2014; Carter et al., 2015; Hagger et al., 2016). More recent motivational accounts, instead of focusing on capacity, propose that performance is sensitive to changes in motivational state. As such, the degree and intensity of cognitive control recruitment follows from an evaluation of its benefits (e.g. monetary rewards) and costs (Shenhav et al., 2013), where control is integrated as an intrinsic cost (Kool et al., 2013). Relatedly, Inzlicht and colleagues complemented the motivational models by describing

that the phenomenology of fatigue is a signal to stop focusing and orient to new activities with higher utility (Inzlicht et al., 2014). This account is similar to the idea of opportunity cost proposed by Kurzban. Due to the problem of simultaneity, we cannot commit to multiple activities requiring the same (neural) resources. Thus, while focusing on one task, we miss out on other perhaps more rewarding opportunities (Kurzban et al., 2013). According to this account, the phenomenology of effort here relates to the ramping up of an opportunity cost and reflects the cost of staying engaged.

In the light of these motivational accounts, one might hypothesize that enhanced distractibility (partly) reflects changes in preference and not just an inability to focus or to let go. Distractible colleagues might rather be unmotivated to focus and prefer to process (also distracting) stimuli. To start to address this question, in chapter 6, we aim to develop a novel discounting paradigm that allows to tease apart the motivation for flexible versus stable cognitive processes. This thesis builds primarily on these motivational accounts and assesses the contribution of catecholamines to cost-benefit decision-making about cognitive control recruitment. Thus, in the next paragraph, I present neural and neurochemical background on cognitive control and its avoidance.

NEURAL AND NEUROCHEMICAL MODULATION OF COGNITIVE CONTROL (AVOIDANCE)

Neural mechanisms of the motivation for cognitive control have been studied in various ways. On the one hand, it is crucial to study the activity of neural networks when executing cognitive control and ultimately relate these to the subsequent avoidance. In such a way we can assess what kind of cognitive activities are perceived as aversive and what they have in common. Maybe the cost of control is related to the recruitment of specific brain regions or signals? On the other hand, people study the neural signature of decision making itself. How are value and cost represented and how do they alter decisions to engage or avoid cognitive control? The same distinction holds for work on the neurochemical modulation where the role of different neuromodulators in cognitive control execution is studied, but also in choices about its avoidance. Here, I will provide a short overview, but given its relevance for the thesis chapters, I will focus primarily on the modulation of cognitive control and its avoidance by catecholamines.

Cognitive control

Many executive functions are known to implicate the prefrontal cortex (PFC; Figure 1.1A) (Fuster, 2000; Koechlin et al., 2003; Miller and Cohen, 2001). Prefrontal lesions have been shown to impair performance on different tasks requiring task-switching, working memory and distractor inhibition in monkeys and humans (Baldo and Shimamura, 2002; Chao and Knight, 1995; Jacobsen and Nissen, 1937; Müller and Knight, 2006; Tsuchida and Fellows, 2008). Of course, the prefrontal cortex does not act in isolation (Middleton and Strick, 2000), but is part of a larger network, including cortico-basal ganglia loops that link prefrontal cortex and the striatum (Alexander et al., 1986; Haber, 2003). This frontostriatal network is affected by multiple neuropsychiatric disorders including ADHD and schizophrenia that are also accompanied by deficits in executive functions (Cubillo et al., 2012; Morey et al., 2005; Robbins, 1990). The interaction of the prefrontal cortex with the basal ganglia seems to be of particular importance when tasks or environments require flexible adaptations (Cools et al., 2004). Lesions in the basal ganglia resulted in deficits in the updating of current goal representations in animals (Oberg and Divac, 1975; Taghzouti et al., 1985). In humans, BOLD signal in the striatum (Figure 1.1A), part of the basal ganglia, has been observed during tasks that require cognitive flexibility, e.g. task switching, attentional set-shifting and reversal learning (Cools et al., 2002a, 2004; Leber et al., 2008; Rogers et al., 2000; van Schouwenburg et al., 2010a). As such, the prefrontal cortex has been suggested to support the stabilization of goals and distractor resistance while the striatum has been associated with the de-stabilization of goals with the purpose of letting in new environmental stimuli for flexible responses (Hazy et al., 2007; van Schouwenburg et al., 2010a). In that way, the prefrontal cortex and striatum have been suggested to interact to establish the balance between cognitive stability and flexibility (Cools, 2011; Frank et al., 2001; Hazy et al., 2007). It seems that not only frontostriatal activity is needed for successful implementation of cognitive tasks but also its modulation by dopamine.

Dopamine is a neurotransmitter that acts as a neuromodulator. Thus, instead of a direct role in the activation or inhibition of single neurons like classical neurotransmitters (i.e. glutamate and GABA), dopamine release potentiates or weakens signal transfer in a diffuse network of brain regions (Stahl, 2008). Dopamine neurons reside in the midbrain, in the ventral tegmental area (VTA) and substantia nigra pars compacta (SNc) and project throughout large parts of the brain, but in particular to the basal ganglia and prefrontal cortex, where dopamine receptors are dense (see Figure 1.1C). Dopamine is synthesized from

its precursors tyrosine and L-DOPA and is further converted to noradrenaline. Noradrenaline and dopamine together then comprise the catecholamines.

An important role for dopamine in cognitive control performance, mainly working memory, has been evidenced a long time ago by Brozoski, who showed in monkeys that prefrontal dopamine depletion led to impairments in working memory to the same degree as complete ablation of the PFC (Brozoski et al., 1979). Since then, the administration of dopamine agonists (i.e. stimulation of dopamine receptors) and antagonists (i.e. blocking dopamine receptors) to humans and monkeys have been shown to improve and impair working memory performance, respectively (Luciana et al., 1992; Mehta et al., 1999). In addition, amphetamine and methylphenidate have been found to increase BOLD signal during working memory tasks, especially in the PFC (e.g. Fallon, Schaaf, Huurne, & Cools, 2016; Mattay et al., 2000). While the exact mechanism remains unclear, effects of dopamine on working memory might reflect dopamine-induced increases in the signal-to-noise ratio of neuronal firing in the PFC, leading to increased stabilization of currently goal-relevant representations (Durstewitz and Seamans, 2008; Durstewitz et al., 2000; Seamans and Yang, 2004; Servan-schreiber et al., 1990).

But also dopamine in the basal ganglia is important for cognitive control, evidenced for example by cognitive impairments in Parkinson's disease. Reduced input of dopaminergic neurons to the basal ganglia have been associated with specific impairments in flexible cognition (Aarts et al., 2012; Cools et al., 2001). In addition, the administration of bromocriptine, a stimulator of D2 receptors, which are abundant in the basal ganglia, impaired distractor resistance in humans (Bloemendaal et al., 2015) and modulated basal ganglia signals during cognitive switching (Cools et al., 2007).

One hypothesis for how the brain arbitrates between stable versus flexible states is with the use of a gating mechanism that regulates the inputs to PFC. When the gate is open, sensory input can update working memory, but when closed, distracting input is suppressed. Several models have been proposed for how a gating mechanism might be implemented, all of which assign an important role to dopamine (Braver and Cohen, 2000; Frank et al., 2001; Rougier et al., 2005). As such, gating signals and updating of working memory representations in PFC should be accompanied by the phasic release of dopamine. According to one model, similar to the role of the basal ganglia in action selection (Gerfen and Surmeier, 2011; Mink, 1996), where BG provides a 'Go' versus 'NoGo' modulation of frontal action representations, it has a 'gating-like' function in

working memory: more 'Go' activity, which is triggered by dopamine release due to expected reward or drug treatment, stimulates update of WM representations in the PFC (Hazy et al., 2007). This is in line with the observation that BOLD signals in the BG and the PFC were increased when novel stimuli triggered attention switches (van Schouwenburg et al., 2010b) and striatal activity when information needed to be updated (Fallon et al., 2016).

In sum, based on studies assessing neural and neurochemical contribution to cognitive control, we can conclude that the prefrontal cortex and its modulation by dopamine support cognitive stability while striatum and its modulation by dopamine seem to support cognitive flexibility (Figure 1.1B). This implies that, depending on their locus of effect, pharmacological interventions can yield opposite effects. In chapter 5, I study the neural and behavioral consequences of administering the catecholamine precursor tyrosine on working memory performance with demand for cognitive stability versus flexibility.

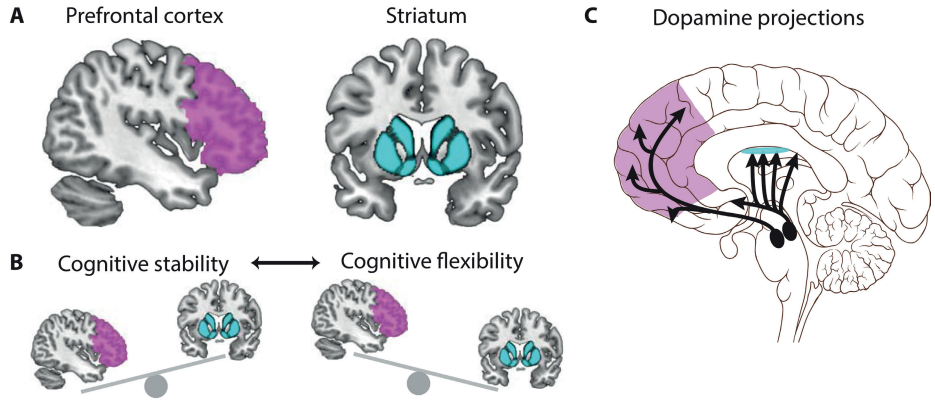

FIGURE 1.1 | A The prefrontal cortex is marked in violet, the striatum in cyan. **B** An illustration of the hypothesis that the prefrontal cortex supports primarily cognitive stability, while the striatum enables flexible cognition. **C** Simplified presentation of projections of the ascending neuromodulator dopamine to the prefrontal cortex (again violet) and striatum (cyan). A and B were prepared in MRIcron by overlaying masks of PFC (aal atlas) and striatum (https://osf.io/jkzwp/) on a standard MNI template. C is adapted from chapter 2.

Cognitive control avoidance

When studying the motivation to engage in or avoid cognitive control tasks, an interesting question is to what degree neural activity during the execution predicts subsequent avoidance. Few studies have tried to achieve this with mixed results: McGuire and colleagues have shown in two experiments that prefrontal cortex activity during task-switching positively correlated with the self-reported desire to

avoid a task and demand avoidance as assessed with the demand selection task (described in 1.3; McGuire & Botvinick, 2010). This suggests that prefrontal cortex activity registers the cost of control. This is in line with a recent account proposing the dorsal anterior cingulate cortex signals the allocation of control based on an evaluation of the expected value of control (Shenhav et al., 2013, 2017). However, in a recent study, in which demand was manipulated parametrically by employing multiple levels of task-switching proportions, the effect did not replicate (Sayalı and Badre, 2019). Task-switching was again accompanied by activity in frontoparietal network, but this activity did not correlate with subsequent demand avoidance. Surprisingly, here the degree of default mode network de-activation related to demand avoidance. Even though it seems to be still unclear whether the recruitment of specific anatomical regions during effort execution reflects the cost of control and what its implications for subsequent avoidance are, there is rich body of evidence indicating that investing cognitive control is valenced and is integrated as a cost during cost-benefit decision-making. The 'expected value of control' account mentioned above, describes that the degree and intensity of cognitive control recruitment is the consequence of weighting its benefits against its cost, in which the cost of cognitive effort is integrated. Based on different streams of evidence, we hypothesize that striatal dopamine plays a key role during this value-based decision-making process by signaling the value (benefit minus cost) of control recruitment (Boureau et al., 2015; Cools, 2016; Westbrook et al., 2013). I will provide an overview of the evidence below, but note that it is discussed in more detail in a literature review in chapter 2 and subsequent chapter introductions.

First of all, in the domain of physical effort there is a clear role defined for striatal dopamine in altering choices about engagement versus avoidance. Animals, in which a lesion or pharmacological intervention interferes with striatal dopamine transmission show reduced willingness to climb a barrier to obtain a reward, while still being able to climb and still preferring the larger reward in the absence of an obstacle (e.g. Bardgett, Depenbrock, Downs, & Green, 2009; see Salamone, 2009 for review). Stimulation of striatal dopamine increased the frequency of choices for the effortful option (Floresco et al., 2008a; Yohn et al., 2015). In humans, this pattern has been replicated in patients with Parkinson's disease suffering from loss of striatal dopamine cells. Patients seem to be less motivated to invest physical effort (e.g. in the form of squeezing a handgrip; McGuigan et al., 2019) and dopaminergic treatment remedies the loss of motivation (Chong et al., 2015). The idea is that by stimulating dopamine release, signals of the value of an action are augmented resulting in more effortful choices. This generally concurs with neurocomputational models of dopamine in the basal ganglia, such

as the OPAL model and supportive empirical evidence (Collins and Frank, 2014), showing that prolonging (striatal) dopamine likely enhances the benefit while also reducing the cost of actions by having opposite effects on the D1 (GO) and D2 (NO-GO) pathways of the basal ganglia. Recordings in monkeys support a similar role in effort-based decision making. When reward and (physical) effort were independently manipulated and monkeys were cued with the identity of an upcoming trial, activity in dopamine neurons increased with an increase in expected reward. Interestingly, the signal was also sensitive to the upcoming effort level, such that the same reward was 'worth less' when it was accompanied by high versus low physical effort (Floresco, 2015; Varazzani et al., 2015). This puts the striatum in a position to integrate benefit and cost of an upcoming action. In line with a similar role in the cognitive domain, Botvinick has shown that reward-induced nucleus accumbens activity was sensitive to how much *cognitive effort* someone has spent (Botvinick and Rosen, 2009). The same amount of monetary reward induced less nucleus accumbens activity in participants that had just finished a high versus low demanding task block, suggesting that the value was reduced due to effort spent. Interestingly, this activity was inversely related to dorsal anterior cingulate cortex activity during (switch-) task execution, following the idea that dACC provides effort-demand information (Shenhav et al., 2013), perhaps to the NAcc (Botvinick and Rosen, 2009). The finding of reduced reward-related activity after cognitive effort is similar to the observation that behaviorally response conflict acts as an aversive signal (Dreisbach and Fischer, 2012) and strengthens avoidance learning (Cavanagh et al., 2014). More specifically, the presence of response conflict in a Simon task modified learning about action values, such that the value of received rewards was downgraded due to response conflict (Cavanagh et al., 2014, 2017). Importantly, these effects varied with conditions and manipulations associated with changes in striatal dopamine, such as genetic polymorphisms and pharmacological dopamine manipulations (Cavanagh et al., 2014).

More indirect evidence for a role for dopamine in motivation for cognitive control stems from the incentivization effect that I described in 1.3: reward expectation often improves cognitive performance (Botvinick and Braver, 2015). We know that unexpected reward receipt and reward expectation elicit phasic dopamine release (Schultz, 1997, 2017). A performance improvement after reward might suggest that striatal dopamine release affects performance by increasing the value of control. In line with this account, by combining incentivization and effort discounting, Massar and colleagues have shown that motivation can boost sustained attention through increased effort (Massar et al., 2016). The role for dopamine in this process was made explicit in recent modeling work, which shows

that the incentive effect on performance is explained best by a model including a cost of control parameter (Manohar et al., 2015). It seems that reward, signaled by dopamine release, "pays the cost of control". Critically, this effect was diminished in Parkinson's disease patients, supporting that dopamine biased the benefits over the cost of control in healthy participants.

In sum, there is rich evidence suggesting (indirectly) that dopamine is a key player when it comes to decision-making about cognitive effort. Based on this evidence, we expect that increases in dopamine will increase the benefits, while reducing the costs of actions and hypothesize that this extends to decisions about cognitive actions. First causal evidence comes from a rodent task, in which amphetamine administration increased high effort choices. However, no studies have been conducted in humans that directly assess the consequences of a dopamine challenge in healthy adults on decision-making about cognitive effort. We therefore setup two pharmacological experiments to quantify how catecholamine challenges alter value-based decision making about cognitive control investment. In chapter 3, we administer the catecholamine transporter blocker methylphenidate and assess demand avoidance in a large young sample to probe individual differences. Chapter 4 describes how the catecholamine precursor tyrosine alters subjective value of cognitive effort in older adults. In the next paragraph (1.5), I will summarize how healthy aging has been shown to affect catecholamine transmission, cognitive control and its motivation before introducing the specific pharmacological interventions and individual differences in intervention effects (1.6).

AGING

When we think of aging, perhaps looking at our parents or grandparents, the overall stereotype is that various functions decline, ranging from motor abilities, such as running or walking to cognitive abilities, including remembering the shopping list or switching off the stove after cooking. In line with the general view on cognitive decline, healthy aging has been characterized by impairments when assessing performance on cognitive control tasks in the lab, including working memory (Cai and Arnsten, 1997; Gazzaley et al., 2005; Turner and Spreng, 2012), response inhibition (Bloemendaal et al., 2016) and distractor resistance (Clapp and Gazzaley, 2012; Gazzaley et al., 2007a; McNab et al., 2015). It has been argued that primarily the online maintenance of information is affected due to impaired internally guided, top-down suppression of irrelevant working memory items (Gazzaley et al., 2005; Jost et al., 2011). This suggests that cognitive stability is impaired while flexible updating might in fact be improved due to greater

reliance on (distracting) environmental cues (for a review, see Lindenberger & Mayr, 2014). There is some evidence against this account, including reports on impairments in other tasks requiring flexible updating of current goal representations, such as task-switching (Kray et al., 2002) and reversal learning (Vo et al., 2018). As introduced in 1.4.1, the processes of cognitive stability versus flexibility have been shown to rely on distinct neural regions (PFC versus striatum; Figure 1.1B) and their stimulation by dopamine. Older adults turn out to be an interesting study population not only due to perhaps shifts in the stability/flexibility tradeoff, but also because healthy aging is accompanied by changes in the dopamine system (Bäckman et al., 2006). A recent meta-analysis of 95 positron emission tomography (PET) and single-photon emission-computed tomography (SPECT) studies revealed lower prefrontal and striatal D1 and D2 receptor densities and striatal dopamine transporters with increasing age (Karrer et al., 2017). Findings regarding dopamine synthesis are more mixed with reports on reduced (Ota et al., 2006) as well as enhanced dopamine synthesis (Braskie et al., 2008) in older age. Due to the mixed findings, the meta-analysis concludes that there are no significant changes in dopamine synthesis. However, there is evidence for a link between age-related dopamine changes in prefrontal cortex and age-related impairments in working memory performance in healthy older adults (Bäckman et al., 2006, 2011; Goldman-Rakic and Brown, 1981; Landau et al., 2009; MacDonald et al., 2012). In aged animals, a causal relationship has been established between prefrontal cortex dopamine and working memory by repleting prefrontal cortex dopamine with a D1 receptor agonist improved performance on working memory tasks (Cai and Arnsten, 1997; Mizoguchi et al., 2009). In chapter 5, we assess whether the administration of tyrosine, which has been shown to stimulate dopamine synthesis (see 1.6.1), changes performance on a working memory task that probes distinct demands for flexibility versus stability. Tyrosine is hypothesized to restore deficits in distractor inhibition by increasing prefrontal activity in older adults. To address this question, we combine the pharmacological intervention and behavioral task with functional magnetic resonance imaging (fMRI) allowing us to assess whether behavioral changes rely on neural effects in distinct networks.

Any performance changes as a function of age or treatment can (as introduced in 1.3) be a consequence of impairments in the ability to conduct a certain task, reduced motivation to do so or a combination. This interpretation is informed also by reports on reduced motivation of older adults to conduct a demanding N-back task compared with young adults (Westbrook et al., 2013). Given age-related declines in dopamine transmission and our hypothesis that dopamine contributes to cost-benefit decision making about cognitive control recruitment

(see 1.4.2), in chapter 4 we assess whether tyrosine increases the motivation for cognitive control in older adults by employing the cognitive effort discounting procedure described in 1.3.

PHARMACOLOGY

There are different ways of studying the effects of catecholamines on cognitive functioning in humans. Think of patient studies with Parkinson's disease, ADHD or schizophrenia (Chong et al., 2015; Cools, 2006) or assessing variance in the catecholamine system in terms of genetic mutations, polymorphisms or quantifying its synthesis using positron emission tomography (e.g. Aarts et al., 2010; Geurts, Huys, den Ouden, & Cools, 2013). Each approach has different implications. In this thesis, we manipulate catecholamines in the healthy population by acute pharmacological interventions. One advantage is that we can manipulate catecholamines in a relatively naive and homogenous system comparing placebo to intervention sessions. Thus, effects are acute, cannot be ascribed to chronic changes due to disease or chronic drug treatment and are compared within-subjects. Some might argue that a disadvantage is that these drug studies in healthy adults don't serve any applied (clinical) aim and might in fact promote the use of 'smart drugs'. However, next to addressing our fundamental research questions on how the healthy brain responds to changes in catecholamine levels, there is also societal relevance of this work in the absence of direct translation into clinical settings. There are reports that more and more healthy students and academics use 'smart pills', such as Ritalin (i.e. methylphenidate), Adderall (i.e. amphetamines) or tyrosine to boost their cognitive performance (Maher, 2008). While drugs that potentiate catecholamine neurotransmission are generally thought to enhance cognitive control, they certainly do not have enhancing effects in all people. There is large individual variability in the direction and extent of catecholaminergic drug effects on human cognition (Cools and D'Esposito, 2011; Samanez-Larkin and Buckholtz, 2013) with reports on impaired instead of improved performance (Cools and D'Esposito, 2011; van de Rest et al., 2017). Thus, knowing beforehand who would benefit in which situations has large implications. Here, I first introduce the two pharmacological drugs that we administer before addressing such individual differences in drug responses, which are relevant for our approach in chapter 3.

Pharmacological interventions

In the scope of this thesis, we conduct two pharmacological studies in which we administer methylphenidate to healthy young adults (Chapter 3; Figure 1.2C) and tyrosine to healthy older adults (Chapter 4 and 5; Figure 1.2D). These interventions have both been shown to alter catecholamine transmission, however by different mechanisms of action.

Tyrosine is one of the large neutral amino acids and biochemical precursor of the catecholamines. It is naturally present in protein-rich food such as cheese, milk, fish or seeds but also available as over-the-counter food supplement. While tyrosine has different peripheral functions in the body, it acts centrally by passing the blood-brain-barrier in competition with other large neutral amino acids, such as tryptophan and phenylalanine. In the midbrain, it is converted to L-DOPA by the rate-limiting enzyme tyrosine hydroxylase (TH; Daubner, Le, & Wang, 2011) and to dopamine by aromatic l-amino acid decarboxylase (AADC). Dopamine is subsequently converted to noradrenaline in the locus coeruleus (Carlsson and Lindqvist, 1978; Tam and Roth, 1997). The oral administration of tyrosine has been shown to significantly enhance central catecholamine synthesis in rodents (Cuche et al., 1985; Fernstrom, 1983; Gibson and Wurtman, 1976; Scally et al., 1977; Sved et al., 1979; Tam et al., 1990) and humans (Growdon et al., 1982). Plasma levels slowly ramp up and reach peak concentrations ~90 minutes after administration and remain significantly elevated up to 8h (Glaeser et al., 1979). In young adults, tyrosine administration has been shown to improve cognitive control functions that are commonly associated with catecholamine transmission, such as working memory, response inhibition, and task switching (see Deijen, 2005; Jongkees, Hommel, Kühn, & Colzato, 2015). Following multiple previous studies (e.g. Mahoney, Castellani, Kramer, Young, & Lieberman, 2007; Shurtleff, Thomas, Schrot, Kowalski, & Harford, 1994), we administer 150 mg/kg L-tyrosine powder mixed with banana-flavored yoghurt. This is a relatively high dose, as it is 4-5 times higher than the advised daily tyrosine intake (WHO 1985: 14 mg/kg; Basile-Filho et al., 1998; Food and Nutrition Board of the Institute of Medicine: 2.2-2.6g/day). Importantly, tyrosine is not commonly prescribed as medication but an over-the-counter product, advertised online for cognitive enhancement and ingredient of different prescription-free 'smart drugs', such as NervaCore.

Methylphenidate in contrast, mainly known as Ritalin, is generally associated with its pharmaceutical effects, as it is commonly prescribed to increase cognitive performance in ADHD patients (Coghill et al., 2013; Faraone and Buitelaar, 2010; Leonard et al., 2004). Instead of stimulating catecholamine synthesis, it blocks catecholamine transporters that are responsible for clearing dopamine

and noradrenaline from the synaptic cleft (Volkow et al., 2002a). If blocked, catecholamine reuptake of the presynaptic neuron is inhibited leading to increased catecholaminergic stimulation. Plasma concentrations peak after 2 hr with a half-life of 2–3 hr (Kimko et al., 1999). Next to improving cognitive functions in ADHD patients (e.g. Coghill et al., 2013), acute administration of a single dose to healthy volunteers has been shown to improve various cognitive functions (Elliott et al., 1997; Rogers et al., 1999; Samanez-Larkin and Buckholtz, 2013). We administer one capsule containing 20 mg of methylphenidate. 20 mg is comparable with a single dose used by ADHD patients, however patients might take multiple pills a day depending on the individualized therapy scheme.

To conclude, tyrosine and methylphenidate have both been shown to alter the catecholamine transmission and performance on different cognitive control tasks. It is important to note that drug effects cannot be ascribed selectively to changes in dopamine or noradrenaline because a) tyrosine is a precursor of dopamine and noradrenaline and b) methylphenidate blocks transporters of dopamine (DAT) and noradrenaline (NET).

Individual differences

As mentioned above, there is large individual variability in the direction and extent of catecholaminergic drug effects on human cognition (Cools and D'Esposito, 2011; Samanez-Larkin and Buckholtz, 2013). We believe, and earlier research has shown, that the individual differences in drug effects reflect dependency on baseline levels of dopamine (Cools and D'Esposito, 2011). For example, higher striatal dopamine synthesis capacity in healthy students, as measured by positron emission tomography (PET), was related to better learning from reward than from punishments. However, the administration of bromocriptine, a dopamine receptor agonist, impaired reward learning in these high-synthesis subjects while improving it in participants with lower dopamine synthesis (Cools et al., 2009). When we want to predict who will benefit from catecholaminergic drugs, it might not be a good solution to acquire PET measures of every single person, because administering radioactive PET ligands is expensive and invasive. However, several measures have been shown to correlate with dopamine synthesis and have been suggested to be used as proxy variables. Thus, in chapter 3 we recruit a large sample to assess individual differences in drug responses with the longer-term goal to be able to predict, based on different measures, who will benefit in which situations by e.g. methylphenidate administration.

We include in the study two putative proxy measures: working memory capacity as assessed with the listening span, which has been observed to correlate positively with striatal dopamine synthesis (Cools et al., 2008; Landau et al., 2009) and trait impulsivity measured by the Barratt Impulsiveness Scale, which has been associated with dopamine receptor availability and striatal dopamine release (Buckholtz et al., 2010; Kim et al., 2013; Lee et al., 2009; Reeves et al., 2012). Previous work indicates that taking into account these proxy variables allows to reveal sometimes contrasting drug effects. Working memory capacity was predictive of catecholaminergic drug effects on cognitive control tasks, including Wisconsin Card Sorting Task (Kimberg et al., 1997), N-back task (Mattay et al., 2000), spatial working memory (Mehta et al., 2000) and reversal learning (van der Schaaf et al., 2013). Similarly, trait impulsivity has been shown to correlate with effects of catecholaminergic drugs on attention switching (Cools et al., 2007) and probabilistic reversal learning (Clatworthy et al., 2009). There have been other measures proposed to approximate dopamine or noradrenaline transmission, such as eye blink rate (Groman et al., 2014; Müller et al., 2007; but Dang et al., 2017; Sescousse et al., 2018), color vision (Roy et al., 2003) or pupil dilation (Joshi, Li, Kalwani, & Gold, 2016; but Costa & Rudebeck, 2016). However, in chapter 3, we focus on two measures that have directly been assessed to correlate with dopamine synthesis using PET in the healthy human population and shown in the past to predict drug effects. Future studies should quantify also the contribution of other putative proxy variables.

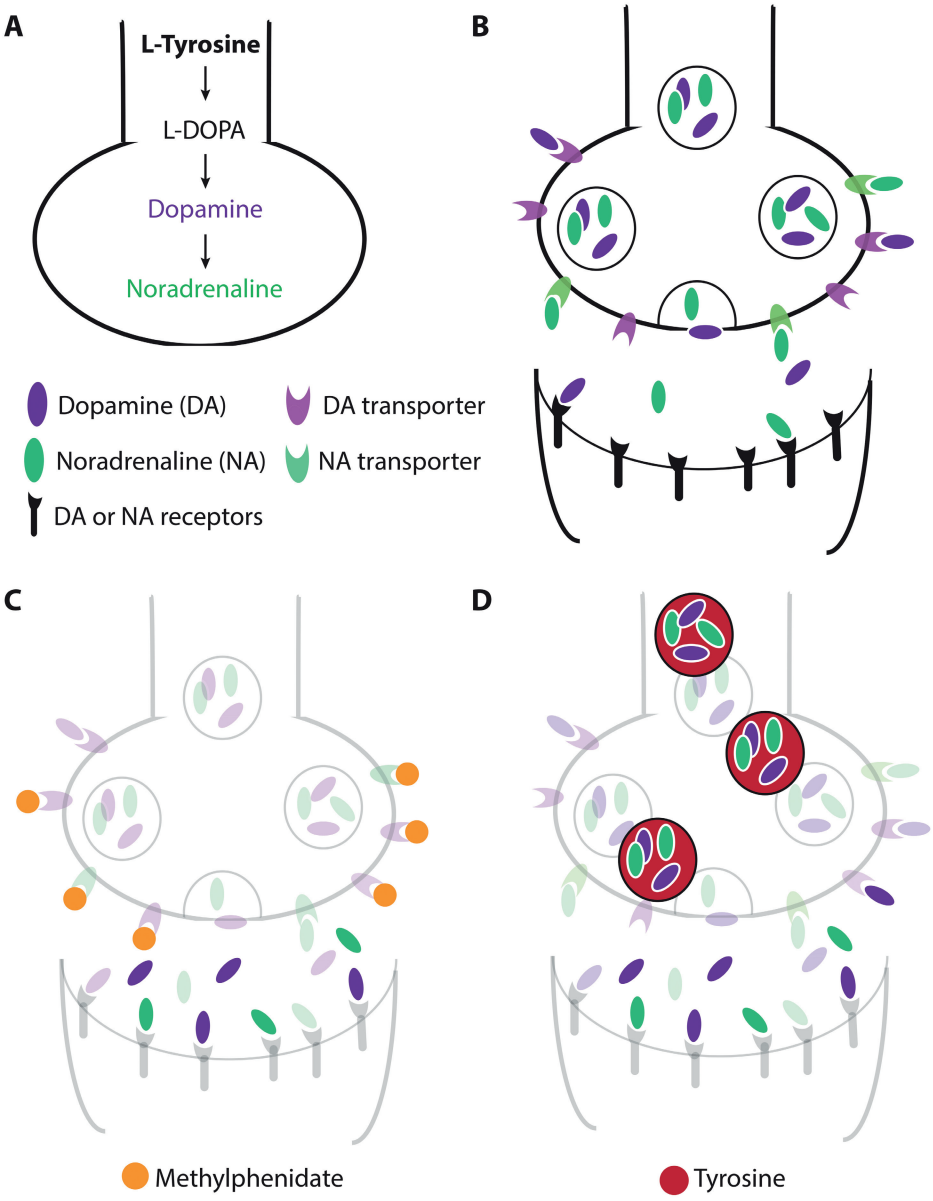

FIGURE 1.2 | A Simplified representation of the last steps of catecholamine (i.e. dopamine and noradrenaline) synthesis. **B** Illustration of catecholamine transmission. Catecholamines are released from presynaptic neurons into the synaptic cleft. Released catecholamines are then either taken back up by the pre-synaptic neuron or act post-synaptically via post-synaptic catecholamine receptors. **C** Methylphenidate alters catecholamine transmission by blocking their pre-synaptic transporters, resulting in increased catecholamine transmission. **D** Tyrosine has been shown to increase catecholamine synthesis and thereby alter catecholamine transmission.

THESIS OUTLINE

The overarching goal of this thesis is to characterize the role of catecholamines and specific task-demands in shaping our motivation for cognitively demanding processes in the healthy population.

In **chapter 2**, we highlight in a literature review the contribution of the major ascending neuromodulators dopamine, noradrenaline and serotonin to the avoidance of cognitive demand. We present a hypothesis that might account for paradoxical intervention effects in the domain of motivation for physical versus cognitive effort avoidance. Due to the more global, overarching scope, I present this literature review before the empirical studies. Note that results of chapter 3 are integrated in this literature review.

Based on our hypothesis that dopamine contributes to decision making about cognitive control (see 1.4.2), in **chapter 3 and 4,** we assess how choices about cognitive control execution (i.e. motivation) are altered when challenging the catecholamine system. More specifically, in **chapter 3,** we administer in a within-subject design the catecholamine transporter blocker methylphenidate (see 1.6.1) and measure cognitive demand avoidance (see 1.3) in a healthy young population. The large sample size (N = 100) allows us to stratify methylphenidate effects by individual differences in putative proxy measures of dopamine transmission (see 1.6.2): working memory capacity and trait impulsivity scores. In **chapter 4**, we ask whether the administration of the catecholamine precursor tyrosine decreases the cost of control in healthy aging, previously associated with reduced motivation for cognitive control and age-related changes in the dopamine system (see 1.5). In a within-subject design, using a cognitive effort discounting procedure (see 1.3), we quantify tyrosine effects (see 1.6.1) on the cost of executing a demanding N-back task.

Adaptive behavior and many cognitive functions rely on an arbitration between cognitive stability and flexibility (see 1.2). These two seemingly opposing processes were hypothesized to implicate distinct neural regions and their modulation by dopamine (see 1.4.1). Thus, in **chapter 5**, we assess the neural and behavioral consequences of tyrosine on the flexibility/stability tradeoff in healthy aging by combining functional magnetic resonance imaging with an adapted delayed match-to-sample task probing flexible and stable working memory processes. Note that this experiment was conducted in the context of the same study (population) as described in chapter 4. In addition to characterizing whether catecholamine effects depend on the demand for flexible and stable cognition,

we develop in **chapter 6** a novel paradigm that allows to assess the subjective cost of executing tasks requiring cognitive flexibility versus stability.

Taken together, this thesis presents a multimodal, multidisciplinary approach by combining literature review, causal interventions (i.e. pharmacology), well-established and novel behavioral paradigms, and neuroimaging to increase our understanding of the role of catecholamines in our motivation for cognitive control.

In **chapter 7**, I summarize the main findings of the research presented in this thesis. Further, I discuss limitations of this research, future directions and speculate about its implications for society and education.

CHAPTER 2

Chemical neuromodulation of cognitive control avoidance

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ABSTRACT

Why do we so often fail to exert cognitive control, even though we are in principle able to do so? In this review, we begin to address this question by considering the contribution of the major ascending neuromodulators that are often implicated in cognitive control and motivation, in particular dopamine, noradrenaline and serotonin. Accumulating evidence indicates that cognitive control is subjectively costly and people generally choose to refrain from mentally effortful tasks, despite, at times, devastating consequences. This tendency to avoid cognitive control tasks has been shown to be sensitive to catecholaminergic interventions in rodents and humans, where choices about cognitive control can be altered even in the absence of performance changes. Such effects might reflect modulation by dopamine and/or noradrenaline of a variety of mechanisms that contribute to our motivation for cognitive control. These likely include the calculation and integration into behavior of both the expected value (i.e. cost versus benefit), as well as outcome uncertainty of exerting cognitive control. In addition, serotonin might impact cognitive control avoidance by modulating specifically the computation of effort costs. Advancing our understanding of the distinct roles of the various chemical neuromodulators will help elucidate the computational mechanisms that contribute to our tendency to avoid difficult cognitive tasks.

INTRODUCTION

Cognitive control is effortful, subjectively costly and people are generally biased to avoid it (Botvinick and Braver, 2015; Kool et al., 2017; Shenhav et al., 2013; Westbrook and Braver, 2016). They prefer to perform a task with less rather than more task-switching (Kool et al., 2010) and with lower rather than higher working memory load (Westbrook et al., 2013). On average, people also choose to forego a higher monetary reward to avoid a more demanding task (Massar et al., 2015; Westbrook et al., 2013). This can be considered paradoxical, given the following observations. First, cognitive control is a hallmark of the human mind and the brain region commonly associated with cognitive control, the prefrontal cortex (Duverne and Koechlin, 2017), is exquisitely well developed. Accordingly, we are very good at exerting cognitive control. Second, exerting cognitive control has obvious benefits for performance, and most of us are aware that failures of cognitive control can have disastrous consequences, ranging from obesity and monetary crises to murder. Finally, there is a growing consensus that cognitive control functions, are unlikely to be metabolically more costly than other functions, associated, for example, with the visual cortex (Kurzban et al., 2013; Molden et al., 2012; Vadillo, Gold, & Osman, 2016, but Holroyd, 2015). Therefore, a key open question is why do we so often fail to exert cognitive control, even though we are in principle able to do so (Cools, 2016; Shenhav et al., 2017). We begin to address this question by considering the contributions to value-based choice about cognitive control of a set of major ascending neuromodulators that have been strongly implicated in motivation, choice and cognitive control, in particular dopamine, noradrenaline and serotonin (Figure 2.1A). Note that few empirical studies have so far addressed this specific question. Thus, we present ideas that build on current literature, but need to be tested in future studies.

DOPAMINE AND COGNITIVE CONTROL AVOIDANCE

Effortful cognitive control has long been associated with optimal catecholamine transmission. For example, patients with disorders that implicate dopamine, like Parkinson's disease or attention deficit/hyperactivity disorder (ADHD), exhibit cognitive control deficits which can be remedied by dopaminergic medication (Coghill et al., 2013). Moreover, dopamine is also a key ingredient in drugs that are used to boost cognitive control in healthy adults (Linssen et al., 2014). Paradoxically, however, altering dopamine transmission by medication or by promising reward can also impair cognitive performance (Aarts et al., 2014a; Cools and D'Esposito, 2011). For example, in Parkinson's disease, the dopaminergic medication doses that are well established to improve motor

control can contribute to the development of impulse control disorder, putatively by impairing cognitive control (Weintraub et al., 2015). Here, we consider the possibility that such paradoxical effects might reflect, in part, modulation by dopamine of value- (and effort cost) based choice about whether or not to exert motor and cognitive control (Collins and Frank, 2014). Indeed the phasic firing of midbrain dopamine neurons are well accepted to contribute to reward prediction error signaling (Montague et al., 1996; Schultz, 1997), which drives temporal difference learning and value-based choice, not only of actions that have high value but also of valuable (while costly) cognitive tasks (Boureau et al., 2015; Collins and Frank, 2014).

As made explicit in the expected value of control (EVC) model (Shenhav et al., 2017), one way in which dopamine might bias such value-based learning and choice about cognitive tasks is by altering the (expected) value of cognitive control, which corresponds to the benefit minus the costs of control. According to neurocomputational models of dopamine in the basal ganglia, such as the OPAL model and supportive empirical evidence (Collins and Frank, 2014; Skvortsova et al., 2017), prolonging (striatal) dopamine likely enhances the benefit while also reducing the cost of actions by having opposite effects on the D1 (GO) and D2 (NO-GO) pathways of the basal ganglia. Thus, based on this evidence, we argue that increases in dopamine will increase the benefits, while reducing the costs of cognitive control. Based on further empirical evidence for an 'inverted U'-shaped relationship between dopamine and reward- versus punishment-based learning (Cools and D'Esposito, 2011; Cools et al., 2009), we also hypothesize that excess or supraoptimal levels of dopamine might paradoxically reduce the benefits versus the costs of cognitive control, perhaps by acting via a presynaptic mechanism of action, thus leading to a net reduction in dopamine synthesis and/or release.

The nature of the control cost is currently under active study. Some have argued that it represents an intrinsic conflict-related cost (Cavanagh et al., 2014, 2017; Shenhav et al., 2017), while others highlight that it might correspond to an opportunity cost of time, equal to either the value of the next best alternative (Kurzban et al., 2013) or, following work on dopamine's role in motor motivation (Beierholm et al., 2013; Niv et al., 2007) to an average net reward per unit time (Boureau et al., 2015). Regardless of the origin of the putatively dopaminergic cost of cognitive control, empirical evidence for an effect of dopamine on value-based choice about cognitive control is still scarce. So far, two studies have revealed that challenging catecholamine transmission by amphetamine or methylphenidate administration, which prolongs the activity of both dopamine and noradrenaline, alters the willingness to engage in cognitive effort. Work with experimental animals

revealed that administration of amphetamine motivated rodent 'slackers' (but not 'workers') to choose a perceptually more demanding option for a higher reward (Cocker et al., 2012). However, follow-up work from the same group suggested that this effect was mediated by changes in noradrenaline rather than dopamine transmission, as selective dopamine antagonists did not alter demand avoidance (Hosking et al., 2015). In parallel, work with young healthy human volunteers has shown that the administration of methylphenidate (20 mg, oral) altered the avoidance of a classic cognitive control task, task-switching (Froböse et al, 2018; Chapter 3), in a demand selection paradigm previously shown to be sensitive to demand avoidance (Kool et al., 2010). The effect of methylphenidate depended on participants' degree of trait impulsivity, a measure that has been associated with enhanced drug-induced dopamine release and reduced D2/D3 (auto-)receptor availability (Buckholtz et al., 2010; Dalley et al., 2007; Lee et al., 2009). More impulsive participants became more demand avoidant relative to low-impulsive participants (Froböse et al., 2018). Intriguingly, in the latter study, methylphenidate did not alter the ability to implement task-switching, as measured during the performance of the task-switching and –repetition trials that followed each choice (Figure 2.1B), although the drug did render performance across trial types faster as well as more accurate, consistent with a general performance enhancing effect. Thus, in this study methylphenidate impacted only the avoidance and not the execution of cognitive control, with methylphenidate actually undermining impulsive participants' motivation to exert control. The hypothesis that this effect reflects modulation of the cost of cognitive effort by dopamine is currently under study.

Which mechanism might underlie the paradoxical effects of methylphenidate in high-impulsive individuals, where it potentiates the avoidance of cognitive control? One possibility, as referred to above, is that the cost of cognitive control was increased, because methylphenidate elicited supraoptimal levels of dopamine in these individuals with high trait impulsivity. Trait impulsivity has been shown to be accompanied by enhanced baseline levels of striatal dopamine release and low (but perhaps more sensitive) presynaptic dopamine D2 receptor availability in the midbrain (Buckholtz et al., 2010). Indeed, methylphenidate has previously been argued to act presynaptically, especially in high dopamine states, by triggering a self-regulatory mechanism, thus leading to a net reduction in dopamine release (Grace, 2001; Seeman and Madras, 2002).

An alternative, more speculative possibility is inspired by opportunity cost accounts of tonic dopamine's role in motivating vigor (physical effort) (Beierholm et al., 2013; Griffiths and Beierholm, 2017; Niv et al., 2007). Generalization of this

account led to the hypothesis that an increase in tonic dopamine motivates people to avoid slow cognitive control strategies because such an increase is accompanied by an increase in the opportunity cost of time (Kurzban et al., 2013). In one account the opportunity cost of time is equal to the average reward rate of the environment (Boureau et al., 2015). Although one study demonstrated that dopaminergic medication effects on physical effort-based decision making were independent of the possibility to save time (Zénon et al., 2016), another recent study provided some preliminary supportive evidence that strategic adjustments in the degree to which people perform fast and accurately on Simon, task-switching and perceptual decision tasks do indeed depend on fluctuations in the average reward rate (Otto and Daw, 2019). People with high levels of tonic dopamine might evaluate control as relatively more costly than people with lower dopamine tone because their estimate of the average reward rate in the environment is increased.

One key implication of this hypothesis is that dopamine-induced increases in an opportunity cost of time might account, in part, for the contrasting motor and cognitive effects of dopaminergic medication in Parkinson's disease, described above. According to this account, increases in tonic dopamine would be accompanied by increases in the cost of time, which would enhance the motivation for physical vigor (Niv et al., 2007), thus remediating bradykinesia, yet reduce the motivation for time costly cognitive control processes (Boureau et al., 2015), thus potentiating impulse control problems (Figure 2.1C). An account of dopamine's effects in terms of time costs is particularly promising in the context of the recent observation that dopamine neurons control the judgment of time (Soares et al., 2016).

Direct empirical evidence for a role of dopamine in cognitive motivation comes from a separate line of work, indicating that effects of monetary incentive reward (the promise of a bonus) on cognitive control vary as a function of striatal dopamine levels. This was shown to be the case in patients with Parkinson's disease depending on dopamine cell loss (Manohar et al., 2017), as well as in healthy volunteers depending on striatal dopamine synthesis capacity, as indexed by 6-[^{18}F]fluoro-$_{L}$-*m*-tyrosine (FMT) positron emission tomography (Aarts et al., 2014b). Intriguingly, in these studies, the relationship between striatal dopamine levels and the effect of incentives on cognitive control was negative, such that higher striatal dopamine was associated with more detrimental effects of reward on cognitive control (Aarts et al., 2014b). Conversely, patients with Parkinson's disease, which is accompanied by severe dopamine depletion in the striatum, have been shown to exhibit paradoxically greater beneficial effects of reward

on cognitive control than controls (Aarts et al., 2014a). Although the mechanism underlying these effects on incentivized cognitive control remains unclear, they are certainly reminiscent of the pattern of paradoxical effects of methylphenidate on the avoidance of cognitive control. Indeed, changes in the value of cognitive control might surface, in these tasks, in terms of changes in (the effect of reward on) task performance (Chong et al., 2015). This concurs with the recent finding that the effect of reward on task (-switching) performance correlated with participants' scores on the need for cognition scale (Sandra and Otto, 2018), which had been associated with the valuation of cognitive control in earlier work (Westbrook et al., 2013). In the current set of tasks, patients with Parkinson's disease might exhibit greater beneficial effects of reward on cognitive control, because there is greater cost to be offset by increases in the benefits of cognitive control.

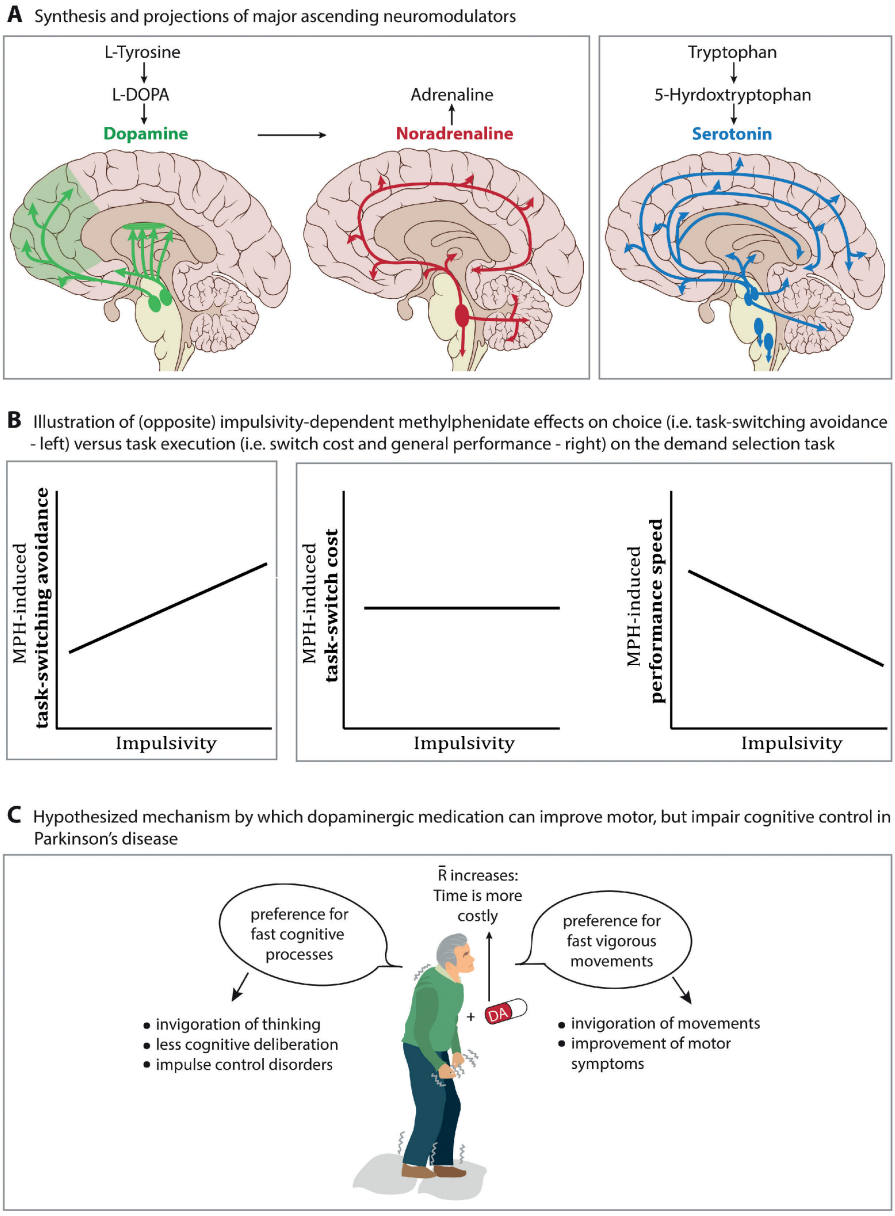

FIGURE 2.1 | **A** Simplified presentation of synthesis pathway and projections of the major ascending neuromodulators dopamine, noradrenaline, and serotonin. **B** Schematic overview of the (opposite) effects of methylphenidate on the avoidance versus execution of task-switching. Methylphenidate increased task-switching avoidance in more, relative to less impulsive participants, whereas task-switching performance was unaffected. In contrast, methylphenidate actually enhanced performance in more impulsive participants,

evidenced by speeding of responses (illustration based on data presented in Froböse et al., 2018). **C** Dopaminergic medication in Parkinson's disease increases dopamine levels and has been shown to remediate some motor symptoms, while at the same time, contributing, in a considerable proportion of patients, to impulse (cognitive) control disorder. Increased dopamine tone has been hypothesized to elevate the cost of time due to higher average net reward per unit time ($\bar{R}$; Niv et al., 2007). This might account, in part, for the contrasting motor and cognitive effects of dopaminergic medication, which would enhance the motivation for physical vigor, yet reduce the motivation for time costly cognitive control processes.

NORADRENALINE AND COGNITIVE CONTROL AVOIDANCE

Many drugs, including amphetamine or methylphenidate, prolong catecholamine transmission in a nonspecific manner by targeting both dopamine and noradrenaline transporters (Kuczenski and Segal, 2001). There are multiple reasons for thinking that such drug effects on motivated cognition reflect not just modulation by dopamine, but also noradrenaline, not least for its well-known association with arousal and fatigue.

For example, according to the classic adaptive gain theory of locus coeruleus function, task engagement is modulated by activity of the locus coeruleus, which favors either exploitation (task engagement) or exploration (task disengagement) depending on a tonic or phasic mode of action (Aston-Jones and Cohen, 2005). In line with this, baseline pupil diameter at trial onset, a measure that has been associated with locus coeruleus activity (Varazzani et al., 2015), was found to correlate with lapses of attention in a sustained attention task (Van den Brink et al., 2016), with participant's tendency to explore in a gambling task (Jepma and Nieuwenhuis, 2011), with decisions to disengage from a (discrimination) task (Gilzenrat et al., 2010) and with mental fatigue (Hopstaken et al., 2015). However, in contrast to predictions of the adaptive gain theory, prolonging tonic noradrenaline levels pharmacologically by administering reboxetine, a selective noradrenaline reuptake inhibitor, failed to alter task (dis)engagement or exploratory behavior despite intervention effects on non-specific autonomic nervous system parameters (Jepma et al., 2010). Thus, the jury is still out with regard to noradrenaline's role in exploration and task engagement. One way in which the locus coeruleus-noradrenaline system might alter task engagement and demand avoidance is by encoding unexpected (outcome) uncertainty or surprise due to errors in judging uncertainty (Preuschoff et al., 2011). For instance, greater outcome uncertainty might elicit greater task engagement given the greater likelihood of unsigned (surprise) prediction error signals at outcome (Sara and Bouret, 2012), and thus greater potential for new learning, knowledge acquisition and curiosity relief (Van Lieshout et al., 2018). Conversely, greater

certainty about the outcome of performance, whether it is good or bad, might elicit boredom or learned helplessness respectively, thus reducing the opportunity for new learning and task engagement. Recent empirical evidence indicates that blocking noradrenaline, by propranolol, increases participants' confidence in good performance on a dot-motion task relative to placebo (Hauser et al., 2017). It would be interesting to contrast directly in future studies the putative role of noradrenaline in mediating a putative link between outcome uncertainty and task engagement with a putative role of dopamine in task engagement as a function of the expected value of an outcome, thus the probability (rather than uncertainty) of performing well.

SEROTONIN AND COGNITIVE CONTROL AVOIDANCE

Like the catecholamines, serotonin is a major neuromodulator that is strongly implicated in both motivation and cognitive (impulse) control. Serotonin transmission is perhaps best known for its association with (learning about) aversive outcomes, waiting and behavioral inhibition (Miyazaki et al., 2014; den Ouden et al., 2013), although there is also extensive evidence for a complementary role in appetitive processing and reward (Cohen et al., 2015; Matias et al., 2017). In line with the idea that serotonin also plays a role in (the learning about time and/or effort) costs, the optogenetic activation of serotonergic neurons in the midbrain dorsal raphe nucleus reduced the cost of waiting. Timed activation decreased premature responding in a delayed reward task, promoting animals' patience to wait for a reward. Relatedly, an 8-week selective serotonin reuptake inhibitor intervention (escitalopram) in healthy humans improved decision-making about reward and (physical) effort costs by reducing specifically effort costs, leaving unaffected the weight of monetary incentives (Meyniel et al., 2016). A key question for future work is whether such a dissociation extends from the domain of physical effort to that of cognitive effort.

CONCLUSIONS

In this review, we highlight the potential contribution of the major ascending neuromodulators, in particular dopamine, noradrenaline and serotonin, to our tendency to avoid cognitive control. We suggest that these chemical neuromodulators might alter cognitive control by altering not just the ability but also the willingness to exert cognitive control. In line with this hypothesis, catecholaminergic challenges, like amphetamine and methylphenidate, have been shown to alter demand avoidance while leaving unaltered the ability to

perform well on a cognitive control task. Based on accumulating evidence from chemical and functional neuroimaging studies for a role for striatal dopamine in our motivation for cognitive control, we hypothesize that these catecholaminergic effects reflect in part modulation of striatal dopamine. Striatal dopamine might alter choices about cognitive control (avoidance) by modulating (learning about) the expected value (i.e. cost) of cognitive task performance. However, we also consider the role of noradrenaline in cognitive control (avoidance), and speculate that noradrenaline might contribute by modulating, instead, our uncertainty or confidence in the outcome of performance. Lastly, we hypothesize that serotonin might affect the motivation for cognitive control by modulating (time and/or effort) costs, specifically. Overall, this review highlights the relevance of advancing our understanding of the various cognitive computations carried by the different ascending neuromodulators for elucidating the basis of our tendency to avoid cognitive control.

CHAPTER 3

Effects of methylphenidate on the avoidance of cognitive control

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ABSTRACT

The catecholamines have long been associated with cognitive control and value-based decision-making. More recently, we proposed that the catecholamines might modulate value-based decision-making about whether or not to engage in cognitive control. We test this hypothesis by assessing effects of a catecholamine challenge in a large sample of young, healthy adults (n = 100) on the avoidance of a cognitively demanding control process: task switching. Prolonging catecholamine transmission by blocking reuptake with methylphenidate altered the avoidance, but not the execution of cognitive control. Crucially, these effects could be isolated by taking into account individual differences in trait impulsivity, so that participants with higher trait impulsivity became more avoidant of cognitive control, despite faster task performance. One implication of these findings is that performance-enhancing effects of methylphenidate may be accompanied by an undermining effect on the willingness to exert cognitive control. Taken together, these findings integrate hitherto segregated literatures on catecholamines' roles in value-based learning/choice and cognitive control.

INTRODUCTION

Catecholamine neurotransmitters (dopamine and noradrenaline) have long been implicated in key aspects of goal-directed behaviour, including on the one hand cognitive control (Arnsten, 1998; Brozoski et al., 1979; Cools and D'Esposito, 2011; Cools et al., 2004; Goldman-Rakic, 1997) and on the other hand value-based learning, motivation and choice (Collins and Frank, 2014; Niv et al., 2007; Robbins and Everitt, 1996; Salamone et al., 2005; Schultz, 2017). Recently, catecholamines have been proposed to also mediate their integration: value-based learning and choice about whether or not to recruit cognitive control (Cools, 2016; Westbrook and Braver, 2016). This idea implies that catecholaminergic drugs, such as methylphenidate (MPH), alter not just the ability to execute cognitive control, but also the willingness to exert or conversely, the desire to avoid, cognitive control. Here, we test this hypothesis by assessing the effects of a catecholamine challenge on the avoidance of cognitive control.

Catecholaminergic modulation of cognitive control

Cognitive control refers to the ability to flexibly adjust our behaviour to changing internal and external demands in order to attain (long-term) goals (Fuster, 1989; Monsell, 2003, 2017). Disorders accompanied by cognitive control deficits, such as attention deficit/ hyperactivity disorder (ADHD), Parkinson's disease and schizophrenia, are commonly treated with drugs that alter catecholamine transmission (Arnsten, 1998; Dagher and Robbins, 2009; Frankle and Laruelle, 2002; Prince, 2008). In ADHD, for example, MPH is usually the first-line medication and is generally found to remedy cognitive deficits (Coghill et al., 2013; Faraone and Buitelaar, 2010; Leonard et al., 2004), such as impairments in task switching (Cepeda et al., 2000; Kramer et al., 2001), response inhibition (Aron et al., 2003), and working memory (Mehta et al., 2004). In addition, psychostimulants, such as MPH have been shown to enhance cognitive function in healthy volunteers (Linssen et al., 2014), consistent with their use by students and academics to boost functioning in periods of high cognitive demand (Maher, 2008). Acute administration of a single dose of psychostimulants to healthy volunteers has indeed been shown to improve task switching (Samanez-Larkin and Buckholtz, 2013), extradimensional set-shifting (Rogers et al., 1999), spatial working memory (Elliott et al., 1997), response inhibition (Spronk et al., 2013), distractor-resistant working memory (Fallon et al., 2016) and selective attention (Ter Huurne et al., 2015). Thus, catecholaminergic drugs can both remedy cognitive control deficits in patients and enhance cognitive control in the healthy population.

However, while drugs that potentiate catecholamine neurotransmission, like MPH, are generally thought to enhance cognitive control, they certainly do not have enhancing effects in all people. Indeed, there is large individual variability in the direction and extent of catecholaminergic drug effects on human cognition (Cools and D'Esposito, 2011; Cools et al., 2004; Samanez-Larkin and Buckholtz, 2013). These individual differences in drug effects are thought to reflect dependency on baseline levels of dopamine (Cools and D'Esposito, 2011; Cools et al., 2004) and covary with proxy variables, such as trait impulsivity (Buckholtz et al., 2010; Kim et al., 2013; Lee et al., 2009; Reeves et al., 2012) and working memory capacity (Cools et al., 2008; Landau et al., 2009). Participants with higher trait impulsivity have been shown to exhibit greater beneficial effects of catecholaminergic drug administration across tasks including attention switching (Cools et al., 2007) and probabilistic reversal learning (Clatworthy et al., 2009). Such impulsivity-dependent effects of catecholaminergic drugs correspond well with the cognitive enhancing effects of MPH in ADHD (Rapoport et al., 1980), with greater MPH-induced changes in dopamine release in more severely affected ADHD patients (Rosa-Neto et al., 2005) and with greater beneficial effects of MPH on impulsive responding in higher impulsive experimental rodents (Caprioli et al., 2015). Thus, we expected that MPH-effects on cognitive control can be isolated by taking into account proxy variables, such as individual trait impulsivity.

Catecholaminergic modulation of learning and choice about cognitive control

In parallel, a second, so far relatively segregated line of evidence supports a key role for the catecholamines, dopamine in particular, in value-based learning and choice (Collins and Frank, 2014; Cools et al., 2011; Maia and Frank, 2015; van der Schaaf et al., 2013; Schultz, 2001; Swart et al., 2017). It is well-established that phasic firing of midbrain dopamine neurons contributes to the encoding of reward prediction errors (Montague et al., 1996; Schultz, 1997; Tobler et al., 2005), driving reinforcement learning and consequently promoting the selection of actions with higher predicted values. It has been argued that the same principle applies to the selection of cognitive goals, such that dopaminergic reward prediction error signals can contribute to the value-based learning and selection of cognitive goals (Braver and Cohen, 1999; Collins and Frank, 2014; Frank and Badre, 2012; Frank et al., 2001; Hazy et al., 2007).

This evidence concurs with recent expected value accounts of cognitive control (Botvinick and Braver, 2015; Kool et al., 2017; Kurzban et al., 2013; Shenhav et

al., 2017), which propose that the degree (and intensity) of engagement in an upcoming cognitive computation is based on a cost-benefit analysis. In line with this account, it has been shown repeatedly that enhancing motivation, for example by offering reward, affects performance on cognitive control paradigms (Aarts et al., 2011; Botvinick and Braver, 2015; Chib et al., 2012, 2014; Manohar et al., 2015; Padmala and Pessoa, 2011). Increasing the value or benefit of a demanding computation, such as task switching, seems to outweigh perceived demand costs.

Evidence is accumulating that cognitive demand indeed carries an intrinsic cost (Botvinick and Braver, 2015; Westbrook and Braver, 2016), a hypothesis that is supported by studies showing that, on average, healthy participants are demand avoidant. They prefer to perform a task with a lower cognitive demand, such as less task switching (Botvinick, 2007; Gold et al., 2015; Kool et al., 2010; McGuire and Botvinick, 2010) or lower working memory load, they choose to forego a higher monetary reward to avoid a more demanding task (Massar et al., 2015; Westbrook et al., 2013) and expend physical effort in order to reduce cognitive demand (Risko et al., 2014).

A role for the catecholamines in biasing meta-learning and -choice about cognitive effort follows also from abundant evidence implicating dopamine in physical effort avoidance. Enhancing dopamine transmission in non-human animals increases selection of high effort/high reward trials (Chong et al., 2015; Floresco et al., 2008a; Le Bouc et al., 2016; Salamone et al., 2016), while the opposite is true for reductions in dopamine functioning (Bardgett et al., 2009; Salamone et al., 2016). In these studies, it is evident that dopamine manipulations altered effort-based choice rather than the capacity to exert effort per se because animals were still equally able to execute the physical effortful task of climbing a barrier (Cousins et al., 1996; Yohn et al., 2015). In human patients with Parkinson's disease, characterized by striatal dopamine depletion, dopaminergic medication also increased their willingness to invest physical effort on higher reward trials when patients were tested on, relative to off their usual dopaminergic medication (Chong et al., 2015; Floresco et al., 2008a; Le Bouc et al., 2016; Salamone et al., 2016).

There is suggestive empirical evidence that similar mechanisms underlie learning and choice about cognitive demand (Botvinick et al., 2009; Kurniawan et al., 2013): Prolonging catecholamine transmission by amphetamine administration motivated rats to choose a cognitively more demanding option for a higher reward, although this was true only for rodents who were more demand-avoidant at baseline (Cocker et al., 2012; Hosking et al., 2015).

In keeping with the proposal that dopamine is implicated in the strategic recruitment and/or value-based selection of cognitive control (Boureau et al., 2015; Hazy et al., 2007), effects of cognitive demand on avoidance learning were shown to depend on striatal dopamine (Cavanagh et al., 2014, 2017). More specifically, the presence of response conflict in a Simon task modified learning about action values, such that the value of received rewards was downgraded due to response conflict and a lack of reward after response conflict increased avoidance (Cavanagh et al., 2014, 2017). These effects varied with conditions and manipulations associated with changes in striatal dopamine. For example, they varied as a function of a genetic polymorphism implicating striatal dopamine (DARPR-32), were modulated by a selective D2 receptor agonist (cabergoline) challenge and were altered in patients with Parkinson's disease, characterized by striatal dopamine depletion (Cavanagh et al., 2014, 2017). A separate line of evidence comes from incentive motivational work, showing that incentive effects on cognitive control vary as a function of striatal dopamine levels in patients with Parkinson's disease, and healthy volunteers (Aarts et al., 2012, 2014b; Manohar et al., 2015). Together, these prior findings raise the question of whether effects of catecholamine manipulations on cognitive control tasks might reflect (in part) changes in value-based learning/choice about cognitive control, in addition to reflecting changes in the ability to execute cognitive control per se. We note that, by manipulating catecholamines, we cannot draw conclusions about a selective role of dopamine in cognitive control avoidance. Indeed, there is also abundant evidence for a role for noradrenaline in demand avoidance (see discussion).

The present experiment

In the present experiment, we administered a low, oral dose of MPH to a large group of young healthy volunteers to address our primary question of interest: Does manipulation of catecholamine transmission alter the avoidance of cognitive demand, here task switching? Second, we also investigated effects of MPH on the execution of task switching (performance). To expose individual variation in response to MPH, we obtained putative proxy measures of baseline dopamine transmission: trait impulsivity scores for their association with dopamine (auto) receptor availability and striatal dopamine release (Buckholtz et al., 2010; Dalley et al., 2007; Kim et al., 2013; Lee et al., 2009; Reeves et al., 2012), as well as working memory span, associated with striatal dopamine synthesis capacity (Cools et al., 2008; Landau et al., 2009). Given prior evidence for greater MPH-induced improvement of learning in higher impulsive participants (Clatworthy et al., 2009; see above), we anticipated greater MPH-induced increases in the

learning of demand avoidance in higher impulsive participants. Conversely, our hypothesis with regard to working memory capacity was bidirectional, given prior reports of positive, but also negative associations between working memory capacity and cognitive effects of MPH (Mehta et al., 2000; van der Schaaf et al., 2013).

METHODS

Participants

106 healthy, young adults participated in this study and were recruited via flyers around the campus and the digital participant pool of the Radboud University, Nijmegen. All participants were native Dutch speakers and provided written informed consent to participate in the study. Participants were screened extensively according to pre-defined exclusion criteria (Supplemental Material 3.1).

Data from five participants were incomplete due to medical (irregular heart rate: n = 1, elevated heart rate and nausea: n = 1), and technical (n = 1) problems and drop-outs (n = 2). One additional participant was discarded due to a lack of task understanding (explicitly reported and evidenced by below-chance performance). Thus, the analyses include 100 adult participants (50 women, mean age 21.5, SD = 2.31, range 18 - 28). Two participants had trouble swallowing the capsule such that for one participant the capsule dissolved orally before swallowing and for the other participants content of the capsule was dissolved in water. We assessed whether relevant results were changed when excluding these participants.

We performed a power analysis using G*Power 3.1.9.2 software (Faul, Erdfelder, Buchner, & Lang, 2009; Faul, Erdfelder, Lang, & Buchner, 2007). Previous work from our group had revealed a correlation of 0.74 between a proxy measure of dopamine transmission, working memory capacity, and effects of MPH on reward-learning with 19 participants (van der Schaaf et al., 2013). To be conservative, given the small sample size of that previous study and given that we are using a different experimental task, we anticipated that the true effect size for the present study would be maximally half this size (r = 0.37). Our sample size of 100 (and subsequent subsample of 74: see Results section) provides 97.6% (92.2%) power to detect such an effect size, for a two-sided test with an alpha-level of 0.05.

Additional demographic and questionnaire information of included participants is reported in Table 3.1. All procedures were in accordance with the local ethical guidelines approved by the local ethics committee (CMO protocol NL47166.091.13) and in line with the Helsinki Declaration of 1975. The study

was also registered with the Dutch National Trial register (trialregister.nl, number NTR4653). Data and code for the study are freely available at https://osf.io/62tkh.

Study sessions and pharmacological intervention

A within-subjects, placebo-controlled, double-blind, cross-over design was employed. Participants visited the institute twice for study sessions of around 4.5 hours. The sessions started approximately at the same time of the day (maximal deviation: 45 minutes), with an interval of one week to 2 months between testing days. After signing an informed consent form, session 1 started with a medical screening (~20 minutes) to check for exclusion criteria (Supplemental Material 3.1). We administered a digit span test (forward and backward; (Wechsler et al., 2008), Dutch reading test (NLV; (Schmand et al., 1991) and participants received a single oral dose of methylphenidate (MPH; Ritalin®, Novartis, 20 mg) on one and a placebo substance on the other day. The order of administration was counterbalanced and double-blind. MPH is known to block transporters of both dopamine (DAT) and noradrenaline (NET), thereby preventing reuptake of catecholamines (Volkow et al., 2002b). For this reason, any intervention effect needs to be interpreted as reflecting modulation of catecholamine transmission, and not selectively dopamine or noradrenaline. Plasma concentrations peak after 2 hours with a half-life of 2-3 hours (Kimko et al., 1999). To test participants at maximal plasma levels, participants underwent a cognitive test battery starting 50 minutes after drug intake, including the demand selection task (described in Demand selection task section), the paradigm of primary interest for our research question. The delay between the administration of MPH or placebo and the start of the demand selection task was on average 80.9 (SD = 3.7) minutes. The second testing day was identical to the first one, except that participants performed a listening span test instead of the medical screening (also ~20 minutes, see Listening span task section). The cognitive test battery consisted in total of six paradigms (Figure 3.1A). The order of paradigms was constant across sessions and participants, such that a Pavlovian-to-instrumental transfer task (cf. Geurts et al., 2013) and a social learning task (cf. Cook, Den Ouden, Heyes, & Cools, 2014) preceded the demand selection task on both days, and was followed after a break, by a valenced Go/NoGo learning task (Swart et al., 2017), working-memory task (cf. Fallon et al., 2016), and a probabilistic reversal learning task (cf. den Ouden et al., 2013).

For safety reasons blood pressure and heart rate were measured three times throughout the days (start of testing day, before task battery, after task battery). At the same time points, participants' mood and medical symptoms were assessed

using the Positive and Negative Affect Scale (PANAS; Watson, Clark, & Tellegen, 1988), the Bond and Lader Visual Analogue Scales (calmness, contentedness, alertness; Bond & Lader, 1974) and a medical Visual Analogue Scale (symptoms, such as headache or muscle pain; Supplemental Material 3.2). Between the two testing days, participants completed self-report questionnaires at home (see Questionnaires section).

Demand selection task

To assess avoidance of cognitive control, we employed the demand selection task developed by Kool et al., (2010), programmed using the Psychophysics toolbox (Brainard, 1997; Pelli, 1997) in Matlab. Stimuli were 16 random color fractals used as choice cues and colored (yellow or blue) digits ranging from 1 to 10 (excluding 5) (Figure 3.1B). Stimuli were presented on a gray background and responses were made using a pc mouse.

An example trial sequence is presented in Figure 1.1C. Participants were shown two color patches as choice cues. After choosing between the two patches, by moving the mouse cursor onto one cue, a digit from 1 to 10 (but not 5) appeared at the center of the chosen cue. Depending on the color of the digit, the task of the participants was to either indicate whether the digit is odd or even (i.e. parity judgment for yellow digits), or whether the digit is smaller or larger than 5 (i.e. magnitude judgment for blue digits). Judgment was made by clicking the left or right mouse button. After the response, the cursor returned to the center of the screen and the next two choice cues were presented.

Task demand was manipulated by assigning different task switching probabilities to the two choice cues. When choosing one choice cue, the digits switched colors (i.e. task) with respect to the previous trial on 90% of trials. When choosing the other cue, the task repeated on 90% of trials. The option with higher task switching probability represents the more demanding option, based on evidence of task switching requiring extensive cognitive control (Monsell, 2003) and reports of lower accuracy in earlier studies using this task (Kool et al., 2010). The task switching manipulation was unknown to the participants. Choice behaviour (i.e. demand avoidance) and performance on the task switching task (i.e. reaction time and accuracy) were the dependent variables of interest.

Participants first practiced 40 trials of only magnitude/parity judgments using the blue and yellow digits as stimuli. Participants were then instructed on the choice task emphasizing that they will choose between two cues repeatedly and the blue

or yellow digits will appear at the cue location after they have moved the cursor towards the cue. They were instructed that they could switch between the cues at any point and when they develop a preference for one choice cue, it is fine to keep choosing the same. Instructions were followed by 4 practice choice trials to illustrate the paradigm, but using different cue patches to the actual task. The task consisted of 600 trials, divided across 8 blocks of 75 trials each. Choices and magnitude/parity judgments were not time restricted, i.e. responses were self-paced. The visual identity and location of the 2 choice cues were constant within a block, whereas every new block introduced new choice cues, located in different positions on the screen. The two choice cues were always separated by 180 degrees on an imaginary circle (radius $\approx$ 11.5 mm) around the center of the screen. The change in visual identity and location of choice cues aimed to prevent motor, location or aesthetic cue preferences confounding the effect of interest (Kool et al., 2010). We assessed participants' awareness of the task switching manipulation using a debriefing questionnaire on the second testing day after task completion. Specifically, we evaluated participants to be aware of the manipulation when they responded positive to the question whether they felt that numbers below one of the two pictures had a tendency to switch between colors more often while the other picture tended to repeat the same color.

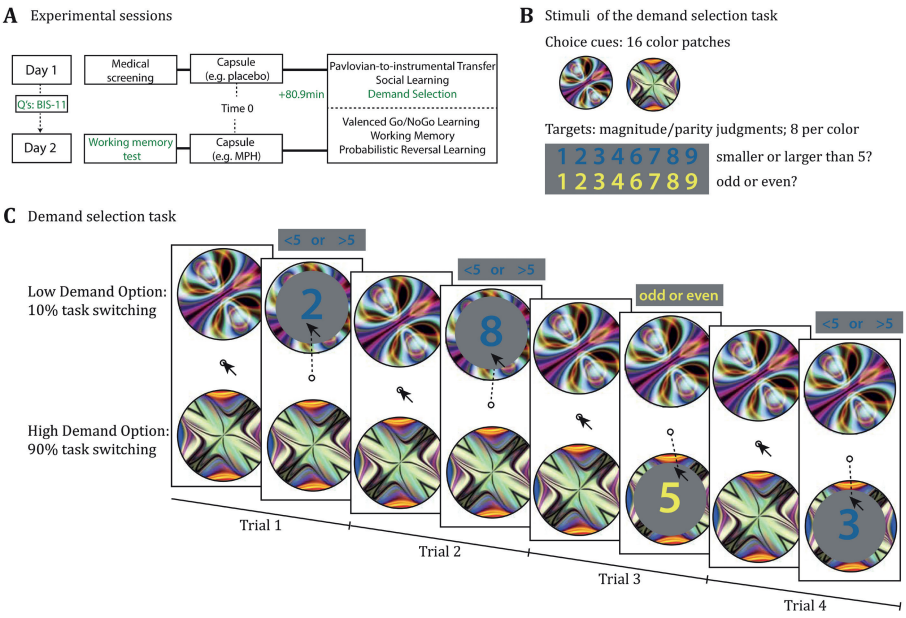


FIGURE 3.1 | A Schematic representation of testing days. Medical screening took place on the first day, a working memory test (i.e. listening span) on the second day. The remaining of the testing days were identical for both days, with methylphenidate (MPH) administration on one day and placebo on the other. Drug administration was followed by a task battery. Between the testing days, participants completed a series of self-report questionnaires, including the BIS-11 impulsiveness inventory. **B** Example stimuli of the demand selection task are presented. Circular color patches are used as choice cues; the color of the digits indicates which task had to be executed (magnitude versus parity judgment). **C** Example trial sequence of demand selection task. Participants were shown two color patches as choice cues. On every trial, participants chose between the two patches, by moving the mouse cursor towards one cue. A digit from 1 to 10 (but not 5) appeared at the target location (putative mouse path indicated here by dashed line). Depending on the color of the digit, participants either indicated whether the digit was odd or even (i.e. parity judgment for yellow digits), or whether the digit was smaller or larger than 5 (i.e. magnitude judgment for blue digits) by clicking the left or right mouse-button. Responses were self-paced.

Listening span task

The listening span task (Daneman and Carpenter, 1980; Salthouse and Babcock, 1991) was administered at the beginning of the second test session to obtain an estimate of participants' working memory capacity, as a putative proxy of baseline dopamine synthesis capacity. During this test, participants listened to pre-recorded sentences and were given two tasks: They answered simple written multiple-choice questions about the content while remembering the last word of each sentence for later recall. The number of sentences on each trial (i.e. the span) increased up to 7 over the course of the task. Three series of the same span were conducted. The

trial was coded as successful if the answers to the multiple-choice questions were correct and if all last words were remembered and reported in the correct order. Based on participants' performance a listening span was calculated ranging from 0 to a maximum of 7. The highest level for which two out of the three series were correctly remembered comprised the *basic span*. Half a point was added if one serie of the following span was correctly completed, resulting in the measure of *total span*. For the listening span task, internal consistency has been shown to be adequate (0.70 - 0.90) based on coefficient alphas and split-half correlations (Conway et al., 2005; Salthouse and Babcock, 1991). Also test-retest correlations were high, approaching 0.70 - 0.80 across different studies varying in delay (Conway et al., 2005). *Total span* and total number of words recalled have both been shown to correlate positively with dopamine synthesis capacity (Cools et al., 2008; Landau et al., 2009). Previous studies have reported a medium (Landau et al., 2009) to large (Cools et al., 2008) effect size for the correlation between listening span scores and dopamine synthesis capacity. In addition, listening span scores have been shown to predict dopaminergic drug effects (Cools and D'Esposito, 2011; Kimberg and D'Esposito, 2003; van der Schaaf et al., 2014).

Questionnaires

A series of questionnaires was completed by participants at home between the two test sessions. The trait impulsivity questionnaire was key to our research question and will be described in more detail below. The other questionnaire data were acquired for exploratory purposes, not pursued here, and are presented in Table 3.1.

Trait impulsivity

The Barratt Impulsiveness Scale (BIS-11; (Patton et al., 1995) was administered to assess participants' degree of trait impulsivity. The scale is a self-report questionnaire, consisting of 30 statements that participants rate on a 4-point Likert scale ("never" to "almost always"). Examples are "I buy things on impulse" or "I am future oriented". Scores on this questionnaire can range from 30 to 120. BIS-11 total scores have been shown in a large sample ($N > 1000$) to have good internal consistency following a Cohen's alpha of 0.83 and strong test-retest reliability at one month, evidenced by a correlation of 0.83 (Stanford et al., 2009). Scores have been found to be associated with dopamine D2/D3 receptor availability in the midbrain, and enhanced dopamine release in the striatum (Buckholtz et al., 2010; Kim et al., 2013; Lee et al., 2009; Reeves et al., 2012) and

has been shown to predict effects of MPH on learning (Clatworthy et al., 2009). This measure serves as a second putative proxy of baseline dopamine function for predicting effects of MPH. The effect sizes for the correlations between Barratt total scores and D2/D3 receptor availability ranged from small (Lee et al., 2009) to large (Buckholtz et al., 2010).

TABLE 3.1 | Demographics and questionnaire data

	Characteristic	Measure	Score
Demographics	Age	Years, mean [range]	21.5 [18-28]
	Gender	Men/women (number)	50/50
Experimental information	Order	Placebo first / MPH first (number)	52/48
	Average delay MPH to task	Minutes*	81.2 (3.6)
Neuropsychological assessment	Verbal intelligence	NLV	93.6 (7.8)
	Working memory capacity	Listening span: total span	4.8 (1.1)
		Digit span** Forward Backward	8.3 (1.9) 7.2 (1.6)
Self-report questionnaires	Impulsivity	BIS-11: total score	61.8 (8.6)
	Need for Cognition	NCS	63.3 (10.5)
	Depressive symptoms	BDI	3.6 (3.8)
	Behavioral activation	BAS: total score	23.4 (4.0)
	Behavioral inhibition	BIS	16.3 (3.6)
	Anxiety symptoms	STAI	32.6 (6.9)
	Social support	MDSPSS: total score	5.9 (0.8)
	Social status	BSMSS: total score	47.8 (12.7)
	Social dominance	SADQ: social score	4.1 (0.8)
	Aggressive dominance	SADQ: aggressive score	2.6 (0.6)

*2 missing values; ** scores represent an average across two testing days
Demographic and background characteristics of participants included in the analysis (n = 100). Questionnaires included the Need for Cognition Scale (NCS; Cacioppo and Petty, 1982; Cacioppo et al., 1984), Beck Depression Inventory (BDI; Beck et al., 1996), Behavioral Inhibition Scale/Behavioral Activation Scale (BIS/BAS; Carver and White, 1994), Spielberger Trait Anxiety Inventory (STAI; Spielberger et al., 1983), Multidimensional Scale of Perceived Social Support (MDSPSS; Zimet et al., 1988), Social and Aggressive Dominance Questionnaire (SADQ; Kalma et al., 1993) and Barratt Simplified Measure of Social Status (BSMSS; Barratt, 2006).

If not indicated differently, scores represent group averages and the standard deviations between brackets. Reported scores are comparable with observations in healthy populations in earlier reports. Listening span, e.g. Salthouse and Babcock, 1991; Digit span, e.g. van der Schaaf et al., 2014: FW mean = 8.5; BW mean = 7.9; BIS-II, e.g. Buckholtz et al., 2010: mean = 59.5, NCS, e.g. Westbrook et al., 2013: mean = 64.5; BDI, e.g. Schulte-Van Maaren et al., 2013: mean = 3.7; BIS/BAS, e.g. Franken, Muris, & Rassin, 2005: mean BIS = 13.8, mean BAS = 24.5; STAI, e.g. De Weerd et al., 2001: mean ≈ 34; MDSPSS, e.g. Canty-Mitchell and Zimet, 2000: mean = 5.5; BSMSS, e.g. Cook et al., 2014: mean = 49.0, 42.6; SADQ, e.g. Cook et al., 2014: social mean = 4.0, 3.9; aggressive mean = 2.9, 2.7. The verbal IQ estimate (NLV) seems low in this sample (relative to e.g. van der Schaaf et al., 2014: mean = 101). However, we tested a student population and we expect this value to be low due to the outdated character of the test (1991), not accomodating the changes in language use.

Statistical analyses

The experiment was set up to assess effects of MPH on, first, demand avoidance (cue choice) and, second, the execution of task switching (performance). We assessed demand avoidance by analyzing the proportion of participants' choices of the low demand cue (requiring 10% task switching) versus high demand cue (requiring 90% task switching). Execution of task switching was assessed by analyzing demand costs, which were calculated by subtracting performance (accuracy and (log-transformed) response times (RTs)) on trials on which participants chose the low- versus high-demand option. Following our primary questions, we assessed the effects of MPH on these measures as a function of two putative proxy measures of baseline dopamine function: trait impulsivity, measured with the Barratt Impulsiveness Scale, and working memory capacity, measured with the listening span test.

The data were analyzed with mixed-level models using the lme4 package in R (Bates et al., 2015). This allowed us to account for within-subject variability in addition to between-subject variability. Factors drug [MPH vs. placebo] and demand [low vs. high] (for performance only) were within-subject factors, and impulsivity and listening span scores were between-subject factors. Models included all main effects and interactions, except for the interaction between impulsivity and listening span, as our question did not concern this interaction. All models contained a full random effects structure (Barr, 2013; Barr et al., 2013). P-values reported in the manuscript that pertain to the regressions were estimated using the "esticon" procedure in the "doBy" package which relies on the chi-square distribution (Hojsgaard, 2006). Note that the degree of freedom is always 1 for this statistical test, as we compute significance for a specific regression coefficient at a time (H0: $\Lambda\beta = \beta 0$ where Λ is a (contrast) matrix probing a

specific coefficient). Effects were considered statistically significant if the p-value was smaller than 0.05. We report R^2 for all models using the "r.squaredGLMM" procedure in the "MuMIn" package to provide a more intuitive estimate. However, note that there is no broad agreement yet about the most appropriate way of R^2 estimation for mixed-effects models. An overview of the basic models (cue choice, accuracy, RTs) is presented in Supplemental Table 3.1.

Response stickiness

Surprisingly, participants displayed extremely high rates of response stickiness, as indexed by low proportions of switching between the cues (note that within blocks all cues had fixed locations). To assess whether the observed choice effects were explained or masked by modulation of response stickiness, we constructed a second and third choice model, which extended the basic model with a stay-regressor and then adding its interaction with MPH. The stay-regressor quantified the degree to which participants' choices were the same as their choice on the previous trial and allowed us to investigate whether reported drug effects of interest are significant when accounting for (drug effects on) response stickiness. More specifically, the stay regressor quantified, on a trial-by-trial basis, which choice (low demand, coded as 1, versus high demand, coded as -1) participants would make on the current trial if they repeat the same choice as one trial before. We conducted model comparisons to assess whether the models including response stickiness effects improved our explanation of the data relative to the basic choice model. Model comparison was conducted using the anova function in R, which assesses whether the reduction in the residual sum of squares is statistically significant compared with the simpler model. Results of the winning model will be presented.

To confirm that the MPH-effects on demand avoidance, i.e. our primary choice effect of interest, did not reflect MPH-effects on response stickiness, we also checked whether MPH-effects on response stickiness correlated with MPH-effects on demand avoidance using Spearman correlations (given that the proportion of staying with the same cue violated assumptions of normality and contained outliers) in SPSS 21 (IBM Corp., Armonk, N.Y., USA).

Relationship between demand avoidance and task performance

To assess whether MPH-effects on demand avoidance relate to MPH-effects on task performance (accuracy or RTs), we calculated Spearman correlations between the proportion of low demand choices and demand costs (for RT and accuracy)

and the MPH-effect on these measures using SPSS 21 (IBM Corp.). To quantify evidence for an absence of effects, we also calculated Bayesian correlations between MPH-effects on these various variables using JASP software (Version 0.7.5; JASP Team, 2016) with default priors, which reflect that each value for the correlation coefficient was equally liekely to be obtained (Wagenmakers et al., 2016c).

RESULTS

Methylphenidate alters the avoidance of task switching

Cognitive demand was operationalized by two choice options with opposing task switching probabilities (10% vs. 90%). As expected, participants were overall demand avoidant; participants chose the cue with low task switching probability more often than the cue with the high probability ($M = 0.56$, $SD = 0.13$) (Intercept: $X^2(1) = 20.70$, $p < 0.001$). Demand avoidance was evident both during the placebo and MPH session (Figure 3.2). A minority of participants (26%) reported during debriefing that they were aware of the fact that one choice cue resulted in more task switches than the other cue.

Surprisingly, participants exhibited extremely high rates of response stickiness, as indexed by the low number of trials on which participants switched between cues (across participants and sessions: $M = 5.9\%$, $SD = 17.5\%$) (Supplemental Figure 3.1). Five participants never switched cues in both test sessions. An additional 17 participants never switched cues on one testing day (a further 2 participants switched on every trial). It is unclear how this rate of response stickiness compares numerically to the rates in previous studies, as this measure was not reported. However, the unexpected high rate of response stickiness, in combination with earlier reports of dopaminergic medication effects on response stickiness (Rutledge et al., 2009) led us to ask whether our primary effect of interest on demand avoidance might reflect or be masked by effects on response stickiness. To assess this, we included a stay regressor in the basic choice model (Supplemental Table 3.1). Model comparison with the original basic model lacking the stay regressor showed that a model including a stay regressor (BIC = 54711, marginal $R^2_{GLMM} = 0.122$) explained significantly more variance in choice behaviour than did the basic model (BIC = 150826, marginal $R^2_{GLMM} = 0.004$; $X^2(1) = 96127$, $p < 0.001$). However, the model including both, a stay regressor and a regressor for MPH-effect on staying (BIC = 26607, marginal $R^2_{GLMM} = 0.639$) explained even more variance than the model without the interaction term ($X^2(8) = 28198$, $p < 0.001$). Therefore, we report the results of this extended model below.

Results of this winning model reveal that overall, demand avoidance did not differ between drug sessions (Drug: $X^2(1) < 0.01$, $p = 0.964$). However, we hypothesized that effects of MPH on demand avoidance would crucially depend on putative proxies of dopamine transmission, namely trait impulsivity (indexed by total Barratt Impulsiveness Scale score), and/or working memory capacity (indexed by total listening span). As predicted, MPH-effects on demand avoidance varied

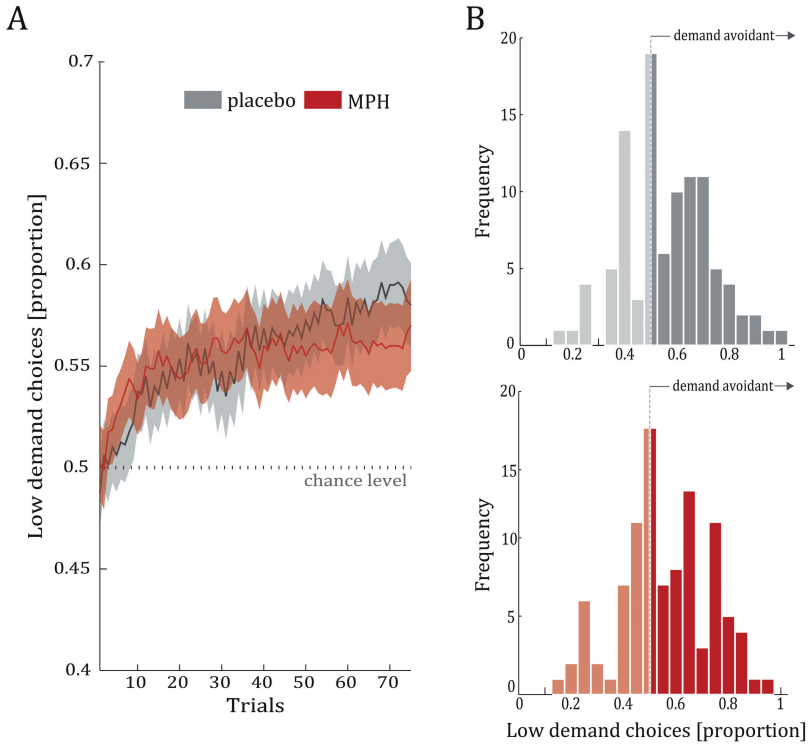


FIGURE 3.2 | **A** Average proportion of low demand choices as a function of trial, averaged per participant over 8 blocks, for placebo (grey) and methylphenidate (MPH; red) sessions. Data lines represent the group average and shaded area represents standard error of the mean. **B** Histograms of low demand choices in the placebo (top) and MPH (bottom) sessions reveal large individual variability in terms of demand avoidance. Frequency represents number of participants. The data follows a bell-shaped distribution and tests of deviation from normality (Shapiro-Wilk) confirmed that we cannot reject the null hypothesis that the data came from a normally distributed population (proportion low demand choices placebo: p = 0.718, proportion low demand choices MPH: p = 0.324).

significantly as a function of trait impulsivity (Drug x Impulsivity: $X^2(1) = 5.33$, $p = 0.021$). The direction of this effect was positive with greater MPH-induced increases in demand avoidance in more impulsive participants (Figure 3.3). The interaction between working memory capacity and the effect of MPH on

demand avoidance was only trending towards significance (Drug x Listening span: $X^2(1) = 2.91$, $p = 0.088$). We therefore focus further analyses on trait impulsivity, while reporting further analyses as a function of working memory capacity in the Supplemental Results 3.1.

In addition, results of the winning model reveal, apart from a main effect of staying with the previously chosen option (Stay: $X^2(1) = 291.16$, $p < 0.001$), that MPH also affected staying (Drug x Stay: $X^2(1) = 7.65$, $p = 0.006$). MPH increased response stickiness relative to placebo. Complete statistics of this choice model are presented in Supplemental Table 3.2.

To confirm that these effects of MPH on response stickiness could not explain the impulsivity-dependent demand avoidance effects, we also investigated whether there was any correlation between MPH-effects on the proportion of staying with the same choice cue and MPH-effects on demand avoidance. There was no such correlation (low demand choices $_{MPH-PLA}$ & proportion staying $_{MPH-PLA}$: $r_s = 0.12$, $p = 0.240$), with Bayesian correlation analysis showing substantial evidence for the null effect ($BF_{10} = 5.14$).

Finally, the size of our sample allowed us to assess whether the impulsivity-dependent effects remained present when excluding participants who appeared to use explicit choice strategies, i.e. failed to explore the choice options at all, either in one (n = 17) or both sessions ($n = 5$), and those who switched between choice cues on every trial, either in one (n = 1) or both sessions (n = 1). We also excluded those participants for whom the capsule dissolved (orally or in water) before swallowing (n = 2, one of those was also a sticky participant) as well as one participant whose score on the BIS-11 deviated more than 3 standard deviations from the mean. Analysis of this smaller dataset ($n = 74$) confirmed the effects obtained from the analysis of the larger sample: MPH altered demand avoidance significantly as a function of trait impulsivity (Drug x Impulsivity: $X^2(1) = 5.80$, $p = 0.016$; Supplemental Figure 3.2; Supplemental Table 3.3). In this cleaner sample of participants who explored both choice options on both testing days, we confirmed that these effects were present also when running a model without taking into account response stickiness: MPH altered demand significantly as a function of trait impulsivity (Drug x Impulsivity: $X^2(1) = 5.60$, $p = 0.018$).

In sum, above control analyses show that observed MPH-effects on demand avoidance are robust, also when taking into account MPH-effects on response stickiness or excluding problematic participants. Furthermore, a correlation

analysis suggests that MPH-effects on response stickiness and demand avoidance are independent.

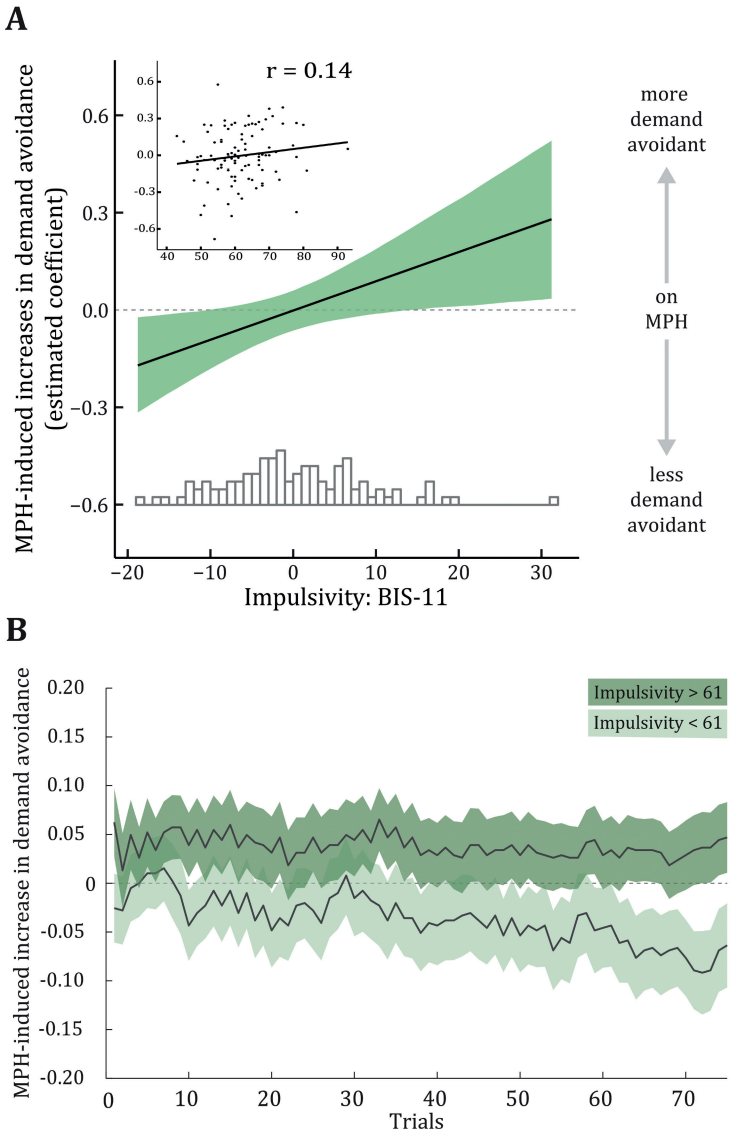


FIGURE 3.3 | Methylphenidate (MPH)-effect on demand avoidance as a function of participants' trait impulsivity (BIS-11) scores. **A** Line represents model-based estimated coefficients of MPH-effect on demand avoidance as a function of (z-scored) trait impulsivity scores. Shaded area represents simulated 95% confidential intervals of the coefficients. The inset shows the raw data: drug effect for every participant (n = 100) across trials as the difference in the proportion of low demand choices (MPH - placebo) as a function of trait impulsivity. **B** Trial-by-trial drug effect averaged across 8 blocks, and across participants (n = 100) of low (n = 49) versus high (n = 48) trait impulsivity groups as a function of trial. 3 participants with scores equal to the median are not included. Shaded areas represent standard error of the difference. See Supplemental Figure 3.3 for the impulsivity-dependent effect of MPH as a function of trial number for placebo and MPH separately.

Avoidance of task switching does not reflect poor performance

Following every cue choice (10% vs. 90% task switching probability), participants were presented with a parity/magnitude judgment task. Overall accuracy was high in this number judgment task ($M = 0.97$, $SD = 0.04$) and, as expected, participants were sensitive to the task switching manipulation. They performed better when the task repeated with respect to the previous trial than when they were presented with a task switch, evidenced by higher accuracy ($M = 0.01$, $SD = 0.02$) ($X^2(1) = 20.43$, $p < 0.001$) and faster RTs ($M = 0.36$, $SD = 0.29$) ($X^2(1) = 119.70$, $p < 0.001$) (Table 3.2). The improved performance for task repetitions consequently affected performance for the two cue options: Participants performed better on trials on which they chose the low demand (10% task switching) relative to high demand (90% task switching) cue (accuracy demand cost: $X^2(1) = 20.93$, $p < 0.001$; RT demand cost: $X^2(1) = 535.73$, $p < 0.001$). We note that participants' choice of the low versus high demanding option determines the degree of exposure to task-switching, so that these measures are not independent. Supplementary analyses confirm that RT switch costs are larger for low-demand choices, where task-switching occurs less frequently (task-switching x demand interaction: $X^2(1) = 371.8$, $p < 0.001$, Supplemental Results 3.3).

TABLE 3.2 | Task performance

Task component	Variable	Placebo	MPH
Demand avoidance (i.e. choices)	Low Demand choice (proportion)	0.56 (0.17)	0.55 (0.18)
	High Demand choice (proportion)	0.44 (0.17)	0.45 (0.18)
Performance	Accuracy (in proportion correct)	0.97 (0.03)	0.97 (0.07)
	Task repeat	0.97 (0.03)	0.97 (0.06)
	Task switch	0.96 (0.04)	0.96 (0.07)
	Switch cost	0.01 (0.02)	0.01 (0.02)
	Low demand	0.97 (0.03)	0.97 (0.06)
	High demand	0.96 (0.04)	0.96 (0.07)
	Demand cost	0.01 (0.02)	0.01 (0.02)
	Response times (in s)	1.06 (0.33)	0.99 (0.26)
	Task repeat	0.89 (0.24)	0.84 (0.21)
	Task switch	1.25 (0.44)	1.16 (0.33)
	Switch cost	0.36 (0.29)	0.32 (0.19)
	Low demand	0.90 (0.24)	0.86 (0.21)
	High demand	1.25 (0.44)	1.16 (0.33)
	Demand cost	0.35 (0.28)	0.30 (0.20)

Mean values (and standard deviations) of choice proportions and performance on the magnitude/parity judgment task (i.e. accuracy, response times, switch and demand costs) for placebo and methylphenidate sessions. Note that these performance scores represent averages, across trials and across participants. Given the multivariate structure of our analyses, which quantify within as well as between subject effects, the statistical analyses are sensitive to capture small but consistent effects.

There were no effects of MPH, relative to placebo, on the size of the switch or demand costs, when assessed across the group as a whole (Drug x Demand for RTs: $X^2(1) = 0.75$, $p = 0.387$, for accuracy: $X^2(1) = 1.20$, $p = 0.274$; Drug x Switch for RTs: $X^2(1) = 0.61$, $p = 0.434$, for accuracy: $X^2(1) = 1.91$, $p = 0.167$). In contrast to the altered demand avoidance, the effect of MPH on the demand cost did not vary as a function of trait impulsivity (for RTs: Drug x Impulsivity x Demand: $X^2(1) = 0.29$, $p = 0.590$, Figure 3.4A; for accuracy: Drug x Impulsivity x Demand: $X^2(1) = 0.001$, $p = 0.968$, Figure 3.4B).

Independent of demand and baseline-measures, MPH increased overall accuracy (Drug: $X^2(1) = 8.97$, $p = 0.003$), and trended towards speeding up responses (Drug: $X^2(1) = 2.98$, $p = 0.084$). Interestingly, these MPH-induced response time (but not accuracy) changes did depend on trait impulsivity (Drug x Impulsivity: $X^2(1) = 7.28$, $p = 0.007$), with greater MPH-induced decreases in response times in more impulsive participants. Complete statistics of the basic performance models are presented in Supplemental Table 3.4. For the purpose of consistency with our approach for the choice analyses, we also conducted model comparisons for the performance models when including a stickiness regressor. Results of the model comparisons are presented in Supplemental Results 3.2.

This pattern of findings suggests that MPH-induced demand avoidance cannot be explained by reduced performance under MPH (i.e. avoidance of failure). MPH increased demand avoidance in more impulsive participants despite MPH-induced speeding of responding and unaffected accuracy (Drug x Impulsivity: $X^2(1) < 0.01$, $p = 0.747$), also not as a function of demand (Figure 3.4B).

Although the reported findings above suggest that performance cannot explain the MPH-induced demand avoidance, we further assessed the potential association with a direct correlation. In other words, we tested whether participants who avoided demand more, did so because the task had become more difficult for them. More specifically, we computed correlations between demand costs (accuracy and RT) and demand avoidance. In line with our reasoning above, the MPH-effect on demand costs (demand cost $_{MPH - PLA}$) did not correlate with the drug effect on demand avoidance (low demand $_{MPH - PLA}$) and even provided evidence, though weak, for the absence of the correlation (accuracy: $r_s = 0.14$, $p = 0.167$, $BF_{01} = 4.80$; RT: $r_s = -0.10$, $p = 0.330$, $BF_{01} = 2.60$).

In sum, analyses of performance data and correlations between performance and demand avoidance provide evidence that observed MPH-effects on demand avoidance are unlikely to be explained by performance changes. This suggests that while the actual performance of the task did not change, this demand was evaluated differently (indexed by degree of demand avoidance). Bayesian analyses provided evidence for independence of the MPH-effects on demand avoidance and performance.

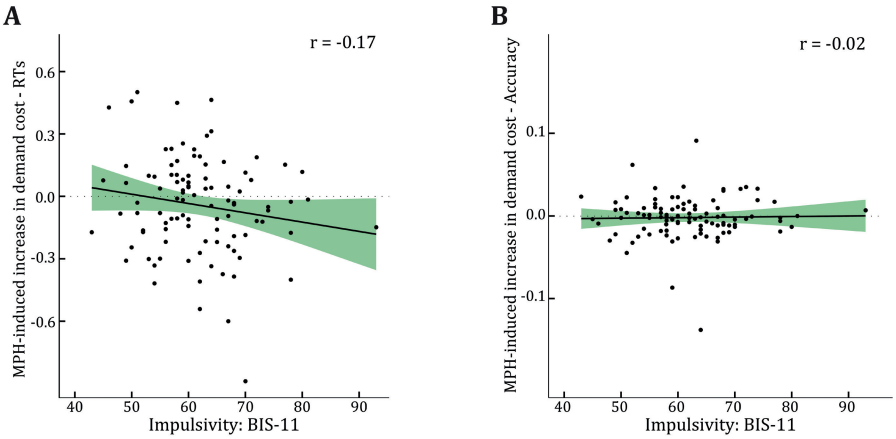


FIGURE 3.4 | Drug effects on performance costs between high and low demand choices. Data points represent methylphenidate (MPH) effects on average demand cost (MPH - placebo) for each participant (n = 100) for **A** response times (in seconds) as a function of trait impulsivity (BIS-11) and **B** accuracy (in proportion correct) as a function of trait impulsivity (BIS-11). Shaded areas represent standard errors of the mean. Both effects are not statistically significant.

DISCUSSION

In this study, we investigated whether prolonging catecholamine transmission alters choices about whether or not to recruit cognitive control (i.e. demand avoidance). Specifically, we hypothesized that challenging the catecholamine system would alter the avoidance of cognitive demand. We tested this hypothesis by assessing the effects of acute administration of oral MPH (20mg), a potent blocker of catecholamine transporters, on task switching avoidance using a demand selection task (Kool et al., 2010). A large sample of young healthy participants (n = 100) was tested to expose individual differences in the response to such catecholaminergic drugs (Cools and D'Esposito, 2011). Given the well-established observation that drug effects vary across individuals as a function of baseline levels of dopamine, we obtained indices of trait impulsivity and working memory capacity, both previously associated with dopamine transmission (Buckholtz et al., 2010; Cools et al., 2008; Dalley et al., 2007; Kim et al., 2013; Landau et al., 2009; Lee et al., 2009; Reeves et al., 2012). As predicted, MPH altered the avoidance of task switching, without changing the execution of task switching itself. Notably, this effect was isolated when taking into account trait impulsivity.

General demand avoidance effects

On average and across sessions, participants chose the low demand option more often than the high demand option, which indicates that our paradigm was sensitive to our construct of interest, i.e. demand avoidance, consistent with prior studies using this or very similar paradigms (Kool et al., 2010, 2013; McGuire and Botvinick, 2010). Moreover, as previous, demand avoidance was observed despite most participants reporting not to be aware of the demand manipulation. Thus we replicate previous observations that anticipated cognitive demand contributes to decision-making, so that decisions are made, partly, in order to minimize demands for exertion or work, a principle sometimes referred to as the law of less work (see also Botvinick, 2007; Westbrook et al., 2013). However, the average proportion of low demand choices was somewhat lower in our study compared with previous work (e.g. Kool et al 2010; see results section; but Gold et al., 2015). It is possible that this reflects the fact that our participants exhibited very high rates of response stickiness (see Response Stickiness), perhaps due to a relatively reduced engagement with or enhanced avoidance of performing the choice task itself.

Methylphenidate alters demand avoidance in a baseline-dependent manner

Our key finding was that MPH affects demand avoidance, but that these effects varied as a function of trait impulsivity, with greater MPH-induced increases in demand avoidance in more, relative to less, impulsive participants. Much progress has been made recently in our understanding of the (psychological, neurochemical, and neural) mechanisms of our motivation to avoid cognitive demand (Chong et al., 2017; Cools, 2016; Shenhav et al., 2017; Westbrook and Braver, 2016). Here, we focus on the psychological and chemical neuromodulatory mechanisms of demand avoidance.

Most generally, the motivational control of goal-directed behaviour is well established to depend on the learning of the value and cost of our actions (Dickinson and Balleine, 1994). Factors that have been suggested to contribute to the motivational control of specifically our cognitive actions include the learning of time (opportunity) costs (Boureau et al., 2015; Kurzban et al., 2013; Otto and Daw, 2019), of intrinsic effort costs related to conflict (Cavanagh et al., 2014; Kool et al., 2013), of error likelihood or performance failure (Dunn et al., 2019) and/or a combination of these factors (Dunn et al., 2016; Shenhav et al., 2017).

We began to address the psychological mechanism underlying our effect on demand avoidance by asking whether it can be attributed to indirect effects on performance costs (error or RT). This is unlikely in the current dataset, for the following reasons. First, there was evidence for an absence of correlations between MPH-induced demand avoidance and MPH-induced performance effects (i.e. demand costs in error rates and RTs) across participants. Second, demand costs were not modulated by MPH. Finally, in more- relative to less-impulsive participants, MPH increased demand avoidance, but actually improved task performance in terms of response speed. Thus, the MPH-induced changes in demand avoidance are unlikely to reflect indirect effects of modulation of (perceived) performance failure.

Instead, we hypothesize that MPH might alter demand avoidance via modulating an intrinsic, or opportunity cost of effort. This hypothesis concurs generally with recent work showing that the effect of demand, manipulated by response conflict, on reward versus punishment learning varies with pharmacological dopamine receptor stimulation as well as individual genetic variation in dopamine transmission (Cavanagh et al., 2014). It might be noted that the present study was not set up (and, given high response stickiness rates, did not allow us) to disentangle the degree to which the MPH-effect on demand avoidance reflects learning (or choice) based on reward (effort relief) or punishment (effort cost).

In the case of learning about simple states and/or actions, it has previously been shown that increases in dopamine potentiate the impact of benefits (reward) on learning and choice, while undermining the impact of punishment (and other costs) on learning and choice (Collins and Frank, 2014; Cools et al., 2009). Critically, as is the case in the present study, evidence indicates that there is large individual variability in the direction and extent of the effects of dopaminergic drugs on the learning and choice. Here, MPH indeed reduces demand avoidance in less, relative to more impulsive participants, perhaps by increasing the value and/or reducing the cost of the high demanding option. With regard to the finding that MPH enhanced demand avoidance in the high impulsive participants, we put forward two possible neurochemical accounts. One possibility is that in these high-impulsive participants, MPH potentiated the demand cost by eliciting supraoptimal levels of dopamine. Trait impulsivity has been shown to be accompanied by enhanced baseline levels of striatal dopamine release and low (but perhaps more sensitive) presynaptic dopamine D2 receptor availability in the midbrain (Buckholtz et al., 2010). Indeed, MPH has previously been argued to act presynaptically by triggering a self-regulatory mechanism, thus leading to a net reduction in dopamine release in high-dopamine subjects

(Grace, 2001; Seeman and Madras, 2002). Based on further empirical evidence for an 'inverted U'-shaped relationship between dopamine and reward- versus punishment-based learning (Cools and D'Esposito, 2011; Cools et al., 2009), we therefore hypothesize that MPH might have increased demand avoidance in the high-impulsive subjects by detrimentally overdosing striatal dopamine levels that were already high in these subjects (Buckholtz et al., 2010; Clatworthy et al., 2009), thereby paradoxically reducing the (subjective) value of mental effort. This hypothesis is currently under study in an ongoing project where effects of MPH are assessed in cognitive effort discounting.

An alternative possibility is that a greater MPH effect on demand avoidance in the high-impulsive subjects represent greater MPH-induced increases in striatal dopamine, thereby potentiating the impact of mental effort relief (i.e. reward) on learning and choice. This concurs with the prior finding that MPH potentiated reward versus punishment learning to a greater degree in subjects with higher working memory capacity, putatively corresponding with higher baseline levels of dopamine (van der Schaaf et al., 2013; Swart et al., 2017). This open question is currently under study.

Critically, there are different reasons for caution when speculating about the mechanism by which MPH potentiates demand avoidance in high impulsive individuals. First, there is discrepancy with regard to the direction of the association between trait impulsivity and dopamine function (Buckholtz et al., 2010; Dalley et al., 2007; Kim et al., 2013; Lee et al., 2009; Reeves et al., 2012). Second, the direction of the link between dopamine and cognitive demand avoidance is unclear. Extrapolation of the physical demand avoidance literature and of neurocomputational models of dopamine in the basal ganglia, such as the OPAL model (Collins and Frank, 2014), suggests a positive link, such that prolonging (striatal) dopamine would enhance the benefit and reduce the cost of control. However, there are also indications for a negative link between dopamine and cognitive motivation, with patients with Parkinson's disease (OFF medication) exhibiting enhanced rather than reduced cognitive motivation (Aarts et al., 2012).

Modulation of demand avoidance by dopamine versus noradrenaline

MPH prolongs catecholamine transmission in a nonspecific manner by targeting both dopamine and noradrenaline transporters (Kuczenski and Segal, 2001; Scheel-Krüger, 1971). Therefore, a key remaining open question is whether the effects of MPH, reported here, reflect modulation of dopamine or noradrenaline.

We hypothesize, in part based on the work by Cavanagh et al. (2014), reviewed above, that our effect of MPH on demand avoidance reflects modulation of striatal dopamine. This concurs with a recent study reporting striatal dopamine increases after administration of a low-dose of MPH (Kodama et al., 2017) and also with our previous finding that the effects of MPH on reward- versus punishment-learning resembled that of the selective dopamine receptor agent sulpiride, which has selective affinity for D2 receptors that are particularly abundant in the striatum (Janssen et al., 2015; van der Schaaf et al., 2014). Moreover, it is generally consistent with prior work, demonstrating a key role for (striatal) dopamine in physical effort-based choice (Buckholtz et al., 2010; Hosking et al., 2015; Salamone et al., 2016; Wardle et al., 2011), although a recent study failed to observe modulation by the selective dopamine antagonists eticlopride and SCH23390 of the willingness to exert cognitive effort (Hosking et al., 2015). Finally, the dopamine hypothesis coincides with our finding that the effect of MPH depended on trait impulsivity, which implicates drug-induced dopamine release (Buckholtz et al., 2010) and changes in D2/D3 receptor availability (Buckholtz et al., 2010; Dalley et al., 2007; Lee et al., 2009; but Kim et al., 2013; Reeves et al., 2012).

Future studies are needed to test the hypothesis that MPH alters demand avoidance via affecting dopamine rather than noradrenaline transmission, for example using a MPH administration design in which participants are pretreated with a selective dopamine receptor antagonist prior to receiving MPH or in which effects of MPH are compared with those of atomoxetine, which leaves unaltered striatal dopamine transmission. This is especially pertinent because of the well-established link between the locus coeruleus–norepinephrine system and mental fatigue (Berridge and Waterhouse, 2003) and the implication of this system in task-related decision processes and optimization of task performance (Aston-Jones and Cohen, 2005). According to the classic adaptive gain theory of locus coeruleus function, task engagement is modulated by activity of the locus coeruleus, which favors either exploitation (task engagement) or exploration (task disengagement) depending on a tonic or phasic mode of action (Aston-Jones and Cohen, 2005). In line with this, pupil diameter, a measure that has been associated with locus coeruleus activity (Varazzani et al., 2015), correlated with lapses of attention in a sustained attention task (Van den Brink et al., 2016), with participant's tendency to explore in a gambling task (Jepma and Nieuwenhuis, 2011), with decisions to disengage from a (discrimination) task (Gilzenrat et al., 2010) and with mental fatigue (Hopstaken et al., 2015). One way in which the locus coeruleus-noradrenaline system might alter task engagement is by encoding surprise due to outcome uncertainty (Preuschoff et al., 2011), or by modulating

participants' confidence in their own performance. Recent empirical evidence indeed indicates that blocking noradrenaline selectively, by propranolol, increases participants' confidence in good performance on a dot-motion task relative to placebo (Hauser et al., 2017). In addition, the injection of clonidine, a selective noradrenergic agonist which reduces central noradrenaline levels, has been sown to reduce choice volatility in a cost/benefit decision task in monkeys (Jahn et al., 2017). Monkeys were inclined to make the same decision when faced with the same type of choice. In our data, we observe the same pattern evidenced by enhanced response stickiness, however after prolonging catecholamine transmission. Future studies should assess a putative contribution of noradrenaline in the estimation of confidence in performance and choice volatility and thereby the role of noradrenaline in the avoidance of effortful cognitive control.

Methylphenidate does not alter the execution of task switching

Unlike MPH-effects on demand avoidance, there were no effects of MPH on the actual performance of the task, as indexed by performance costs in accuracy or response times. Taking into account trait impulsivity did not reveal such an effect of MPH on demand (or switch) costs either. This contrasts with previous work, which showed an amphetamine-induced improvement of task switching (Samanez-Larkin and Buckholtz, 2013). This discrepancy might reflect the fact that the current paradigm was not optimized for measuring (rapid) task switching. In our paradigm, the number judgement trials were separated by the choice events, thus likely reducing sequential effects like task switching, as subjects needed to switch already between the number judgment task and choices. In addition, the frequency of task-switches varied between participants and sessions, as this depended on their previous choices of the low or high demand option. As a result, the paradigm is likely less sensitive to subtle effects of chemical neuromodulatory effects than were the rapidly paced task switching paradigms used previously (Samanez-Larkin and Buckholtz, 2013).

Across high and low demand trials, MPH speeded responding in high- versus low-impulsive participants, consistent with dopamine's well-established role in nonspecific behavioural activation and invigoration of responding (Niv et al., 2007; Robbins and Everitt, 2007). Importantly, the overall speeding of responses was not accompanied by an impulsivity-dependent decrease in accuracy, speaking against a shift in the speed-accuracy tradeoff or more sloppy responding and putatively in favour of cognitive enhancement.

In line with various reports on MPH's potential to enhance cognition after single, low-dose administration (Berridge and Arnsten, 2015; Linssen et al., 2014; Spencer et al., 2015), in this study MPH improved overall accuracy of responding on the task switching task, irrespective of demand or baseline measures.

Response stickiness

We were surprised about the high levels of response stickiness in the choice task. The high degree of response stickiness is unlikely to reflect a lack of task understanding, because we assured after practice blocks that instructions were clear by giving them the opportunity to ask questions and letting participants repeat the instructions. More critically, we observe significant demand avoidance across participants and extremely high accuracy scores on the task-switching task on both testing days. Nevertheless, regardless of its origin, we carefully scrutinized our data to assess the possibility that MPH-effects on stickiness reflect or mask our MPH-effect of interest on demand avoidance. For example, an increase in stickiness might have resulted in a failure to explore and to assign high or low effort costs to the two options. This is particularly pertinent, because we observed in the current data that MPH increased response stickiness across participants, and that a logistic regression model which included (MPH-effects on) response stickiness explained more variance than did a model without response stickiness. Moreover, consistent with our effect, prior work has shown that dopaminergic medication in Parkinson's disease increased response stickiness during a reinforcement learning task (Rutledge et al., 2009). In fact, it is highly unlikely that the impulsivity-dependent effect of MPH on avoidance reflects modulation of response stickiness. First, the logistic regression model which controlled for response stickiness revealed significant effects of MPH on demand avoidance as a function of impulsivity, even when variability in stickiness was removed. Second, there was substantial evidence for an absence of a correlation between the effect of MPH on demand avoidance and that on response stickiness. Third, supplementary analyses revealed that the same effect remained significant after excluding participants who failed to explore the choice cues. Together, these supplementary control analyses strengthened our confidence in the dependence of the MPH-effect on trait impulsivity, generally consistent with previous results showing greater effects of MPH on learning in high versus low-impulsive participants (Clatworthy et al., 2009).

Implications

The measure of trait impulsivity was primarily included in this study for its established relation with baseline dopamine transmission. However, impulsivity is also a clinically relevant dimensional trait implicated in multiple psychiatric disorders, such as (drug) addiction or ADHD. One direct implication of our findings is that while MPH may enhance (task-nonspecific) performance in high-impulsive participants (e.g. by altering response speed), consistent with its performance enhancing effect in ADHD, it may also reduce their motivation for (i.e. value-based learning about) cognitive control. This effect on the avoidance of control might seem paradoxical, given that MPH has been shown to i) remedy cognitive control problems in ADHD patients, who are characterized by high levels of impulsivity (Aron et al., 2003; Cepeda et al., 2000; Coghill et al., 2013; Faraone and Buitelaar, 2010; Leonard et al., 2004; Mehta et al., 2004), ii) to improve performance on attention tasks in high-impulsive rats (Puumala et al., 1996; Robbins, 2002) and iii) to enhance task switching in healthy volunteers (Samanez-Larkin and Buckholtz, 2013). However, none of these studies examined the motivation or willingness to recruit or avoid cognitive control. The present results indicate that any cognition and performance enhancing effects of MPH might be accompanied by an (undermining) effect of MPH on the motivation to exert cognitive control.

A second implication of the present findings is that the cognitive control effects of disorders that implicate the catecholamine system, such as ADHD or Parkinson's disease might (in part) be consequences of changes in the motivation to avoid cognitive control, rather than reflecting changes in the ability to execute control per se (Schneider, 2007). This generally concurs with a characterization of ADHD and Parkinson's disorder as disorders of the will.

Finally, in line with recent work by Kool and colleagues (2017), our results raise the hypothesis that previously established effects of dopamine on the reliance on cognitively effortful (e.g. model-based versus model-free) behavioural control strategies (Deserno et al., 2015; Wunderlich et al., 2012) reflect partly modulation of cost-benefit decision-making rather than ability to execute such strategies.

CONCLUSION

We demonstrate that prolonging catecholamine transmission by MPH administration altered the avoidance of cognitive demand in healthy volunteers. These effects were isolated by taking into account individual differences in trait impulsivity. Control analyses support our conclusion that reported MPH-effects

on demand avoidance are likely results of a modulation of value-based decision-making and not an indirect consequence of modulation of task performance.

SUPPLEMENTAL MATERIALS OF CHAPTER 3

SUPPLEMENTAL METHODS 3.1 | Need for Cognition Scale

The self-report Need for Cognition Scale (Cacioppo and Petty, 1982; Cacioppo et al., 1984) was administered to investigate participants' tendency (trait) to engage in effortful tasks. The scale consists of 18 statements, which participants rate on a 5-point Likert scale ("extremely uncharacteristic of me" to "extremely characteristic of me"). Example statements include "I prefer complex to simple problems" or "I only think as hard as I have to". Scores range from 18 to 90. Results of the relation between participants' need for cognition scores and their degree of demand avoidance are presented in the supplemental results (see Supplemental Results 3.4). In this study, we did not have specific hypotheses for this scale, but aimed to relate to existing work by reporting whether demand avoidance as quantified with the demand selection task relates to this measure. Thus, we correlated the proportion of low-demand choices (i.e. demand avoidance) to participants' scores on the Need for Cognition scale using IBM SPSS for Windows, version 21 (IBM Corp., Armonk, N.Y., USA).

SUPPLEMENTAL METHODS 3.2 | Statistical analyses – additional control analyses

We performed a number of control analyses using a model comparison approach, where we assessed whether the residual sum of squares was reduced when adding any of the following factors: order effects of drug and testing day, gender, and NLV scores (as a measure of verbal intelligence). Results of these control analyses are presented in Supplemental Results 3.5 and Supplemental Table 3.6.

To assess whether our key MPH effects of interest can be accounted for by nonspecific effects of MPH on mood and medical symptoms, we extracted subjective ratings of the PANAS scale (Watson et al., 1988), Bond and Lader Visual Analogue Scale (Bond and Lader, 1974) and the medical analogue scale (Supplemental Material 3.2) and performed a repeated measures MANOVA with the within-subject factors Time (3: start of testing day, before task battery, after task battery) and Drug (2: MPH, placebo) and the six measures as dependent variables (positive affect, negative affect, calmness, alertness, contentedness, medical symptoms) using IBM SPSS for Windows, version 21 (IBM Corp., Armonk, N.Y., USA). Significant effects were followed up with repeated measure ANOVA. Results are presented in Supplemental Results 3.5.

SUPPLEMENTAL MATERIAL 3.1 | Overview of exclusion criteria

- (History of) psychiatric treatment
- (History of) neurological treatment
- (History of) endocrine treatment
- (History of) autonomic failure (e.g., vasovagal reflex syncope).
- (History of) clinically significant hepatic, cardiac, obstructive respiratory, renal, cerebrovascular, metabolic or pulmonary disease
- Family history of sudden death or ventricular arrhythmia
- (History of) epilepsy
- (History of) drug dependence (opiate, LSD, (meth)amphetamine, cocaine, solvents, or barbiturate) or alcohol dependence
- Suicidality
- Abnormal hearing or (uncorrected) vision.
- Use of MAO inhibitor, anaesthetic, anti-depressant or antipsychotic drugs within the week prior to the start of the study.
- Use of psychotropic medication, or of recreational drugs over a period of 24 hours prior to each test session, and use of alcohol within the last 24 hours before each measurement.
- Regular use of corticosteroids.
- Uncontrolled hypertension, defined as diastolic blood pressure at rest > 95 mmHg or systolic blood pressure at rest > 180 mmHg
- Hypotension, defined as diastolic blood pressure < 50 mm Hg or systolic < 95 mm Hg or resting pulse rate < 45 beats/min
- Diabetes
- Family history of schizophrenia, bipolar disorder or major depressive disorder
- Irregular sleep/wake rhythm (e.g., regular nightshifts or cross timeline travel).
- Possible pregnancy or breastfeeding
- Lactose intolerance (placebo pill is a lactose product)

SUPPLEMENTAL MATERIAL 3.2 | Medical symptoms rating scale

1.	No headache	Strong headache
2.	No muscle pain	Strong muscle pain
3.	No dry mouth	Very dry mouth
4.	Not dizzy	Very dizzy
5.	No abdominal pain	Strong abdominal pain
6.	No joint pain	Strong joint pain
7.	No trouble breathing	Trouble breathing
8.	No throat pain	Strong throat pain
9.	No chest pain	Strong chest pain
10.	No eye problems	Strong eye problems

SUPPLEMENTAL RESULTS 3.1 | Effects of MPH as a function of working memory capacity

Listening span scores varied from 2.5 to 7 with a median of 4.5. This median and range is comparable with values observed in previous studies including young populations (Salthouse and Babcock, 1991). The listening span-dependent effects of MPH, described in the main text, are shown in Supplemental Figures 3.4A and 3.4B.

Supplementary analysis after exclusion of participants who failed to explore at all, who switched cues on every trial, for whom the capsule dissolved early as well as an outlier on trait impulsivity scores also did not reveal any significant MPH-effects as a function of working-memory capacity (n = 74: Drug x Listening span: $X^2(1) = 0.68$, $p = 0.408$).

MPH did alter the reaction time demand cost as a function of listening span (Drug x Listening span x Demand: $X^2(1) = 4.11$, $p = 0.043$; Supplemental Figure 5A). High-span participants exhibited MPH-induced decreases in the RT demand cost, whereas low-span participants exhibited MPH-induced increases in the RT demand cost. However, note that in a model that takes into account response stickiness (see Supplemental Results 3.2 and Supplemental Table 3.5), this interaction did not reach significance (Drug x Listening span x Demand: $X^2(1) = 3.63$, $p = 0.057$). There was no span-dependent effect on the error demand cost: Drug x Listening span x Demand: $X^2(1) = 0.20$, $p = 0.657$, Supplemental Figure 3.5B).

In sum, relative to low working memory-span participants, high-span participants (tend to) exhibit MPH-induced improvement in task switching (in terms of RT demand costs), but MPH did not affect demand avoidance robustly as a function of working memory. We are puzzled by the lack of an effect of WM capacity, particularly given the effect of trait impulsivity, which has also been associated with dopamine transmission. We raise two alternative accounts of this pattern, although we also note that we do not provide evidence for a significantly greater impact of impulsivity than of WM capacity. First, trait impulsivity might be a more reliable proxy of baseline dopamine levels than WM capacity. We would argue this is unlikely, particularly given the subjective, self-report nature of the former and not the latter proxy variable. Second, trait impulsivity might index a distinct aspect of dopamine transmission (striatal dopamine release; (Buckholtz et al., 2010; Dalley et al., 2007) that might be more determinant of the effect of MPH on demand avoidance than the dimension captured by WM capacity (striatal and probably prefrontal dopamine synthesis capacity).

Our hypothesis regarding WM span was bi-directional. The finding of beneficial MPH-effects in high-span participants contrasts with prior evidence, showing greater potentiation by MPH of performance on working memory and sustained attention tasks in low- than high-span participants (Del Campo et al., 2013; Mehta et al., 2000). However, on hindsight, the positive correlation between WM span and MPH effects is not surprising, given that, as is the case for impulsivity (Buckholtz et al., 2010), WM span is also associated with higher striatal dopamine function. Moreover, our effect generally concurs with other evidence, indicating, conversely, greater potentiation by MPH of learning in high- than low-capacity subjects (van der Schaaf et al., 2013) as well as greater MPH-induced increases in dopamine release in higher-performing participants (Del Campo et al., 2013). Finally, it fits with the dopamine cell-activity hypothesis (Volkow et al., 2002b) suggesting that DAT blockade (with MPH) induces larger dopamine increases in subjects with high relative to low dopamine cell activity. We remain puzzled by these discrepant effects of working memory span across studies, but speculate that they reflect catecholaminergic modulation of different neural regions with distinct optimal levels of dopamine (e.g. Fallon and Cools, 2015). For example, the enhancing effects of MPH on learning and task switching might reflect catecholaminergic modulation of the striatum, whereas the impairing effects of MPH on working memory and sustained attention, reported previously, might reflect modulation of the prefrontal cortex, consistent with the disproportionate vulnerability of the prefrontal cortex to supra-optimal dopamine (D1) receptor stimulation (Berridge and Arnsten, 2015; Seamans and Yang, 2004; Vijayraghavan et al., 2007; Williams and Goldman-Rakic, 1995). Clearly this speculative hypothesis should be tested using pharmacological fMRI.

SUPPLEMENTAL RESULTS 3.2 | Performance models including stay regressor

For the purpose of consistency with our approach for the choice analyses, we re-ran the performance models (accuracy and response times), when including the response stickiness regressor as main effect and interacting effect with MPH (and demand). We then did model comparisons using the anova function in R to assess whether the reduction in the residual sum of squares is statistically significant compared with the simpler models. For accuracy, a model without any stickiness regressor shows the smallest BIC (31220). Adding a stickiness regressor did not reduce residual sum of squares significantly (versus main effect of stickiness: X^2 (6) = 3.6, p = 0.733; versus interactive effect of stickiness: X^2 (30) = 21.5, p = 0.872). For response times, however, the model with the lowest BIC that shows a significant reduction of residual sum of squares compared with the other two models, is a model that includes stickiness as interactive term (BIC = 137710,

versus basic model: X^2 (30) = 2575.3, p < 0.001); versus stickiness main effect: X^2 (24) = 2113.5, p < 0.001). Results of this winning model are presented in Supplemental Table 3.5.

SUPPLEMENTAL RESULTS 3.3 | Performance models including task-switching

Participants' choices of low versus high demand options determine the degree of task-switching that they encounter and therefore also the 'practice' of one or the other trial type. To quantify this effect, we re-ran performance models (Supplemental Table 3.1, bottom), but now including the factor task-switching as predictor in addition to demand. The model confirms that switch-costs are larger on low demand trials relative to high demand trials. This only holds for response times (task-switch x demand interaction: $X^2(1) = 372.7$, p < 0.001), and not for accuracy (task-switch x demand interaction: $X^2(1) = 0.4$, p = 0.547. Critically, this interaction in response times was not modulated by MPH (Drug x task-switch x demand: $X^2(1) = 1.8$, p = 0.179), also not as a function of impulsivity scores (Drug x task-switch x demand x Impulsivity: $X^2(1) = 1.2$, p = 0.266).

SUPPLEMENTAL RESULTS 3.4 | Need for Cognition Scale and demand avoidance

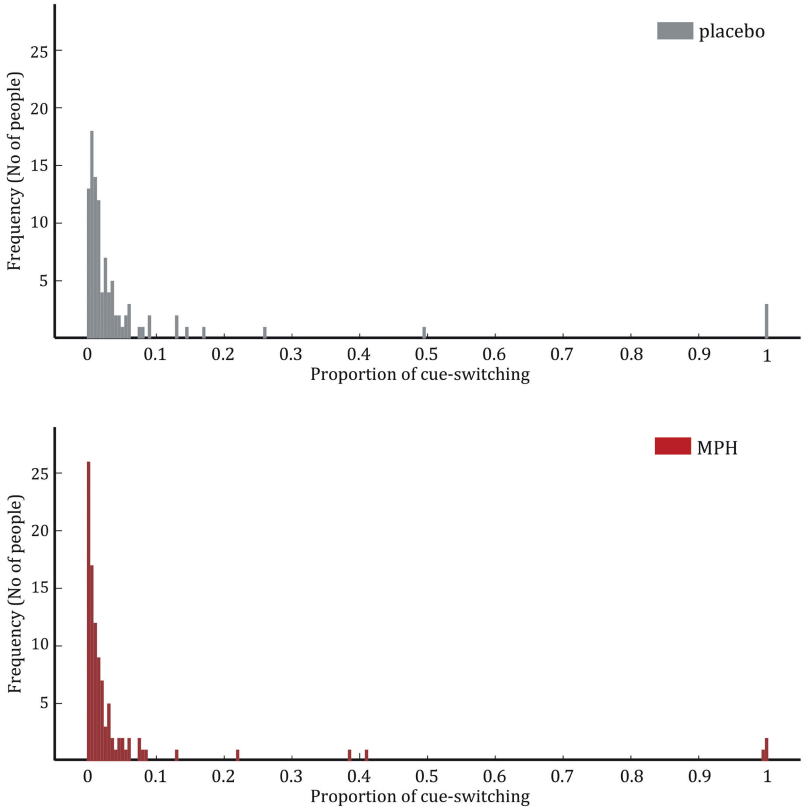
Participants' average score on the Need for Cognition (NFC) scale was 63.3 (*SD* = 10.5) ranging from 38 to 82. These values are comparable with those reported previously (e.g. Westbrook et al., 2013). The Need for Cognition score did not correlate with the degree of demand avoidance in the placebo (NFC & low demand choices: $r = 0.13$, $p = 0.212$), in the MPH session (NFC & low demand choices: $r = -0.07$, $p = 0.498$) or with the effect of MPH relative to placebo on demand avoidance (NFC & low demand choices $_{MPH - PLA}$: $r = -0.15$, $p = 0.133$).

SUPPLEMENTAL RESULTS 3.5 | Additional control analyses

We performed model comparisons with models including potentially confounding variables of no interest. We included the factors order of intervention, testing day, gender, and verbal intelligence (NLV) separately as fixed between-subject factors in the basic models, resulting in 12 comparisons presented in Supplemental Table 3.6. Models including order, day, gender or NLV did not explain more variance than the basic models, except for adding the factor day to the response time model. Including day (*BIC* = 139860) explained significantly more variance than the basic model (*BIC* = 139935; $X^2(1) = 86.60$, p < 0.001). However, significance and interpretation of reported effects were not altered in a model including day.

The administration of MPH altered participants' mood ratings (positive affect, negative affect, alertness, contentedness, calmness) and medical symptoms (Supplemental Material 3.2) significantly (MANOVA: Drug x Time [3]: $V = 0.28$, $F(6,12) = 5.30$, $p < 0.001$) in the absence of differences at time zero before drug administration (Drug: $V = 0.06$, $F(6, 93) = 0.91$, $p = 0.492$). MPH increased subjective report of positive affect ($F(1,98) = 18.26$, $p < 0.001$), alertness ($F(1,98) = 16.88$, $p < 0.001$), medical symptoms ($F(1,98) = 9.60$, $p = 0.003$) and decreased calmness ($F(1,98) = 8.65$, $p = 0.004$), all with respect to baseline (Drug x Time, measurement 1 versus later). To explore whether these mood and medical measures differed between dug sessions at the time point most proximal to the demand selection task, we conducted the same analysis again for the second time point and assessed whether this interacts with impulsivity scores. Results of this repeated measures MANOVA reveal no significant modulation across all measures in multivariate (Drug x Impulsivity: $F(6,93) = 1.31$, $p = 0.260$) nor for each measure in univariate tests. In addition, when correlating drug-induced changes on all six mood and medical measures at this same time point with drug-induced changes in demand avoidance, none of these correlations reached significance (all p-values > 0.2). In sum, it is unlikely that MPH-induced mood or medical changes underlie our effect of interest: an impulsivity-dependent modulation of demand avoidance.

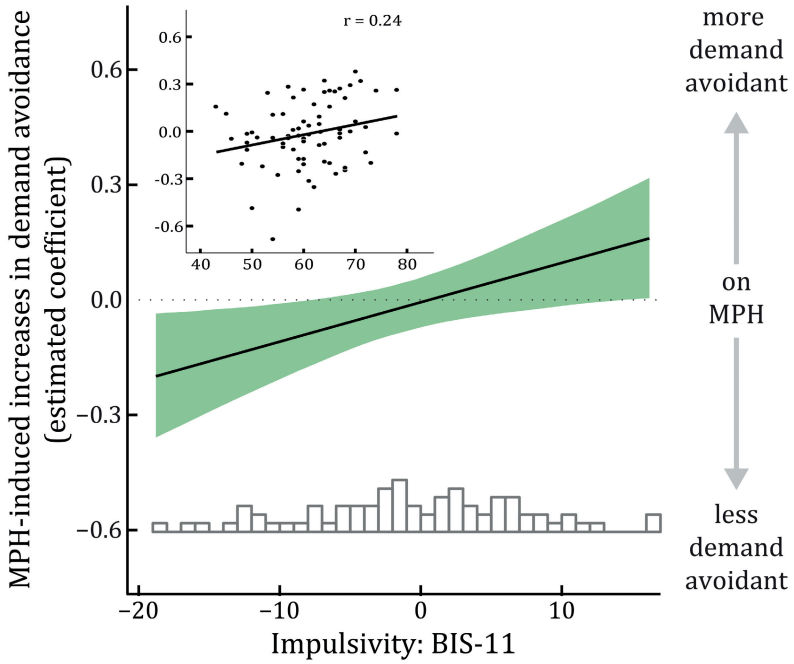
SUPPLEMENTAL FIGURE 3.1 | Response stickiness
Histogram of the proportion of participant's response switches between the two choice options as a function of drug. A high frequency of participants showed low exploration of the two choice options. Choices of 3 participants deviated more than 3 standard deviations from the group's mean regarding their extreme exploration behavior on placebo and methylphenidate sessions (proportion switching above 0.99).



Note that this low rate of exploration would have resulted in extremely skewed distribution of our dependent variable of interest, i.e. demand avoidance. However, by making use of 8 different task blocks where low and high demand options appear at different locations and have different visual identities, the key variable of demand avoidance is not significantly skewed. The distribution of the variable of interest, the proportion of low demand choices, is depicted in Figure 3.2B.

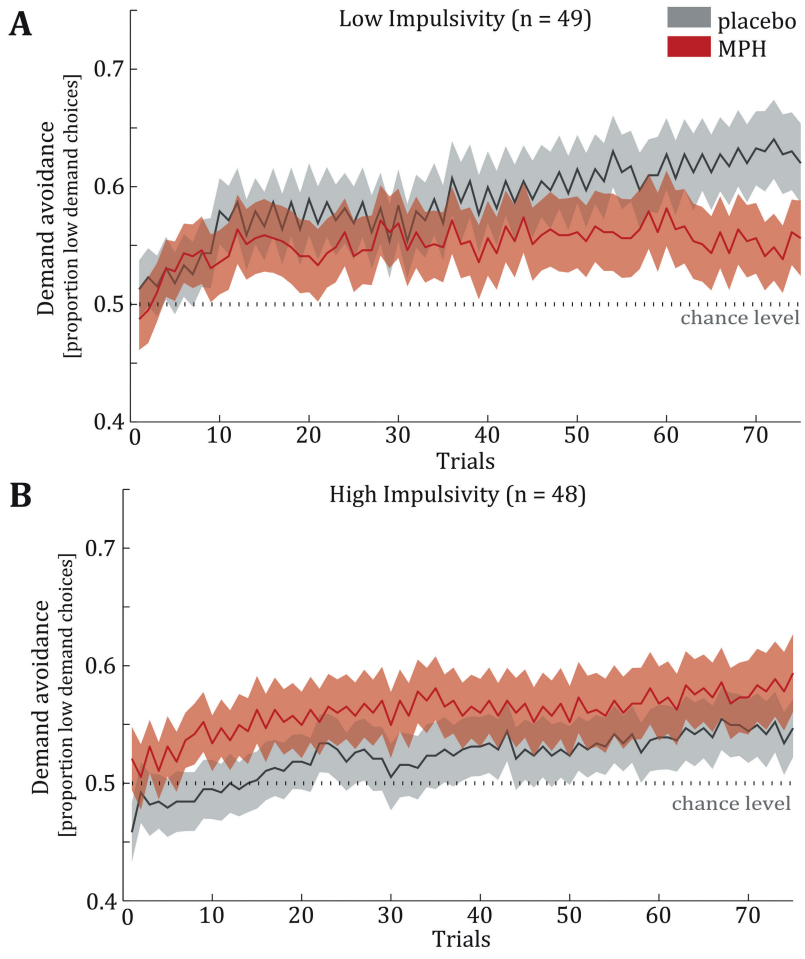
SUPPLEMENTAL FIGURE 3.2 | Reduced sample

Methylphenidate-effect on demand avoidance as a function of participants' trait impulsivity (BIS-11) scores for the reduced sample (n = 74). Line represents model-based estimated coefficients of MPH-effect on demand avoidance as a function of (z-scored) trait impulsivity scores. Shaded area represents simulated 95% confidential intervals of the coefficients. The inset shows the raw data: drug effect for every participant (n = 74) across trials as the difference in the proportion of low demand choices (MPH - placebo) as a function of trait impulsivity.



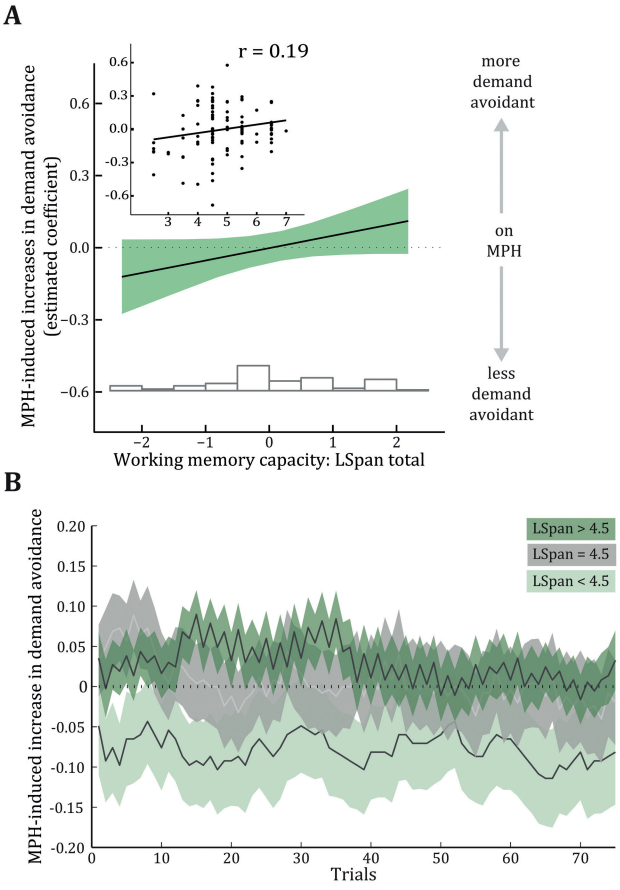
SUPPLEMENTAL FIGURE 3.3 | Placebo and methylphenidate separately

Methylphenidate-effect on demand avoidance varied as a function of participants' trait impulsivity. Data points represent proportion of low demand choices averaged across participants (n = 100) across 8 blocks for **A** low and **B** high impulsive participants as a function of trial. Three participants with median scores are not included in this plot.

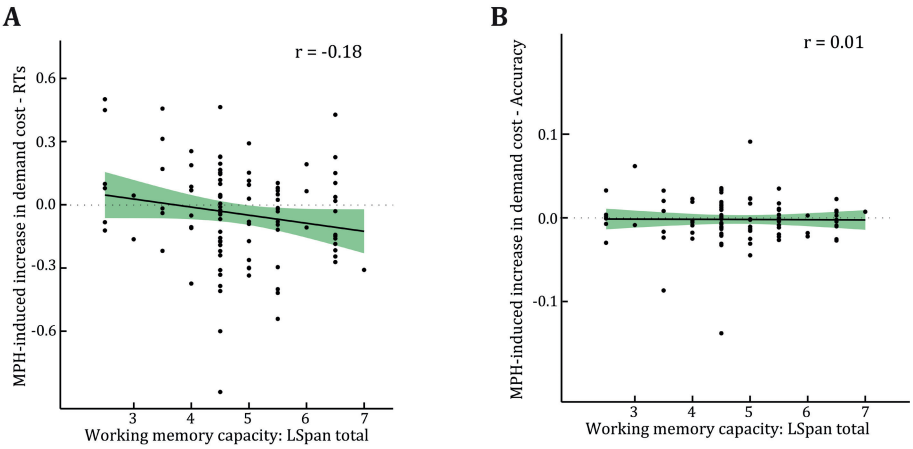


SUPPLEMENTAL FIGURE 3.4 | Demand avoidance as a function of working memory capacity

Methylphenidate (MPH)-effect on demand avoidance as a function of participants' working memory capacity does not reach statistical significance. Data points represent effects of MPH, relative to placebo, on the proportion of low demand choices (MPH minus placebo). **A** Line represents model-based estimated coefficients of MPH-effect on demand avoidance as a function of (z-scored) listening span total scores. Shaded area represents simulated 95% confidential intervals of the coefficients. The inset shows the raw data: drug effect for every participant (n = 100) across trials as the difference in the proportion of low demand choices (MPH - placebo) as a function of listening span scores. **B** Trial-by-trial drug effect averaged across 8 blocks, and across participants (n = 100) of low (n = 23), medium (n = 31) and high (n = 46) listening span groups as a function of trial. Shaded areas represent standard error of the difference.



SUPPLEMENTAL FIGURE 3.5 | Performance as a function of working memory
Drug effects on demand cost in response times (RTs) and accuracy. Data points represent methylphenidate (MPH)-effects on average demand cost (MPH minus placebo) for each participant for **A** response times as a function of working memory capacity (listening span total, significant, p = 0.043) and **B** accuracy as a function of working memory capacity (listening span total, not significant, p = 0.657). Shaded areas represent standard errors of the difference.



SUPPLEMENTAL TABLE 3.1 | Overview of regression models

Dependent variable	Regression models
Choice category: binary	Choice ~ Drug x Impulsivity + Drug x Listening span + (1 + Drug | Participant)
Choice with stay regressor	Choice ~ Drug x Impulsivity + Drug x Listening span + Stay + (1 + Drug + Stay | Participant)
Choice with MPH-effect on stay regressor	Choice ~ Drug x Impulsivity + Drug x Listening span + Drug x Stay + (1 + Drug x Stay | Participant)
Accuracy category: binary	Accuracy ~ Drug x Impulsivity x Demand + Drug x Listening span x Demand + (1 + Drug x Demand | Participant)
Response times category: continuous	RT ~ Drug x Impulsivity x Demand + Drug x Listening span x Demand + (1 + Drug x Demand | Participant)

SUPPLEMENTAL TABLE 3.2 | Statistics of choice model

Coefficient	Estimate (SE)	$X^2(1)$	*p*
Intercept	*-0.184 (0.04)*	*20.70*	***< 0.001***
Drug	*-0.001 (0.03)*	*< 0.01*	*0.964*
Drug x Impulsivity	*0.009 (<0.01)*	*5.33*	***0.021***
Drug x Listening span	*0.052 (0.03)*	*2.91*	*0.088*
Impulsivity	*-0.001 (0.01)*	*0.07*	*0.793*
Listening span	*-0.029 (0.04)*	*0.57*	*0.451*
Staying	*-4.239 (0.25)*	*291.16*	***< 0.001***
Drug x Staying	*0.238 (0.09)*	*7.65*	***0.006***

Logistic regression coefficients indicating the influence of drug, impulsivity, listening span, choice on previous trial (staying) and their interactions with drug on participants' choices (n = 100). Bold p-values denote significance. For this model, the marginal R^2_{GLMM} is 0.639.

SUPPLEMENTAL TABLE 3.3 | Statistics of reduced sample

	Choice		Accuracy		Response times	
Coefficient	**$X^2(1)$**	***p***	**$X^2(1)$**	***p***	**$X^2(1)$**	***p***
Drug	*0.03*	*0.867*	*5.91*	***0.015***	*1.85*	*0.173*
Drug x Imp	*5.80*	***0.016***	*0.02*	*0.876*	*8.87*	***0.003***
Drug x LSpan	*0.68*	*0.408*	*0.69*	*0.408*	*1.92*	*0.165*
Drug x Demand	*N/A*	*N/A*	*1.46*	*0.228*	*0.31*	*0.580*
Drug x Imp x Demand	*N/A*	*N/A*	*1.01*	*0.315*	*0.10*	*0.754*
Drug x LSpan x Demand	*N/A*	*N/A*	*0.17*	*0.679*	*0.64*	*0.425*
Stay	*465.64*	***< 0.001***	*N/A*	*N/A*	*N/A*	*N/A*
Drug x Stay	*4.80*	***0.029***	*N/A*	*N/A*	*N/A*	*N/A*

Performance and choice statistics of effects of interest after the exclusion of participants who failed to explore the choice options at all, either in one (n = 17) or both session (n = 5), those who switched choice options on every cue in one (n =1) or both (n = 1) sessions , those for whom the capsule dissolved (orally or in water) before swallowing (n = 2, one of those was also a sticky participant) as well as one participant whose score on the BIS-11 impulsiveness questionnaire deviated more than 3 standard deviations from the mean. Analysis of this smaller dataset (n = 74) confirmed the effects obtained from the analysis of the larger sample. Marginal R^2_{GLMM} of the choice, accuracy and response times models are 0.698, 0.013 and 0.090, respectively.

SUPPLEMENTAL TABLE 3.4 | Statistics of performance model

	Accuracy			Response times		
Coefficient	**Estimate (SE)**	**$X^2(1)$**	***p***	**Estimate (SE)**	**$X^2(1)$**	***p***
Intercept	*3.868 (0.10)*	*1469.47*	***< 0.001***	*-0.123 (0.02)*	*45.22*	***< 0.001***
Drug	*-0.112 (0.04)*	*7.29*	***0.007***	*0.016 (0.01)*	*2.98*	*0.084*
Drug x Imp	*0.001 (0.01)*	*0.10*	*0.747*	*0.003 (<0.01)*	*7.28*	***0.007***
Drug x LSpan	*0.012 (0.04)*	*0.10*	*0.748*	*0.012 (0.01)*	*1.92*	*0.166*
Imp	*0.015 (0.01)*	*1.57*	*0.211*	*0.002 (<0.01)*	*1.12*	*0.289*
LSpan	*-0.045 (0.09)*	*0.23*	*0.635*	*-0.024 (0.02)*	*1.95*	*0.163*
Demand	*0.106 (0.03)*	*15.50*	***< 0.001***	*-0.139 (0.01)*	*535.73*	***< 0.001***
Drug x Demand	*-0.027 (0.02)*	*1.20*	*0.274*	*-0.003 (<0.01)*	*0.75*	*0.387*
Drug x Imp x Demand	*<0.001 (<0.01)*	*<0.01*	*0.968*	*-0.000 (<0.01)*	*0.29*	*0.590*
Drug x LSpan x Demand	*-0.008 (0.02)*	*0.20*	*0.657*	*-0.007 (<0.01)*	*4.11*	***0.043***

(Logistic) regression coefficients indicating the influence of drug, impulsivity (Imp), listening span (LSpan), task demand and their interactions on participants' performance (n = 100). Bold p-values denote significance. Marginal R^2_{GLMM} of the accuracy and response times models are 0.011 and 0.086, respectively.

SUPPLEMENTAL TABLE 3.5 | RT model including response stickiness

	Response times		
Coefficient	**Estimate (SE)**	**$X^2(1)$**	***p***
Intercept	*0.08 (0.02)*	*10.60*	*<0.001*
Drug	*0.004 (0.01)*	*0.15*	***0.700***
Drug x Imp	*0.003 (<0.01)*	*7.96*	*0.005*
Drug x LSpan	*0.012 (0.01)*	*2.05*	*0.152*
Imp	*0.002 (<0.01)*	*1.16*	*0.281*
LSpan	*-0.018 (0.02)*	*1.11*	*0.293*
Demand	*-0.076 (<0.01)*	*152.39*	*< 0.001*
Drug x Demand	*-0.002 (0.01)*	*0.17*	*0.681*
Drug x Imp x Demand	*-0.000 (<0.01)*	*0.36*	*0.548*
Drug x LSpan x Demand	*-0.006 (<0.01)*	*3.63*	***0.057***
Stay	*-0.070 (0.01)*	*173.84*	***<0.001***
Drug x Stay	*-0.002 (0.01)*	*0.16*	***0.687***
Drug x Demand x Stay	*0.011 (0.01)*	*2.38*	***0.123***

Regression coefficients indicating the influence of drug, impulsivity (Imp), listening span (LSpan), task demand, choice on previous trial (Stay) and their interactions on participants' response times (n = 100). Bold p-values denote deviations in significance relative to the basic RT model that did not account for response stickiness. Note that conclusions presented in the main text are unaltered.

SUPPLEMENTAL TABLE 3.6 | Control analyses

		Basic	**+ NLV**	**+ Day**	**+ Order**	**+ Gender**
Choice	BIC sign.	150826	150838 p = 0.501	150835 p = 0.079	150837 p = 0.464	150835 p = 0.105
Accuracy	BIC sign.	31220	31232 p = 0.695	31231 p = 0.509	31232 p = 0.931	31232 p = 0.924
Response times	BIC sign.	139935	139946 p < 0.364	**139860** **p < 0.001**	139946 p = 0.436	139947 p = 0.806

Model comparison of basic models with control models. Bold p-values denote significance.

CHAPTER 4

Does tyrosine modulate the cost of cognitive control in healthy aging?

This chapter is under review for publication as:

M. I. Froböse, A. W. Westbrook, M. Bloemendaal, E. Aarts, R. Cools (under review). Catecholaminergic modulation of the cost of cognitive control in healthy older adults. Preprint available at: https://doi.org/10.31234/osf.io/kypz3

ABSTRACT

Catecholamines have long been associated with cognitive control and value-based decision-making. More recently, we have shown that catecholamines also modulate value-based decision-making about whether or not to engage in cognitive control. Yet it is unclear whether catecholamines influence these decisions by altering the subjective value of control. Thus, we tested whether tyrosine, a catecholamine precursor altered the subjective value of performing a demanding working memory among healthy older adults (60-75 years). Contrary to our prediction, tyrosine administration did not significantly increase the subjective value of conducting an N-back task for reward, as a main effect. Instead, in line with our previous study, drug effects varied as a function of participants' trait impulsivity scores. Specifically, tyrosine increased the subjective value of conducting an N-back task in low impulsive participants, while reducing its value in more impulsive participants. One implication of these findings is that the over-the-counter tyrosine supplements may be accompanied by an undermining effect on the motivation to perform demanding cognitive tasks, at least in certain older adults. Taken together, these findings indicate that catecholamines alter cognitive control by modulating motivation (rather than just the ability) to exert cognitive control.

INTRODUCTION

While catecholamines (dopamine and noradrenaline) have long been known to impact capacity for cognitive control, the catecholamines have been proposed to also mediate cost-benefit choices about whether or not to exert cognitive control (Cools, 2016; Westbrook and Braver, 2016). According to the expected value of control account, people recruit cognitive control in proportion to expected instrumental value (Shenhav et al., 2013), such that degree (and intensity) of engagement in an upcoming cognitive computation is based on a cost-benefit analysis. Recently, we demonstrated that acute administration of a single oral dose of the catecholamine transporter blocker methylphenidate indeed modulated the avoidance of, but not ability to perform cognitive control in young adults (Froböse et al., 2018; Chapter 3). The effect depended on trait impulsivity, with the most impulsive subjects exhibiting the greatest increases in control avoidance. Here, we extend this work by assessing the effects of a catecholamine precursor on the expected value of cognitive control, again as a function of trait impulsivity.

Catecholamines and (cognitive) effort

The role of catecholamines in decisions about effort expenditure have been the focus of studies for decades (Salamone et al., 2016). A well-replicated finding, in both human and non-human animals is that striatal dopamine blockade or dopamine lesions reliably shift preferences away from high effort/high reward options to low effort/low reward options (Bardgett et al., 2009; Salamone et al., 2016), while increases in striatal dopamine shifts preferences towards high effort/high reward options (Chong et al., 2015; Floresco et al., 2008a; Le Bouc et al., 2016; Salamone et al., 2016). For example, patients with Parkinson's disease, which is characterized by dopamine cell loss in the striatum, forego reward to avoid effort (handgrip squeezes) relative to healthy controls, when tested off their dopaminergic medication. Conversely, when tested on their medication, patients selected high-effort/high-reward options as much as controls, reflecting less physical effort avoidance (Chong et al., 2015). Thus, increases in dopamine transmission have been associated with increased motivation for physical effort.

As is the case for physical action, cognitive control is also effortful / costly such that people tend to avoid it (Botvinick and Braver, 2015; Kool et al., 2017; Shenhav et al., 2013; Westbrook and Braver, 2016). For example, they prefer to perform a task with less rather than more task-switching (Botvinick, 2007; Gold et al., 2015; Kool et al., 2010; McGuire and Botvinick, 2010) and with lower rather than higher working memory load, even when incentives are larger for higher

loads (Westbrook et al., 2013). However, unlike for physical effort, the role of catecholamines is less clear for decision making about cognitive effort. One way in which dopamine might bias choices about cognitive tasks is by altering the (expected) value of cognitive control (i.e. the reward benefits minus the effort cost of control). This follows also from neurocomputational models of dopamine in the basal ganglia, such as the OpAL model, which suggest that increases in (striatal) dopamine tone, result in more emphasis on the benefit, and less on the cost of an action due to more direct pathway excitability, via D1 receptor binding, and less indirect pathway excitability, via D2 receptor binding (Collins and Frank, 2014). Thus, taken together with the hypothesis that cognitive control follows from cost-benefit decision making, we expect that increases in catecholamine synthesis will emphasize the benefits versus the costs of control, thereby increasing the motivation for instrumental cognitive control (Westbrook and Braver, 2016).

There is some evidence that dopamine signaling can offset the costs of cognitive control. In one study, costs were offset by incentives, which are putatively signaled by dopamine release, thus leading to more cognitive and motor control in a visual saccade task (Manohar et al., 2015). Critically, this effect was diminished in patients with Parkinson's disease, supporting a role for dopamine in mediating incentive effects on performance. Since performance could be altered via multiple catecholamine-dependent mechanisms, however, it remains critical to show that catecholaminergic drugs can alter cost-benefit decision-making itself. Direct tests of this prediction have yielded conflicting results. In one study, dopaminergic medication increased the selection of high-cognitive effort/high-benefit tasks in Parkinson's disease (McGuigan et al., 2019). By contrast, a rodent study failed to observe changes in rats' willingness to expend cognitive effort for reward after treatment with a dopamine antagonist (Hosking et al., 2015).

Conflicting results may stem from individual differences in baseline dopamine function and/or cognitive motivation. In one study, amphetamine motivated rodent 'slackers' (but not 'workers') to choose a more perceptually-demanding option for a higher reward (Cocker et al., 2012). In parallel, our recent work with young healthy adults has shown that the administration of methylphenidate (20 mg, oral) altered the avoidance of higher task-switching demands, in a demand selection paradigm (Froböse et al., 2018). The effect of methylphenidate depended on participants' trait impulsivity, a measure previously associated with drug-induced dopamine release and D2/D3 (auto-)receptor availability (Buckholtz et al., 2010). Relative to placebo, methylphenidate increased the avoidance of effortful task-switching to a greater degree in more impulsive participants. These studies indicate that catecholamine interventions might have varying effect on motivated

cognition across different individuals, likely as a function of baseline levels of dopamine function (Cools and D'Esposito, 2011).

While prior work established a link between catecholamines and cognitive demand avoidance, it remains unclear whether catecholamine manipulation influences the value of cognitive control (Froböse et al., 2018). Here we employed a cognitive effort discounting task (COGED) that enabled us to explicitly quantify the value of cognitive control (Westbrook et al., 2013) and its modulation by a catecholamine challenge. The COGED paradigm consists of 2 phases: an effort execution phase, during which participants complete multiple levels of the demanding N-back task (levels 1-4 back) and an effort discounting task, during which participants choose between repeating a more demanding level for more money, or the 1-back for less money. Unlike the demand avoidance paradigm, choices are separated in time from performing the effortful task; as such, choices do not reflect learning of effort costs.

Tyrosine intervention in older adults

A second key way in which we go beyond prior studies is that we administer a catecholamine precursor (i.e. tyrosine) instead of a catecholamine transporter blocker (i.e. methylphenidate). Tyrosine is a precursor of dopamine and noradrenaline and the administration of tyrosine stimulates synthesis and release of catecholamines (Fernstrom, 1983; Glaeser et al., 1979; Growdon et al., 1982; Scally et al., 1977; Sved et al., 1979). The main source of tyrosine is protein-rich food, but tyrosine has also been administered selectively as an over-the-counter food supplement for study purposes and has been shown to alter cognition (Jongkees et al., 2015). In young adults, tyrosine administration has been shown to improve cognitive control functions that are commonly associated with catecholamine transmission, such as working memory, response inhibition, and task switching (see Deijen, 2005; Jongkees et al., 2015 for reviews).

In the present study, we administered tyrosine to older adults, aged 60-75, for the following 2 reasons: 1) Healthy aging has been reported to be accompanied by a decline in dopamine transmission (Bäckman et al., 2006), making older adults perhaps more sensitive to tyrosine administration. A recent meta-analysis revealed lower prefrontal and striatal D1 and D2 receptor densities and striatal dopamine transporters with increasing age (Karrer et al., 2017). Diminished dopamine function is supported by evidence of reduced reward responsivity in elderly, evidenced by impaired reward learning, attenuated BOLD signal in the ventral striatum in response to reward, and less risky choices in gain trials (Eppinger

et al., 2013; Rutledge et al., 2016; Samanez-Larkin et al., 2007) 2) The well-established decline in cognitive functioning with advanced age (Salthouse, 1996), has often been attributed to diminished cognitive control capacity, but may partly reflect motivational rather than capacity constraints. Thus, using the COGED paradigm, older adults have been shown to be less motivated to *engage* in effortful cognition (Westbrook et al., 2013). Given that older adults are thought to exhibit diminished catecholamine function and they are less motivated to engage in cognitive effort, we speculate that lower catecholamine transmission contributes to reduced motivation for control. Following empirical and theoretical work on dopamine's role in cost-benefit analysis of cognitive actions, we hypothesized that the administration of the catecholamine precursor tyrosine can restore motivation for cognitive effort in older adults.

The effects of tyrosine administration have been shown to depend on the baseline state of the system. For example, tyrosine was shown to be particularly effective in enhancing cognitive control when the catecholamine metabolism was enhanced by acute stress or high cognitive demand, while having no or disruptive effects in other conditions where the need for catecholamine transmission is lower (Jongkees et al., 2015; Tam and Roth, 1997). Higher doses of tyrosine have been shown to increase plasma tyrosine concentrations to a greater degree in older than younger adults (van de Rest et al., 2017), and have been associated with poorer N-back performance than lower tyrosine doses (van de Rest et al., 2017). Furthermore, tyrosine was recently found to reduce proactive response inhibition as a function of age (Bloemendaal et al., 2018). Although we do not have direct measures of baseline catecholamine function in our sample, we explored in supplemental analyses whether the effects of tyrosine depended on the two commonly used proxy measures trait impulsivity and working memory capacity (see also Froböse et al., 2018; Swart et al., 2017): trait impulsivity scores for their association with dopamine (auto-)receptor availability and striatal dopamine release (Buckholtz et al., 2010), as well as working memory span, associated with striatal dopamine synthesis capacity (Cools et al., 2008; Landau et al., 2009). Previously, we have shown that trait impulsivity predicts the degree to which methylphenidate modulates demand avoidance (Froböse et al., 2018). Thus, while our study was set up to assess the hypothesis that tyrosine administration would increase the value of cognitive control, we also explored whether tyrosine altered the value of cognitive control in a manner that depended on either of two dopamine proxy measures.

METHODS

Participants

Exclusion criteria for this study were a history of clinically-significant psychiatric, neurological or cardiovascular disorder, abuse of drugs or alcohol, abnormal blood pressure (< 90/60 mmHg or > 160/90 mmHg), medication use that can interfere with tyrosine, blindness or colorblindness, smoking more than 1 pack of cigarettes per week, or contra-indications for MRI. For a complete list of exclusion criteria, see Supplemental Material 4.1.

After a screening session, thirty-three healthy, right-handed adults were initially included for participation. However, four additional participants were excluded or decided to discontinue during or after the first experimental session, due to blood pressure exceeding our inclusion criteria (n = 1) and fMRI-intolerance (anxiety: n = 1; nausea: n = 1, headache: n = 1), leaving a sample of 29 participants who completed both experimental sessions (age: *M* = 66.7, range = 61-71, 16 men). Our paradigm consists of two phases (see Task design section): an effort execution N-back task and a cognitive effort discounting (COGED) task. The COGED task is of primary interest to our research question and we have 29 complete datasets available. Due to technical, back-up problems, we have 26 complete datasets of the effort execution N-back task (day 1 = 27; day 2 = 28), even though all 29 participants completed this task. As our primary research question regards the COGED task, we report questionnaire and neuropsychological assessment data for the complete sample (n = 29) in Table 4.1. All procedures were in accordance with the local ethical guidelines approved by the local ethics committee (CMO protocol NL49758.091.14) and in line with the Helsinki Declaration of 1975.

Procedure

A within-subjects, placebo-controlled, double-blind, cross-over design was employed. Participants visited the institute three times: once for a screening and twice for experimental sessions of around 4.5 hours (Figure 4.1).

The screening session included reviewing additional information about the study and signing informed consent forms and was mainly designed to check for medical exclusion criteria (see Supplemental Material 4.1). To assess specific exclusion criteria, we administered the Hospital Anxiety and Depression scale (HADS, Bjelland et al., 2002), Mini Mental State Examination (MMSE, Folstein et al., 1975) and the Dutch reading test for an estimate of verbal intelligence (NLV, Schmand et al., 1991). In addition, participants' trait impulsivity (BIS-11, Patton

et al., 1995) and Need for Cognition (NCS scale, Cacioppo and Petty, 1982; Cacioppo et al., 1984) were assessed because we had explicit, though exploratory, questions, related to the COGED paradigm (see Task design section). Scores of these self-report questionnaires are presented in Table 4.1. Included participants were also familiarized during the screening session with the cognitive test battery that was administered during the subsequent experimental sessions. This familiarization consisted of practice of a response inhibition task (Bloemendaal et al., 2018), a working memory task (cf. Fallon and Cools, 2014; Fallon et al., 2016) and the N-back task (see Task design section, based on Westbrook et al., 2013). Afterwards, participants were guided to the fMRI facility and their weight was assessed for adequate dosage calculation (see Tyrosine administration section).

The two experimental sessions were identical, except that participants received placebo on one day and tyrosine on the other (counterbalanced across participants). Participants were asked to come to the lab in the morning (at 8 am or 10 am) after overnight fasting: they refrained from eating, drinking except from water, and taking any medication after 10 pm of the previous day. The overnight fast reduces variability in plasma large neutral amino acid levels between participants caused by the previous meal (Fernstrom and Wurtman, 1979). A similar fasting procedure has been adopted in other research using tyrosine supplementation (Banderet and Lieberman, 1989; Colzato et al., 2014; Lieberman et al., 1985; Mahoney et al., 2007; Shurtleff et al., 1994). Sessions started approximately at the same time of the day (maximal deviation was 90 minutes), with an interval of one week to a max of 17 weeks between testing days. After informed consent, participants practiced the response-inhibition task (see Bloemendaal et al., 2018), and right after drug administration (see Tyrosine administration section), each level of the N-back task was rehearsed followed by the practice of another working memory task (cf. Fallon et al., 2016). The cognitive test battery consisted in total of 3 paradigms (Figure 4.1). The order of practice and paradigms was constant across sessions and participants, such that the effort execution N-back task was always administered soon after drug intake (~+ 20min). To isolate effects on choice from effects on execution, the effort execution (i.e. N-back) task was timed to immediately follow ingestion of the intervention, so that tyrosine was highly unlikely to have taken effect during task execution, given its delay in reaching peak concentrations (±2 hours, see Tyrosine administration section). Then, after a break of 90 minutes, the response inhibition task (Bloemendaal et al., 2018) and working memory task (cf. Fallon et al., 2016) were administered during fMRI. After fMRI (duration ~90 minutes), the COGED task was administered together with a N-back redo which is based on participants' choices (see Task design section). The delay between tyrosine

administration and the COGED task (described in Task design section) was on average 189 (+/- 22) minutes, while plasma tyrosine levels have been measured to remain elevated up to 8hrs (see Tyrosine administration section, Glaeser et al., 1979).

After task completion, we administered different neuropsychological tests, including immediate and delayed story recall (Wilson et al., 1989), digit span forward and backward (Groth-Marnat, 2001), Stroop cards (Stroop, 1935), verbal fluency (Tombaugh et al., 1999), box completion (Salthouse, 1996) and number cancellation (Lewis and Kupke, 1977). Summary scores are presented in Table 4.1. For safety reasons, blood pressure and heart rate were measured three times throughout the days (start of testing day, before task battery, after task battery). At the same time points, participants' mood was assessed using the Bond and Lader Visual Analogue Scales (calmness, contentedness, alertness; Bond and Lader, 1974). For exploratory purposes, assessing tyrosine's effect on dopamine metabolites, urine was collected on both testing sessions off drug (i.e. before drug administration) and around the peak of tyrosine concentration (i.e. right after the fMRI part). Intervention effects on mood, blood pressure and urine data (all T1-T0 due to peak level of intervention) are reported in Table 4.1. Supplemental Material 4.2 reports mood and blood pressure data for T2-T0.

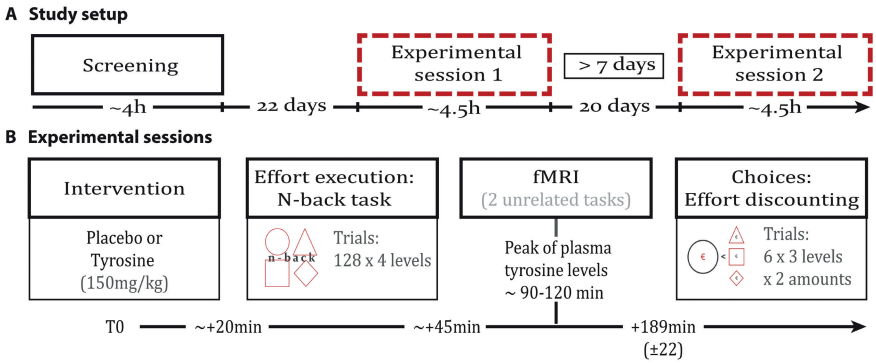


FIGURE 4.1 | Schema of study setup **(A)** and experimental sessions **(B)**. **A** An initial screening was followed by two identical (except for placebo versus tyrosine intervention) experimental sessions. Duration between screening and session 1 was on average 22 days, between the two experimental sessions on average 20 days. To prevent any carry-over effects of pharmacological interventions, the experimental sessions were separated by at least 7 days. **B** During the experimental sessions, participants received placebo or tyrosine and conducted a test battery (see Procedure section). The effort discounting choice task was administered after an fMRI session and took place around 3 hours after the intervention in a behavioral lab.

Tyrosine administration

Participants received tyrosine on one and a placebo substance on the other day, both adjusted to body weight as determined during the screening session (see Procedure section). Following multiple previous studies in young volunteers (Mahoney et al., 2007; Shurtleff et al., 1994; but see e.g. Colzato et al., 2013), we administered 150 mg/kg L-tyrosine powder (BulkpowdersTM, Sports Supplements Ltd. Colchester, Essex, United Kingdom). The placebo product was a mixture of 54 mg/kg dextrine-maltose (Fantomalt by Nutricia) with 110 mg/kg maizena (ratio Fantomalt/cornstarch = ~½). The ratio of Fantomalt to cornstarch was adjusted to ensure that placebo and tyrosine mixture have an equal energy level, similar structure and aftertaste. Tyrosine and placebo powders were mixed with 200 g of banana-flavored yoghurt (Arla Foods Nederland, Nijkerk, The Netherlands) to ensure comfortable ingestion. In a formal blinded sensory experiment, a specialized dietician from the Division of Human Nutrition of Wageningen University (E. Siebelink) confirmed equal taste experience of the two mixtures. Weighting of the doses, preparing and coding the samples were performed by a staff member not involved in the study, thus the order of administration was double-blind.

Tyrosine is a catecholamine precursor: when tyrosine enters the brain via the blood-brain barrier, it is converted into levodopa through the rate-limiting enzyme tyrosine-hydroxylase (TH; Daubner et al., 2011) and then further converted into dopamine through the enzyme aromatic l-amino acid decarboxylase (AADC). In turn, dopamine can be converted into noradrenaline through the enzyme dopamine beta-hydroxylase (DBH; Jongkees et al., 2015; Kaufman & Friedman, 1965). The oral administration of tyrosine significantly enhances central catecholamine synthesis in rodents (Cuche et al., 1985; Fernstrom, 1983; Gibson and Wurtman, 1976; Scally et al., 1977; Tam et al., 1990) and humans (Growdon et al., 1982). Plasma concentrations peak ~2h after administration and remain significantly elevated up to 8h (Glaeser et al., 1979). The administration of 150 mg/kg body weight tyrosine has been shown to significantly increase plasma tyrosine concentrations also in older adults, peaking at 90 minutes and remaining elevated till at least 240 minutes after drug intake (van de Rest et al., 2017). To test participants at maximal plasma levels, participants underwent the cognitive test battery starting ~90 minutes after drug intake. The delay between tyrosine administration and the COGED task (described in Task design section), the paradigm of primary interest for our research question, was on average 189 (+/- 22) minutes.

TABLE 4.1 | Secondary measures

	Measure	Screening	Placebo	Tyrosine	Drug effect
Exclusion criteria	HADS	3.7 (2.6)	N/A	N/A	N/A
	MMSE	29.1 (1.3)	N/A	N/A	N/A
	NLV - IQ estimate	114.9 (8.6)	N/A	N/A	N/A
Effort questionnaire	NCS	50.7 (11.8)	N/A	N/A	N/A
Dopamine proxies	BIS-11	58.2 (6.3)	N/A	N/A	N/A
	Digit span	N/A	13.3 (3.3)*	12.7 (3.7)	t(27) = 1.5, p = 0.145
General neuropsychological assessment	Story recall - immed	N/A	9.8 (2.8)	10.6 (3.2)	t(28) = -1.2, p = 0.254
	Story recall - delay		9.3 (2.7)	9.7 (3.0)	t(28) = -0.6, p = 0.535
	Stroop effect (s)	N/A	84.3 (48.6)*	87.7 (73.7)**	t(26) = -0.2, p = 0.815
	Verbal fluency, total	N/A	46.3 (9.4)	44.0 (10.1)*	t(27) = 1.2, p = 0.246
	Box completion, min	N/A	90.0 (33.7)*	82.5 (19.4)	t(27) = 1.2, p = 0.248
	Digit cancellation, min	N/A	246.8 (31.4)**	250.8 (38.9)*	t(25) = -0.8, p = 0.433
Mood *(T1-T0)*	Calmness	N/A	-0.5 (1.7)	-0.9 (1.9)*	t(27) = 0.7, p = 0.485
	Contentedness	N/A	-0.6 (1.4)	-0.7 (1.3)*	t(27) = 0.1, p = 0.888
	Alertness	N/A	-0.2 (1.1)	-0.1 (1.0)*	t(27) = -0.6, p = 0.584
	Total	N/A	-0.4 (1.0)	-0.4 (1.0)*	t(27) = -0.1, p = 0.906
Blood pressure *(T1-T0)*	Systolic	N/A	4.1 (8.6)	-0.6 (6.7)	**t(28) = 2.1, p = 0.041**
	Diastolic	N/A	-2.7 (5.1)	-2.3 (4.4)	t(28) = -0.3, p = 0.740
	Heart rate	N/A	0.1 (5.1)	-0.2 (3.4)	t(28) = 0.3, p = 0.768

Table 4.1 Continued

	Measure	Screening	Placebo	Tyrosine	Drug effect
Metabolites in urine *(T1-T0)*	DOPAC	N/A	-0.03 (0.3)	0.2 (0.4)	**t(28) = -3.0, p = 0.006**
	HVA	N/A	0.6 (0.8)	0.5 (0.7)	t(28) = 0.9, p = 0.370
	VMA	N/A	0.3 (0.2)	0.3 (0.2)	**t(28) = 2.1, p = 0.048**
	MOPEG	N/A	0.2 (0.1)	0.2 (0.2)	t(28) = 1.5, p = 0.157

Data from questionnaires, neuropsychological assessment (NPA), mood, blood pressure and urine metabolites. Measures are acquired during screening or testing days (see Procedure section). Data represent mean (standard deviation) and when administered in both experimental sessions, results of paired-sample t-tests are presented to assess intervention effects. For the NLV-score and BIS-11 score, data points of 3 and 1 participants(s) were missing, respectively.

Task design

The task design was, except for minor adaptations, identical to that described in Westbrook and colleagues (2013). Each experimental session consisted of an effort execution N-back phase (see Effort execution: N-back task section; Figure 4.2A), the cognitive effort discounting phase (COGED; see Choices: cognitive effort discounting section; Figure 4.2B) and additional N-back rounds based on a random selection from among their choices in the discounting procedure. The entire protocol was programmed and administered using Psychophysics toolbox (Brainard, 1997; Pelli, 1997) in MATLAB.

Effort execution: N-back task

Participants completed the N-back task three times: a longer version during the screening session and a shorter version during the experimental sessions. The tasks were administered in behavioral labs with participants sitting comfortably in front of the screen, hands located on the keyboard. Participants were instructed to complete a working memory task in which they are presented with series of letters in the center of the screen and that they need to respond by indicating whether each letter is a target or non-target by keypress (Figure 4.2A). All versions start with easiest, 1-back level and increased block-wise to the highest, 4-back level. In the 1-back task, participants compared the current letter to the letter presented 1 position (i.e. screen) back and if the letter was identical, they pressed the target

key; if not, they pressed the non-target key. For the 2-back task, a target was defined as identical letter presentation 2 screens back, etc.

The practice phase during screening consisted of three runs for every load level, the experimental sessions had two runs. Each run comprises 64 items (consonants, 24-point Courier New font, 16 targets, black font). Participants were instructed explicitly at the beginning of each new level, which level they were about to complete. In addition to this explicit information, dark grey shapes were presented in the background which participants could learn to associate with the different N-back levels, see Figure 4.2A. Beyond indicating the current task level and rules, the shapes had no other utility for performing the N-back task. Shapes had a diameter of 10 cm and were presented in the center of the lighter gray screen as the background of the letter stimuli on each trial. Participants had 1.5 s to respond to each item by button press, after which items were replaced by fixation cross. The inter-item interval was 0.5 s. Lures (items within N +/- 2, but not exactly N, positions after last presentation) were included in N-back stimulus lists to increase level difficulty: eight for N=1, six for 2, five for 3, and three for N=4. Participants were given feedback about run-wise performance (''% of targets'' and ''% of non-targets correct''). To motivate engagement, and to prevent participants from responding, e.g., ''Non-target'' at the expense of the ''Target'' score, participants were also given feedback of ''Good job!'' if both scores were above 50% or ''Please try harder!'' otherwise. Additionally, after each level of N-back experience, participants completed a self-report questionnaire reflecting on their task experience (see Supplemental Material 4.3). Participants indicated on a Likert scale from 1 to 10 how difficult and effortful they perceived the task and, for higher levels, how effortful the level was compared with level 1.

Choices: Cognitive effort discounting

The discounting procedure was also administered in behavioral labs with task presentation on a pc and responses given on the keyboard. In the discounting procedure, on every trial, participants made choices between a higher N-back level (2-4) for a fixed monetary amount (€2 or €5) and the 1-back task for a lower, variable amount (Figure 4.2B), analogous to adjusting-immediate-amount (AIA) procedures used in intertemporal and risky choice (Holt et al., 2012). Participants were told that they could choose which N-back level they want to repeat for earning a monetary bonus and that one of their choices would be randomly be selected and played out: they would repeat 1-10 runs of the N-back level that they selected and receive the monetary bonus attached to their choice. To reduce avoidance of mistakes rather than effort, we instructed participants

that they would receive the bonus if they do their best and perform comparable to the practice round on the same day.

Choice options were presented on the left and right side of the screen. Levels were referred to by the same shapes that participants learned to associate with each N-back level during practice and effort execution on the same day (see Effort execution: N-back task). To minimize confusion about levels, participants also had access to a paper sheet reminding them of the relevant shape-level associations. The amount of the monetary bonus was presented in the center of the shape (36-point Courier New font, black font). Each of the 3 higher levels (N= 2-4) was paired with the easier 1-back level in two different amount categories: higher levels were either offered at €2 or €5. For the first paring, the amount offered for the easy task was half the amount offered for the harder task, thus €1 or €2.50, respectively. Depending on participants' choices, the amount offered for the easy task was adjusted (see Figure 4.2B.1): when participants chose the harder/high offer option, the amount offered for the easy task on the next pairing was increased; when the easier/low offer option was chosen, the amount offered on the next trial would decrease. The magnitude of amount adjustments was cut in half after each adjustment such that the offer for the easy task converged towards a point of indifference. Figure 4.2C presents the adjustment path for the easy offer when participants always select the easy (red bars) or hard (green bars) task. The choice task comprised a total of 30 choices (level [3] * amount [2] * amount adjustment [5]). Trial types and offer orders were randomized. Choices were self-paced but have a maximal duration of 9 s. The text "Take your time and choose carefully" was presented at the top of the screen during all choices. If no choice was made within 9 s the text "Too slow!" was presented.

The indifference point reflects the monetary amount offered for the easy task on the last trial corrected for the last choice and was assessed for each level (2-4) per amount condition (€2 and €5). "Subjective value" (SV) hereafter refers to indifference points divided by the amount category (€2 or €5), such that all numbers ranged from 0 to 1 for both the low and high amount offers. A SV of 0.8 means that a participant is equally likely to choose one or the other option (i.e. indifferent) when the easier task is worth 80% of the amount offered for the harder task. A lower SV thus indicates that a participant chooses to receive less money but increases the likelihood to redo an easier task. After the choice paradigm, all participants completed their randomly selected choice exactly four more times and were paid the associated amount for each repetition.

Questionnaires and digit span

A series of questionnaires and neuropsychological tests were completed by participants during the screening and experimental sessions. Trait impulsivity, digit span and Need for Cognition Scale were included in our secondary, exploratory analyses and will be described in more detail below. Scores on other acquired measures are presented in Table 4.1.

Trait impulsivity

The Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995) was administered to assess participants' degree of trait impulsivity. The scale is a self-report questionnaire, consisting of 30 statements that participants rate on a 4-point Likert scale ("never" to "almost always"). Examples are "I buy things on impulse" or "I am future oriented". Scores on this questionnaire can range from 30 to 120. The total Barratt score has been found to be associated with reduced dopamine D2/D3 receptor availability in the midbrain, and enhanced dopamine release in the striatum (Buckholtz et al., 2010; Lee et al., 2009) and has been shown to predict effects of MPH on learning (Clatworthy et al., 2009). This measure served as a putative proxy of baseline dopamine function in the exploratory analyses (see Statistical analysis section).

Digit span

Baseline working memory capacity was assessed with a recorded version of the digit span (Groth-Marnat, 2001) at the end of both experimental sessions. The digit span consists of two parts: forward and backward digit span. In the first part, participants' task was to repeat series of numbers that are presented via headphones in the same order as presented (forward). Series start with three numbers and increase up to 9 numbers. Participants complete two trials for each span and their score is identical to the maximum of digits repeated without any error in one of the two trials. The second part is almost identical, except that participants have to repeat the span backwards, beginning with the last digit of the span. The lowest span contains two, and the highest eight digits. Here too, the score is equal to the maximum of digits repeated correctly. Forward and backward scores are added to obtain a total score, such that scores can range from 0 to 17. In the absence of tyrosine effect on this measure, as in earlier studies (van der Schaaf et al., 2013), the average total digit span across two days was selected, because it was thought to provide a more reliable estimate of working memory capacity. The total scores were averaged across the assessments and

used as putative proxy of baseline dopamine function in exploratory analyses (see Statistical analyses section).

Need for cognition

The self-report Need for Cognition Scale (Cacioppo and Petty, 1982; Cacioppo et al., 1984) was administered to investigate participants' tendency (trait) to engage in effortful tasks. The scale consists of 18 statements, which participants rate on a 5-point Likert scale ("extremely uncharacteristic of me" to "extremely characteristic of me"). Example statements include "I prefer complex to simple problems" or "I only think as hard as I have to". Scores range from 18 to 90.

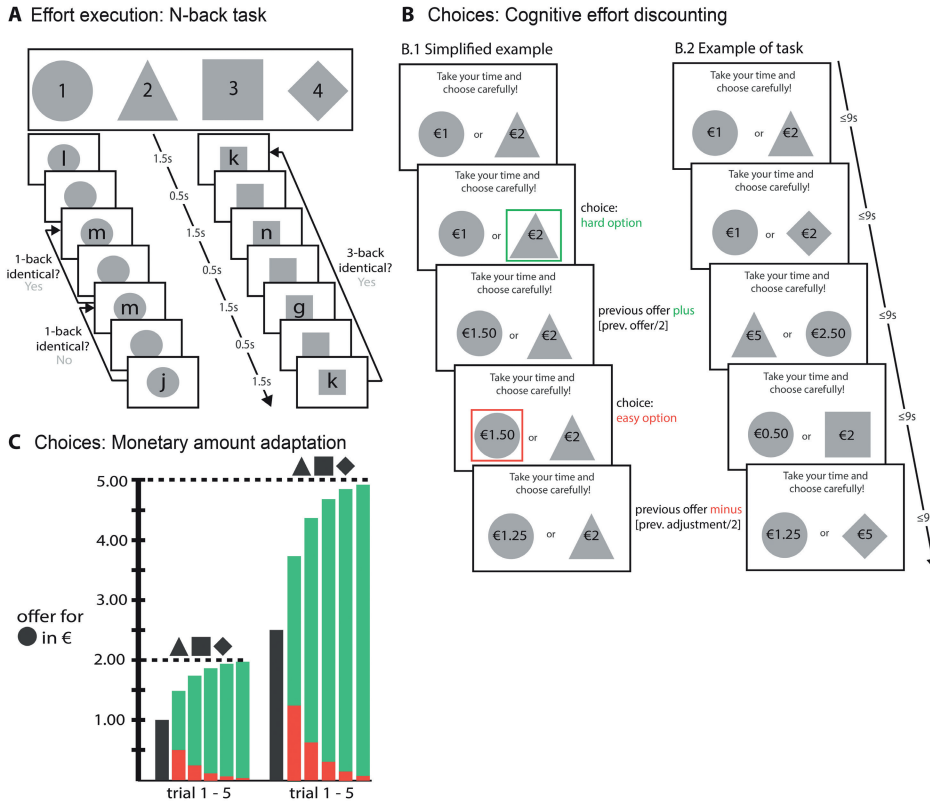


FIGURE 4.2 | The experimental paradigm was based on the procedure described in Westbrook et al., 2013. **A** The N-back task. Letters appeared serially on the screen for 1.5 s, but disappeared after a response was given followed by an ITI of 0.5 s. Every trial had a total duration of 2 s. Participants indicated whether every letter was a target or non-target

by keypress. Target assignment depended on the N-back level represented by shapes. Levels were presented block-wise with increasing difficulty (circle up to diamond). **B** The discounting task. Higher N-back levels (2-4) were paired with the lowest level for varying amounts of money. **B1** A simplified illustration of one trial type: 1-back (circle) versus 2-back (triangle) in the low amount condition (harder task worth €2 instead of €5). The schema presents the monetary amount adjustment as a function of choice. The amount of the harder tasks is fixed, while the easier task varies. When the hard option is chosen, the amount offered for the easy task increases while it decreases when the easy choice is chosen. The amount adjustment reduces exponentially (by the power of 2), see C. **B2** In the real choice task, the trial types (level [3] x amount [2] x amount adjustment [5]) were randomized, resulting in a total of 30 choices. Choices were self-paced but had a maximal duration of 9 s. After the choice is made, a box is presented around the chosen option for 0.75 s. If no response was given, the message "Too slow!" was presented for 0.75 s. Minimal trial duration was set to 2 s. **C** Per harder task level (triangle, square, diamond), 5 choices were presented with respect to circle (1-back) for a varying amount offered for the easy task. Hard tasks were either fixed at €2 or €5. Red bars show the decrement if participants always chose the easy task, while the green bars show the increment if always the hard task was chosen. Participants' choices thus vary in this range. The adjusted amount decreased as a function of trial number of the specific pair. The subjective value is determined based on the last trials adapted following the last choice.

Statistical analyses

Effort execution (N-back task) analysis

The N-back task was used to expose participants to different levels of working memory load. To assess whether performance on the N-back task was sensitive to the load manipulation, we analyzed performance measures: response times and signal detection d' as a measure of sensitivity to targets corrected for the propensity to make a target response (false alarms).

Note that the N-back task was conducted right after drug intake and therefore we did not predict any intervention effects. However, to rule out that N-back performance differed between the experimental session, we assessed drug effects on response times and d' also as a function of N-back levels. The data were analyzed with a linear mixed-effects model approach using the lme4 package in R (Bates et al., 2015). This allowed us to account for within-subject variability in addition to between-subject variability. Drug (tyrosine versus placebo) and level (1-4) were within-subject factors. The model included all main effects and interactions and a full random-effects structure (Barr et al., 2013). To determine p-values, we computed Type 3 conditional F tests with Kenward-Roger approximation for degrees of freedom as implemented in the mixed function of the afex package (Singmann et al., 2017), which in turn calls the function

KRmodcomp of the package pbkrtest (Halekoh and Højsgarden, 2014). Effects were considered statistically significant if the p-value was smaller than 0.05.

Given impulsivity-dependent effects of tyrosine on SV (see Figure 4.5) and to assess whether choice effects could be a consequence of (unexpected) effects of tyrosine on performance, we extended the performance models post-hoc to include participants' trait impulsivity scores (BIS-11) and working memory capacity (digit span average) as between-subject factors. An overview of all performance models is presented in Supplemental Material 4.4 (Models 2.1-2.4).

Choice task (COGED) analysis

The experiment was set up to assess effects of tyrosine on the valuation of cognitive effort. We therefore estimated participants' subjective values for the three higher N-back levels in two amount conditions (€2 or €5) for the placebo and tyrosine sessions. Values range from 0 to 1 and represent the subjective value with respect to the 1-back. Drug (tyrosine vs. placebo), level (2-4) and amount (€2 vs. €5) were within-subject factors. The procedure of model estimation and p-value extraction were identical with that described above. Relatedly, we explored whether tyrosine modulated the speed of choosing (i.e. median choice response time), by running a model with identical predictors as the choice model described here, but median response times as dependent variable.

In further exploratory analyses, we added participants' trait impulsivity (BIS-11) and working memory capacity (digit span average) as between-subject factors to the basic model. Due to missing data for one participant of the trait impulsivity measure, the sample for this analysis is 28. An overview of all SV models is presented in Supplemental Material 4.4 (Models 1.1 and 1.2). Note that Model 1.2 does not include in the random-effects term the factor 'offer amount' due to convergence-warnings. Nevertheless, statistics of the effects of interest as obtained with the complete model are presented for completeness in Supplemental Material 4.9.

Questionnaire data

Self-report N-back

After each N-back level during effort execution (see Effort execution (N-back task) analysis section)), participants judged difficulty, effort and effort with respect to level 1 (for higher levels) using a 1-10 Likert scale (see Supplemental Material 4.3). As for N-back performance and choice data, we analyzed whether the perceived

difficulty and effort increased as a function of N-back level. To assess whether differences in perceived effort existed immediately after drug intake, we analyzed these measures as a function of drug with three separate repeated-measures ANOVAs (difficulty, effort, effort with respect to N = 1) in SPSS 23 (IBM Corp., Armonk, N.Y., USA).

Need for Cognition

We included the Need for Cognition Scale to assess whether we can replicate a (positive) relationship between SV as quantified with the COGED-task and Need for Cognition scores as reported in Westbrook et al., 2013. Thus, we ran another mixed-effects model in R with SV as dependent variable and the factors level and amount as within- and Need for Cognition scores as between-subjects predictors. Results are reported in Supplemental Material **4.**5.

Control analyses

We performed a number of control analyses using a model comparison approach (anova function in R) where we assessed whether the residual sum of squares was significantly reduced when adding any of the following, perhaps confounding, factors to the SV model: order of drug administration, gender, age, and NLV scores (as a measure of verbal intelligence). Furthermore, we added an additional control analysis to assess directly whether the drug effect of interest (see Figure 4.5) was altered when including the factor order in a model (Supplemental Material 4.6).

Given that N-back data is available for 26 instead of 29 participants, we repeated the choice analyses (see Choice task (COGED) analysis section) for the smaller sample as an additional control analysis**.** We also assessed in this sample whether the inclusion of the drug-induced performance changes on the N-back task (d'_{Tyr}-d'_{Pla} and $RT_{Tyr} - RT_{Pla}$) in the choice analyses still reveal the significant modulation (see Figure 4.5). Note that the N-back task was performed shortly after drug administration, before tyrosine-levels are expected to peak (Glaeser et al., 1979; van de Rest et al., 2017).

RESULTS

Effort execution: N-back task

Participants performed well on the N-back task, evidenced by an overall proportion of 0.83 and 0.84 correct responses on the placebo and tyrosine session, respectively. This corresponds to d'-values of 2.02 and 2.03. In line with earlier work (Westbrook et al., 2013), performance was sensitive to the load manipulation: d' decreased as a linear function of N-back levels (level effect: $F(1, 25) = 129.45$, $p < 0.001$; Figure 4.3A), while response times increased (level effect: $F(1, 25) = 20.99$, $p < 0.001$; Figure 4.3B). As expected given our design, tyrosine had no main effects on performance, as assessed by d' (drug effect: $F(1,25) < 0.01$, $p = 0.978$) and response times (drug effect: $F(1, 25) = 0.94$, $p = 0.342$), or interactions with N-back level (for d': drug x level interaction: $F(1, 25) = 0.29$, $p = 0.596$; for RTs: drug x level interaction: $F(1, 25) = 2.86$, $p = 0.103$). This lack of drug effects is not surprising, because participants performed the N-back task immediately after tyrosine administration, so brain tyrosine levels were unlikely to have risen at the time of the N-back task performance. Average performance data (d' and RTs) as a function of level and drug are presented in Table 4.2. For a complete list of statistical effects, see Supplemental Material 4.7.

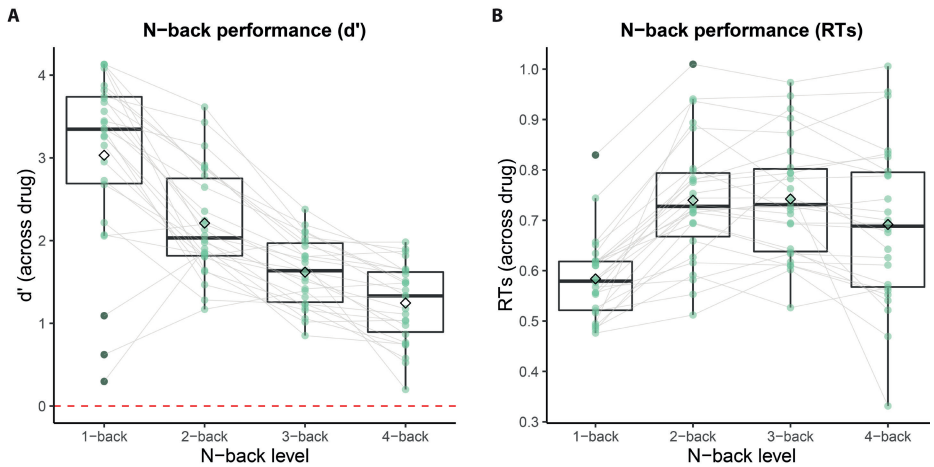


FIGURE 4.3 | Performance on the N-back task as a function of working memory load (i.e. levels) across drug. **A** d', the estimate of participants' sensitivity to targets corrected for the propensity to make a target response (false alarms), decreased as a function of N-back levels.
B Response times increased as a function of N-back level, but showed an inverted U-shape, in line with earlier report using this task (Westbrook et al., 2013). In both graphs, the horizontal lines in the boxplots represent the median, the diamond represents the mean,

green dots are the mean per subject connected by gray lines indicating within-subjects data. Average d' measures contain outliers in level 1 (see gray dots) because on one of the testing days these participants initially swapped keys for target vs. non-target (only in level 1) and had negative d' for one session.

Choices: Cognitive effort discounting

As expected, participants' COGED choices indicate a decline in subjective value (SV) when N-back levels increased (level: $F(1,28) = 54.08$, $p < 0.001$), indicating that effort costs increased with working memory load. Surprisingly, when higher amounts were offered in the discounting task (i.e. €5 instead of €2), participants' SV of the N-back task was slightly lower (amount: $F(1, 28) = 4.77$, $p = 0.037$). While the load effect is in line with earlier reports using this task, the latter amount effect was unexpected given that prior work has shown shallower discounting for larger rewards in both cognitive effort (Westbrook et al., 2013) and delay discounting (Green et al., 2004). In addition to these manipulation checks for SV, we analyzed the speed by which choices are made. Participants chose faster when more money was at stake (i.e. €5 versus €2; amount for RTs: $F(1, 28) = 4.1$, $p = 0.027$). Response times numerically, though not significantly, decreased as a function of N-back level (level for RTs: $F(1, 28) = 4.1$, $p = 0.053$).

Critically, we hypothesized that the administration of tyrosine raises participants' motivation for cognitive control, evidenced by higher SV of the N-back task compared with the placebo session. In contrast to this hypothesis, tyrosine did not significantly increase overall valuation of the N-back task (drug: $F(1, 28) = 0.15$, $p = 0.699$), and there was no significant interaction with level (drug x level: $F(1, 228) = 0.01$, $p = 0.912$; Figure 4.4A). Choice response time analysis revealed that tyrosine numerically increased overall response times, but the effect was not statistically significant (drug: $F(1, 28) = 3.8$, $p = 0.060$). Average SVs are presented in Table 4.2 as a function of level and drug. For a complete list of statistical effects, see Supplemental Material 4.8.

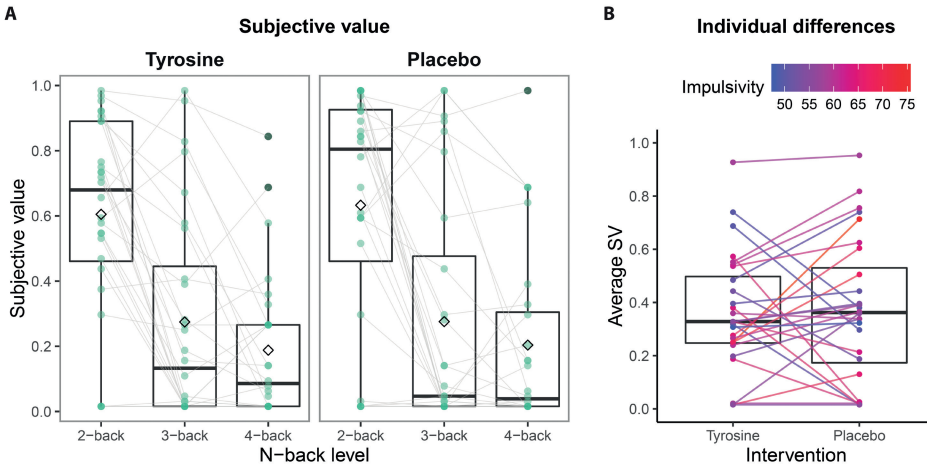


FIGURE 4.4 | Subjective value as measured by the cognitive effort discounting task. **A** Subjective value for tyrosine and placebo sessions as a function of level. The horizontal lines in the boxplots represent the median, the diamond represents the mean, green dots are the average subjective value per subject connected by gray lines indicating within-subject data. Both sessions show that subjective value decreased with increasing working memory load. However, in contrast to our prediction, subjective value did not differ between the interventions. Gray dots reflect individual outliers. **B** Subjective value averaged across levels as a function of drug. The horizontal line in the boxplots represent the median. Lines show the change in subjective value per subject, color-coded for their trait impulsivity score, as a function of drug.

TABLE 4.2 | Task performance

	Level 1	Level 2	Level 3	Level 4	Average
d'	3.03 (1.49)	2.21 (0.70)	1.62 (0.49)	1.25 (0.52)	2.03 (1.12)
placebo	2.92 (1.68)	2.25 (0.73)	1.68 (0.49)	1.25 (0.47)	2.03 (1.15)
tyrosine	3.14 (1.30)	2.17 (0.69)	1.56 (0.50)	1.24 (0.57)	2.03 (1.09)
RT	0.59 (0.09)	0.74 (0.13)	0.74 (0.13)	0.70 (0.16)	0.69 (0.14)
placebo	0.58 (0.18)	0.74 (0.25)	0.75 (0.25)	0.72 (0.27)	0.70 (0.25)
tyrosine	0.60 (0.19)	0.74 (0.24)	0.73 (0.24)	0.68 (0.26)	0.68 (0.24)
Subjective value	N/A	0.63 (0.36)	0.28 (0.35)	0.19 (0.28)	0.37 (0.38)
placebo	N/A	0.65 (0.37)	0.28 (0.37)	0.20 (0.30)	0.38 (0.40)
tyrosine	N/A	0.62 (0.34)	0.27 (0.33)	0.18 (0.26)	0.36 (0.36)

Group average (and standard deviation) of performance data (d' and RT) on the N-back task and subjective value of the cognitive effort discounting task. Note that subjective value scores of higher N-back levels are all calculated relative to level 1, thus no values are available for level 1.

Individual differences: proxy measures of dopamine

Following earlier work indicating that catecholaminergic interventions depend on dopamine baseline levels (Cools, 2016) and the recent study showing that motivation for cognitive control depended on participants' trait impulsivity scores (Froböse et al., 2018), we explored whether tyrosine effects on SV varied as a function of trait impulsivity (BIS-11) and working memory scores (digit span). As in our recent methylphenidate study, tyrosine effects on SV depended on participants' trait impulsivity scores, evidenced by two correlations of medium effect sizes: Tyrosine administration resulted in steeper SV discounting (i.e. higher cost) as a function of N-back levels in more relative to less impulsive participants ($r = -0.37$; drug x impulsivity x level: $F(1, 25) = 5.01$, $p = 0.034$; Figure 4.5). In addition to this level-dependent effect, tyrosine tended to also decrease the overall subjective value (i.e. irrespective of level) as a function of trait impulsivity ($r = -0.33$; drug x impulsivity: $F(1, 25) = 4.19$, $p = 0.051$; Figure 4.5B). Task effects did not significantly vary as a function of working memory capacity (drug x digit span: $F(1, 25) = 1.29$, $p = 0.268$; drug x digit span x level: $F(1, 25) = 1.03$, $p = 0.320$). A complete list of statistical effects is presented in Supplemental Material 4.8.

Although we considered it unlikely that tyrosine could have altered N-back performance, given the timing of the intervention, we tested this assumption by adding impulsivity (and digit span) scores as covariates to the N-back models. This analysis also allowed us to assess whether this impulsivity-dependent effect of tyrosine on effort discounting is an indirect consequence of an impulsivity-dependent effect on performance (e.g. reflecting error avoidance). As expected, given that the N-back task was performed before tyrosine levels were peaking, we did not observe such impulsivity-dependent tyrosine effects for d' (drug x impulsivity: $F(1, 22) = 0.03$, $p = 0.863$; drug x impulsivity x level: $F(1, 22) = 1.02$, $p = 0.323$). Tyrosine also did not alter overall response times as a function of impulsivity (drug x impulsivity: $F(1, 22) = 2.25$, $p = 0.148$). However, surprisingly, tyrosine administration attenuated level-related slowing to a greater degree in more impulsive participants (drug x impulsivity x level: $F(1, 22) = 4.86$, $p = 0.038$). For a complete list of statistical effects, see Supplemental Material 4.7. To further exclude that the tyrosine-induced reduction in SV was driven by failure-avoidance in more impulsive participants, we assessed whether we could replicate the (significant) modulation of SV by tyrosine and impulsivity when including tyrosine-induced performance changes in the SV model. Note that this control analysis is based on 25 instead of 29 datasets due to missing N-back ($n = 3$) and impulsivity ($n = 1$) data and might thus also suffer from

a reduction in power to detect an effect. However, despite the smaller sample and the inclusion of (drug-induced) d'-scores, we replicate the effect of interest (drug x level x impulsivity: $F(1, 19) = 4.8$, $p = 0.041$), suggesting that an indirect modulation via failure (i.e. error) avoidance is unlikely. Given the (unexpected) observation of an impulsivity-dependent response time effect, we repeated this analysis when including drug-induced response time changes. Here we observed that the modulation of SV by tyrosine and impulsivity was no longer significant (drug x level x impulsivity: $F(1, 19) = 3.1$, $p = 0.096$). In sum, tyrosine enhanced the speed of difficult task performance in more impulsive participants, while also reducing their subjective value (or increasing the subjective cost) of difficult task performance. These findings suggest that the effects on SV do not reflect time-on-task avoidance, as faster instead of slower task performance was accompanied by lower SVs.

Finally, to assess whether the effect of tyrosine on cognitive effort discounting might reflect modulation of mood, we also assessed impulsivity-dependent effects of tyrosine on mood changes (total scores T1-T0), as assessed with the Bond and Lader analogue scale. Results of a repeated measures ANOVA showed no significant effects of tyrosine on mood changes (see Table 4.1), also not as a function of impulsivity (drug x impulsivity: $F(1,25) = 2.7$, $p = 0.115$).

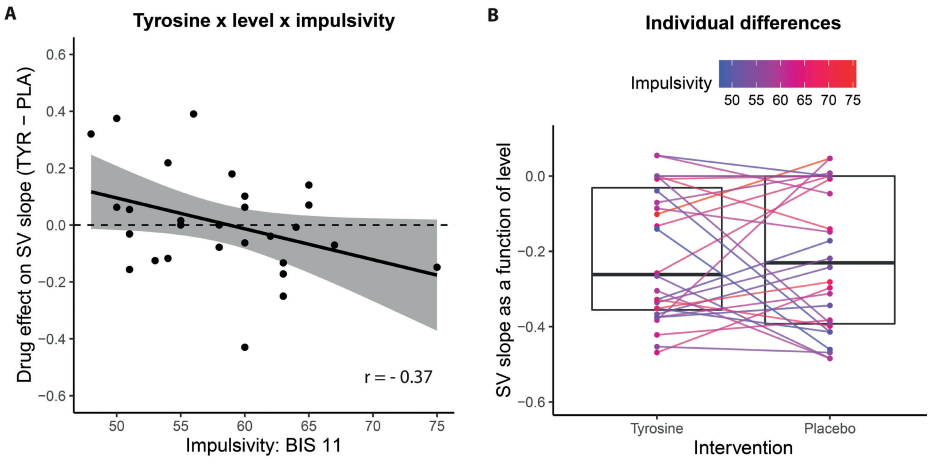


FIGURE 4.5 | Tyrosine-effect on subjective value vary as a function of participants' trait impulsivity (BIS-11) scores. **A** Black dots represent per participant the difference scores (tyrosine minus placebo) of the decrease (i.e. slope) of the subjective value as a function of N-back levels. Negative scores reflect more pronounced discounting (i.e. steeper subjective value slope) on tyrosine compared with placebo. The black line represents conditional means given the linear model used and shaded area represents the 95% confidence interval. The correlation between impulsivity scores and subjective value slope on placebo

is r = 0.38, suggesting that more impulsive participants have a shallower reduction in SV as a function of increasing demand (i.e. N-back level). The correlation on tyrosine is r = 0.03. **B** Subjective value slopes as a function of drug. The horizontal line in the box-plots represent the median. Lines show the change in subjective value slope per subject, color-coded for their trait impulsivity score, as a function of drug. Negative values on the y-axis indicate that SV decrease as a function of higher N-back levels: a steeper slope represents steeper discounting with respect to level 1.

Self-report N-back questionnaire

As expected, subjective ratings of perceived difficulty and effort increased as a function of N-back level, evidenced by a main effect of level on difficulty ($F(3,81) = 136.3$, $p < 0.001$) and effort ($F(3,81) = 69.6$, $p < 0.001$) rating. Also the perceived effort for completing higher N-back levels compared with level 1 increased linearly ($F(2,54) = 71.1$, $p < 0.001$). Consistent with our expectation, given that the task and these questionnaires were administered only shortly after the intervention, we do not observe any modulation of perceived difficulty or effort ratings as a function of drug (drug effect for difficulty: $F(1,27) = 0.1$; for effort: $F(1,27) = 0.8$; for relative effort: $F(1,27) = 0.8$), also not as a function of level (drug x level for difficulty: $F(3,81) = 0.8$; for effort: $F(3,81) = 0.9$; for relative effort: $F(2,54) = 1.4$). When entering trait impulsivity scores as a covariate, unlike the effect in the COGED paradigm, we do not observe any significant impulsivity-dependent drug effect on subjective effort ratings relative to the 1-back task, a measure most similar to the COGED task (drug x impulsivity: $F(1,25) = 0.4$, $p = 0.539$; drug x impulsivity x level: $F(2,50) = 1.7$, $p = 0.198$). This analysis strengthens the confidence that effects observed on the choice task are specific to the tyrosine intervention and were not observed on self-reported effort scores right after effort execution.

DISCUSSION

In this study, we set out to assess whether a catecholamine precursor alters motivation of cognitive control in older adults. More specifically, we hypothesized that augmenting catecholamine synthesis with tyrosine increases the subjective value of performing the N-back task for money. For this reason, we employed an established economic discounting procedure (Westbrook et al., 2013) that has previously been shown to be sensitive to cognitive load and aging. Our aim was to investigate tyrosine's effect on decision-making about cognitive effort, rather than tyrosine's role in N-back performance. Therefore, participants were exposed to the N-back task right after drug-intake (~20 min) at which point tyrosine should not have taken effect. Conversely, the effort discounting task was administered when catecholamine levels were expected to be enhanced.

In line with earlier reports, we observed that participants' performance decreased, and effort discounting increased, as a function of working memory load (i.e. N-back level) (Westbrook et al., 2013). However, contrary to our prediction, tyrosine did not alter the subjective value of cognitive effort as a main effect. We predicted a positive main effect of tyrosine on motivation for cognitive control, given prior evidence linking increased dopamine function with willingness to expend physical effort in animal models (Hamid et al., 2016; Salamone et al., 2016), reduced physical effort discounting in humans (Chong et al., 2015) and neurocomputational models implicating striatal dopamine in increasing sensitivity to effort benefits versus costs (Collins and Frank, 2014). Moreover, recent work has shown that increased dopamine might promote not just physical effort, but cognitive control as well, by offsetting effort costs (Manohar et al., 2015; McGuigan et al., 2019). We expected that older adults might be particularly sensitive to benefits of tyrosine administration, given reports on reduced dopamine transmission (Karrer et al., 2017) and, perhaps relatedly, reduced motivation to engage in effortful control (Westbrook et al., 2013). Despite multiple lines of evidence that dopamine increases willingness to expend effort, our results indicate that tyrosine administration does not have simple uniform effects on motivation for cognitive effort across all participants.

Instead of a main effect, we observed in exploratory analyses an interaction with individual differences such that tyrosine effects depended on participants' baseline impulsivity. Specifically, the (demand-induced) subjective value of control decreased with tyrosine administration in participants with high baseline impulsivity, while it was increased, if anything, in less impulsive participants. This interaction between drug status and impulsivity is a small effect, but interesting because it mirrors a similar interaction between the catecholamine agonist methylphenidate and impulsivity in our previous study that had greater statistical power to assess individual differences ($n = 100$) (Froböse et al., 2018). In that study, participants with low impulsivity showed neutral or even reduced avoidance of cognitive demand, while those with high baseline impulsivity increased demand avoidance when given methylphenidate. The present results constitute an important extension of this prior work in two ways. First, they provide a critical conceptual replication of the result that catecholaminergic interventions can alter willingness to expend cognitive effort as a function of impulsivity despite differences in task, drug, and population. Second, we utilized a discounting task which explicitly measures cost-benefit decision-making, allowing us to directly test the hypothesis that pharmacological catecholamine manipulation modulates the subjective value of cognitive effort. The methylphenidate-dependent effects on demand avoidance in the prior study were plausibly linked to cost-benefit

decision-making. However, the inference was indirect given that 1) no explicit rewards / benefits were on offer, 2) demand avoidance may have reflected ability to detect demand differences rather than increased sensitivity to effort costs, *per se* (cf. Gold et al., 2015) and 3) effort-execution (i.e. task-switching) in addition to choices were conducted on drug.

Our aim here was not only to extend previous work by teasing apart effort-execution and choices by administering them in two separate tasks, but also to show that tyrosine alters choices specifically without the possibility of performance modulation by having the N-back task performed off drug. Because of logistic reasons and plasma tyrosine levels reaching their peak level only after 90-120 minutes (Glaeser et al., 1979; van de Rest et al., 2017), we administered the N-back task shortly after tyrosine administration. Surprisingly, performance analyses indicate an impulsivity-dependent response time modulation which is also consistent with effects observed after methylphenidate administration (Froböse et al., 2018): Tyrosine attenuated level-related slowing in more impulsive participants. This finding evidences that, contrary to our expectation, tyrosine modulated performance as early as 20 minutes after tyrosine ingestion. Thus, as in the methylphenidate study, reduced motivation for cognitive effort (i.e. lower subjective value) on tyrosine was accompanied by level-dependent speeding, indicating, if anything, relatively better performance on the day of tyrosine administration. Although we remain puzzled by the fact that we observe any modulation of performance by tyrosine that early after administration, the direction of effect is not in line with a performance failure account. Self-report ratings of perceived effort support this interpretation, as ratings did not show (impulsivity-dependent) drug effects.

In sum, the two studies converge in suggesting that dopamine interventions affect motivation for cognitive effort as a function of trait impulsivity, with undermining effects in more impulsive participants. Individual differences in trait impulsivity have been associated with baseline dopamine transmission (Buckholtz et al., 2010) and have been shown to modulate drug effects on reversal learning (Clatworthy et al., 2009), working memory (Cools et al., 2007), and striatal interconnectivity (Piray et al., 2015) in young adult samples. As such, instead of finding a main effect, our findings align with the proposal that the effects of catecholaminergic drugs vary with individual differences in baseline levels of dopamine (Cools and D'Esposito, 2011).

Why does tyrosine reduce SV in more impulsive participants?

One reason that tyrosine might have attenuated the subjective value of cognitive effort is by paradoxically *decreasing* dopamine synthesis and dynamic dopamine response to offer presentation for more impulsive individuals, via D2 autoreceptors. Thus, a reduction in dopamine synthesis might result in a shift towards more cost and less benefit sensitivity. Indeed, while phasic DA release following offer presentation makes decision makers more sensitive to offer benefits and less sensitive to offer costs (Collins and Frank, 2014; Schelp et al., 2017), autoreceptor binding can attenuate phasic DA release (Ford, 2014; Frank and O'Reilly, 2006). Thus, pharmacologically increased DA tone could, via increased autoreceptor signaling, reduce phasic DA release, making more impulsive decision-makers less willing to accept high-cost, high-benefit offers. This account assumes that tyrosine administration primarily increased pre-synaptic (autoreceptor) rather than post-synaptic D2 binding in older adults and that impulsive individuals differ in their pre-synaptic signaling sensitivity. Supporting the first assumption, the administration of phenylalanine, the precursor of tyrosine, to rats increased striatal dopamine release at lower doses, but attenuated dopamine release at higher doses (During et al., 1988). In line with this finding, there is evidence for up-regulated striatal dopamine synthesis in older adults (Berry et al., 2016; Braskie et al., 2010), which has been associated with impaired task- switching performance (Berry et al., 2016). Thus, we speculate that a surge of precursor converted to dopamine in a system with already up-regulated dopamine synthesis may 'over-dose' the system triggering a shutdown of TH activity, via cytoplasmic dopamine or D2 receptors (Fisone et al., 2001). This would explain the observation that higher doses of tyrosine (both 150 and 200 mg/kg) were associated with reduced working memory performance compared with a lower dose (van de Rest et al., 2017). In support of the second assumption, more impulsive individuals have lower presynaptic dopamine D2 receptor availability and greater amplitude phasic responses to instrumental cues at baseline (Buckholtz et al., 2010). Thus, more impulsive individuals may be particularly sensitive to the consequences of dopamine agonism for autoreceptor signaling. In sum, this account predicts that tyrosine reduced dopamine in older adults and more impulsive individuals will see the largest paradoxical reduction in phasic dopamine release with dopamine agonists. This mechanism has elsewhere been posited to explain why the agonist methylphenidate can reduce impulsive responding in individuals with ADHD (Seeman and Madras, 2002).

Another reason that increased dopamine tone might increase cognitive effort discounting, for some people, relates to striatal dopamine's putative role in regulating action selection as a function of opportunity costs. In short, dopamine tone has been proposed to convey local environmental richness, and therefore the opportunity costs of 'sloth' (Niv et al., 2007). Thus, in the competition between cognitive control, and habits, higher dopamine tone conveying higher opportunity costs may promote an action selection bias for fast habits over slow control actions (Boureau et al., 2015). This effect of increasing dopamine on action selection may also influence explicit cost-benefit decision-making about cognitive control of the type studied here (Kurzban et al., 2013). Thus, individuals with high dopamine tone might be speculated to perceive their environment as particularly opportunity costly. In this context, tyrosine-related reductions in the value of cognitive effort as well as level-dependent speeding on the N-back task can be considered adaptive.

LIMITATIONS

Our hypotheses were motivated by a robust literature on dopamine's role in physical effort and cost-benefit decision making. However, tyrosine does not selectively increase dopamine: Oral administration in young adults has been shown to also affect plasma noradrenaline levels (Kishore et al., 2013). Future studies are needed to test the hypothesis that tyrosine alters motivation of cognitive control via affecting dopamine rather than noradrenaline transmission. This is especially pertinent because of the well-established link between the locus coeruleus–norepinephrine system and mental fatigue (Berridge and Waterhouse, 2003) and the implication of this system in task-related decision processes (Aston-Jones and Cohen, 2005), task engagement and meta-cognitive regulatory functions (Hauser et al., 2017; Hopstaken et al., 2015). Moreover, instead of a main effect of tyrosine administration on the subjective value of cognitive effort, we observe that tyrosine effects were modulated by trait impulsivity scores. Despite the fact that these results are consistent with our recent larger scale study (n = 100; Froböse et al., 2018), we are aware that the effect is small and that our sample of 29 participants is low. As such, replication of this effect is advised in a larger sample, ideally in which the effort execution takes place before any intervention is administered.

CONCLUSION

We demonstrate that tyrosine administration altered the subjective value of cognitive effort in healthy older volunteers (aged 60 - 75 years). However,

contrary to our hypothesis that tyrosine alters overall valuation of the N-back task, exploratory analyses suggest an interaction between drug and individual differences in trait impulsivity. Interestingly, as in our recent methylphenidate study, tyrosine reduced the motivation for cognitive effort in more relative to less impulsive participants. Thus, we show that cost-benefit decision-making about task engagement is sensitive to changes in catecholamine synthesis and the direction of effect depends on individual differences in trait impulsivity, a putative proxy of baseline dopamine function.

SUPPLEMENTAL MATERIALS OF CHAPTER 4

SUPPLEMENTAL MATERIAL 4.1 | Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Clinical dementia as measured by Mini Mental State Examination score < 24)
- Severe depression or anxiety as measured by HADS score > 11
- Estimated IQ < 85 (based on Nederlandse Leestest voor Volwassenen (NLV) -score)
- (History of) clinically significant psychiatric disorder
- (History of) clinically significant neurological disorder, such as brain infarct, Parkinson's Disease, chronic migraine, Diabetes Mellitus
- First degree family history of schizophrenia, bipolar disorder or major depressive disorder
- Thyroid problems and low-protein diet
- Endocrine or metabolic disorders such as hepatic or renal problems
- Under treatment for
  - o cardiac or vascular diseases and use medication for these conditions;
  - o abnormal blood pressure < 90/60mmHg or > 160/90 mmHg (to be determined during the
  - o intake session)
- Using medication that can interfere with tyrosine's action; monoamine oxidase inhibitors and other antidepressants, sympathomimetic amines, and opioids
- General medical conditions, such as repetitive strain injury (RSI) or sensori-motor handicaps, blindness or colorblindness, as judged by the investigator
- (History of) abuse of drugs or alcohol
- Habitual smoking, i.e. more than a pack of cigarettes per week
- Participation, current or within the past twelve months, in a specific cognitive training study or previous study using the same paradigm as the current study
- Contra-indications for MRI:
  - o Metal objects or fragments in the body that cannot be taken out
  - o Active implants in the body
  - o Using med ical plasters
  - o Epilepsy
  - o Previous head surgery
  - o Claustrophobia

SUPPLEMENTAL MATERIAL 4.2 | Mood / Blood pressure T2-T0

	Measure	*Screening*	*Placebo*	*Tyrosine*	*Drug effect*
Mood *(T2-T0)*	Calmness	N/A	0.0 (2.2)	-0.3 (1.5)	t(28) = 0.6, p = 0.566
	Contentedness	N/A	0.2 (0.6)	0.1 (1.0)	t(28) = 0.4, p = 0.689
	Alertness	N/A	0.0 (1.4)	0.4 (1.4)	t(28) = -1.2, p = 0.266
	Total	N/A	0.0 (1.0)	0.2 (1.1)	t(28) = -0.5, p = 0.599
Blood pressure *(T2-T0)*	Systolic	N/A	7.2 (11.4)	7.9 (10.8)*	t(27) = -0.3, p = 0.763
	Diastolic	N/A	1.9 (4.4)	3.9 (5.2)*	t(27) = -1.9, p = 0.062
	Heart rate	N/A	-2.0 (7.6)	-1.3 (6.3)*	t(27) = -0.6, p = 0.541

Data of mood and blood pressure assessments. Data represent mean (std) and results of paired-sample t-tests to assess intervention effects. Missing data points are marked by *.

SUPPLEMENTAL MATERIAL 4.3 | Questionnaire N-back

For essay questions, please answer using your own words. There is no need to go into great detail, a few sentences should be enough for each question.

1. Please describe what you did to complete the CIRCLE task.

2. How difficult would you rate the CIRCLE task, on a scale of 1 to 10?
(very easy) 1 . . . 2 . . . 3 . . . 4 . . . 5 . . . 6 . . . 7 . . . 8 . . . 9 . . . 10 (very difficult)

3. How much effort did the CIRCLE task require, on a scale of 1 to 10?
(very little effort) 1 . . . 2 . . . 3 . . . 4 . . . 5 . . . 6 . . . 7 . . . 8 . . . 9 . . . 10 (very effortful)

4. Please describe what you did to complete the TRIANGLE task.

5. How difficult would you rate the TRIANGLE task, on a scale of 1 to 10?
(very easy) 1 . . . 2 . . . 3 . . . 4 . . . 5 . . . 6 . . . 7 . . . 8 . . . 9 . . . 10 (very difficult)

6. How much effort did the TRIANGLE task require, on a scale of 1 to 10?
(very little effort) 1 . . . 2 . . . 3 . . . 4 . . . 5 . . . 6 . . . 7 . . . 8 . . . 9 . . . 10 (very effortful)

7. How much effort did the TRIANGLE task require compared to the CIRCLE task?
The TRIANGLE task required … (check the most appropriate)

much less effort	slightly less effort	about the Same	slightly more effort	much more effort

… compared to the CIRCLE task.

8. Please describe what you did to complete the SQUARE task.

9. How difficult would you rate the SQUARE task, on a scale of 1 to 10?
(very easy) 1 . . . 2 . . . 3 . . . 4 . . . 5 . . . 6 . . . 7 . . . 8 . . . 9 . . . 10 (very difficult)

10. How much effort did the SQUARE task require, on a scale of 1 to 10?
(very little effort) 1 . . . 2 . . . 3 . . . 4 . . . 5 . . . 6 . . . 7 . . . 8 . . . 9 . . . 10 (very effortful)

11. How much effort did the SQUARE task require compared to the CIRCLE task?
The SQUARE task required … (check the most appropriate)

much less effort	slightly less effort	about the same	slightly more effort	much more effort

… compared to the CIRCLE task.

12. Please describe what you did to complete the DIAMOND task.

13. How difficult would you rate the DIAMOND task, on a scale of 1 to 10?
(very easy) 1 . . . 2 . . . 3 . . . 4 . . . 5 . . . 6 . . . 7 . . . 8 . . . 9 . . . 10 (very difficult)

14. How much effort did the DIAMOND task require, on a scale of 1 to 10?
(very little effort) 1 . . . 2 . . . 3 . . . 4 . . . 5 . . . 6 . . . 7 . . . 8 . . . 9 . . . 10 (very effortful)

15. How much effort did the DIAMOND task require compared to the CIRCLE task?
The DIAMOND task required … (check the most appropriate)

much less effort	slightly less effort	about the same	slightly more effort	much more effort

… compared to the CIRCLE task.

SUPPLEMENTAL MATERIAL 4.4 | Models

1. Choice	
Model 1.1:	**SV** ~ Drug * Level * Amount + (1 + Drug * Level * Amount | SubNo)
Model 1.2	**SV** ~ Drug * Level * Amount * (**BIS-11 + Digit span**) + (1 + Drug * Level | SubNo)
2. Performance	
Model 2.1: d'	**d'** ~ Drug * Level + (1 + Drug * Level | SubNo)
Model 2.2: RT	**log(RT)** ~ Drug * Level + (1 + Drug * Level | SubNo)
Model 2.3: d'	**d'** ~ Drug * Level * **(BIS-11 + Digit Span)** + (1 + Drug * Level | SubNo)
Model 2.4: RT	**log(RT)** ~ Drug * Level * **(BIS-11 + Digit Span)** + (1 + Drug * Level | SubNo)

SUPPLEMENTAL MATERIAL 4.5 | Need for cognition and SV

Using this exact paradigm, the measure of SV has been shown to correlate positively with participants' self-reported need for cognition scores (NCS). Including NCS in the choice model, unlike the earlier report, NCS scores did not relate to SV of the N-back task across drug (NCS effect: $F(1, 27) = 0.41$, $p = 0.530$).

SUPPLEMENTAL MATERIAL 4.6 | Control analyses

We performed a number of control analyses using a model comparison approach, where we assessed whether the residual sum of squares was reduced when adding any of the following, perhaps confounding, factors to the SV model: order of drug administration, gender, age, and NLV scores (as a measure of verbal intelligence). Results of these control analyses confirm that none of the four models including these factors, one at a time, reduced the residual sum of squares significantly (all comparisons with basic model: $X^2(1) < 0.1$, $p > 0.90$). In more recent projects, the order of catecholaminergic drug administration seems to interact with drug effects on subjective value of cognitive control (*in preparation*). Thus, here we assessed directly whether (i) our effect of interest (see Figure 5.5) remains significant when taking into account order and (ii) whether effects interact with order. The analysis confirms that our effects of interest are not explained by order-effects: Drug x Level x BIS: $F(1, 208) = 4.5$, $p = 0.034$; Drug x Level x BIS x order = $F(1, 208) = 0.1$, $p = 0.770$.

Given that N-back data is available for 26 instead of 29 participants, we repeated the COGED analyses for the smaller sample as an additional control analysis: also in the reduced sample tyrosine significantly reduced the SV of the N-back task to a greater degree in more impulsive participants (drug x impulsivity: $F(1, 22) = 4.60$, $p = 0.043$) and trend-wise as a function of N-back level (drug x impulsivity x level: $F(1, 22) = 3.90$, $p = 0.061$).

SUPPLEMENTAL MATERIAL 4.7 | Statistical effects of performance analyses

Effects	**Performance**			
	Model 2.1: d'	Model 2.2: RT	Model 2.3: d'	Model 2.4: RT
Level	**F(1,25) = 129.5, p < 0.001**	**F(1,25) = 21.0, p < 0.001**	**F(1,22) = 147.6, p < 0.001**	**F(1,22) = 18.5, p < 0.001**
Drug	F(1,25) = 0.0, p = 0.978	F(1,25) = 0.9, p = 0.342	F(1,22) = 0.0, p = 0.872	F(1,22) = 1.9, p = 0.178
Drug x Level	F(1,25) = 0.3, p = 0.596	F(1,25) = 2.9, p = 0.103	F(1,22) = 0.4, p = 0.512	F(1,22) = 3.9, p = 0.062
IMP	N/A	N/A	**F(1,22) = 8.9, p = 0.007**	F(1,22) = 0.0, p = 0.851
Drug x IMP	N/A	N/A	F(1,22) = 0.0, p = 0.863	F(1,22) = 1.5, p = 0.236
Drug x Level x IMP	N/A	N/A	F(1,22) = 1.0, p = 0.323	**F(1,22) = 4.9, p = 0.038**
Digit Span	N/A	N/A	F(1,22) = 2.0, p = 0.167	F(1,22) = 0.0, p = 0.885
Drug x Span	N/A	N/A	F(1,22) = 0.1, p = 0.822	F(1,22) = 4.0, p = 0.058
Drug x Level x Span	N/A	N/A	F(1,22) = 0.4, p = 0.544	**F(1,22) = 6.0, p = 0.023**

SUPPLEMENTAL MATERIAL 4.8 | Statistical effects of choice analyses

Effects	**Choices**	
	Model 1.1	Model 1.2
Level	**F(1,28) = 54.1, p < 0.001**	**F(1,25) = 51.5, p < 0.001**
Drug	F(1,28) = 0.2, p = 0.699	F(1,25) = 0.1, p = 0.744
Drug x Level	F(1,228) = 0.0, p = 0.912	F(1,25) = 0.0, p = 0.853
Amt	**F(1,28) = 4.8, p = 0.037**	**F(1,212) = 5.2, p = 0.023**
Drug x Amt	F(1,228) = 0.9, p = 0.338	F(1,212) = 0.9, p = 0.342
Level x Amt	F(1,228) = 2.8, p = 0.093	F(1,212) = 2.9, p = 0.088
Drug x Amt x Level	F(1,228) = 0.0, p = 0.912	F(1,25) = 0.0, p = 0.853
IMP	N/A	F(1,25) = 0.2, p = 0.673
Drug x IMP	N/A	F(1,25) = 4.2 p = 0.051
Drug x Level x IMP	N/A	**F(1,25) = 5.0, p = 0.034**
Drug x Amt x IMP	N/A	F(1,212) = 0.3, p = 0.605
Drug x Level x Amt x IMP	N/A	F(1,212) = 0.1, p = 0.809
Digit Span	N/A	F(1,25) = 5.6, p = 0.026
Drug x Span	N/A	F(1,25) = 1.3, p = 0.268
Drug x Level x Span	N/A	F(1,25) = 1.0, p = 0.320
Drug x Amt x Span	N/A	F(1,212) = 0.2, p = 0.667
Drug x Level x Amt x Span	N/A	F(1,212) = 1.6, p = 0.211

SUPPLEMENTAL MATERIAL 4.9 | Statistical effects of full model

Statistical effects of Model 1.2 now including 'offer amount' as random effect. Note that this model gives convergence-warnings due to model complexity. In-text, we describe results of Model 1.2 presented in Supplemental Material 4.8. However, this table shows that our main conclusions on impulsivity-dependent tyrosine effects hold.

Effects	**Model 1.2 + random effect of 'offer amount'**
Drug x IMP	F(1,25) = 4.2 p = 0.052
Drug x Level x IMP	**F(1,25) = 4.7, p = 0.041**

4

CHAPTER 5

Does tyrosine modulate the flexibility/stability tradeoff in working memory in healthy aging?

This chapter is in preparation for submission as:

M. I. Froböse, M. Bloemendaal, S. J. Fallon, B. B. Zandbelt, E. Aarts, R. Cools (in preparation). Does tyrosine modulate the flexibility/stability tradeoff in working memory in healthy aging?

ABSTRACT

Healthy aging has been associated with changes in catecholamine functioning and decrements in working memory performance. Following prior psychopharmacological evidence from young adults, we assessed whether the administration of a catecholamine precursor to older adults alters working memory performance and associated BOLD signal in fronto-striatal circuitry as a function of task demands. More specifically, we hypothesized that tyrosine improves cognitive stability (i.e. distractor resistance) accompanied by increased BOLD signal in the prefrontal cortex, while impairing cognitive flexibility (i.e. updating working memory representations). We therefore administered an adapted delayed match-to-sample task in a within-subjects design to 29 healthy older adults (60-75 years). Surprisingly, tyrosine reduced the ability to stabilize relevant representations and ignore irrelevant information, evidenced by a larger distractor cost on trials requiring stabilization compared with that on flexible update trials. This effect was accompanied by a tyrosine-induced increase in update- versus ignore-related activity in the right anterior cingulate cortex. Thus, tyrosine promoted the gating of both relevant and irrelevant information into working memory, while also enhancing flexible update-related medial frontal signal. These findings demonstrate that the effects of a catecholamine challenge depend on task demands and raise the hypothesis that tyrosine biases the aging brain away from cognitive rigidity towards distractibility, by modulating the prefrontal cortex.

INTRODUCTION

Catecholamine transmission has long been implicated in cognitive control, including working memory (Arnsten, 1998; Brozoski et al., 1979; Goldman-Rakic, 1997). A key role for catecholamines is also supported by pharmacological interventions, showing that administration of dopamine receptor agonists and antagonists respectively improved and impaired performance on a working memory task in healthy young adults (Luciana et al., 1992; Mehta et al., 1999). Critically, healthy aging is characterized by impairments in working memory (Cai and Arnsten, 1997; Gazzaley et al., 2005; Turner and Spreng, 2012) and reduced dopamine transmission (Bäckman et al., 2006; Karlsson et al., 2009; Karrer et al., 2017). In aged animals, repleting prefrontal cortex dopamine with a D1 receptor agonist improved performance on working memory tasks (Cai and Arnsten, 1997; Mizoguchi et al., 2009). These findings invite the assessment of potential beneficial effects on cognition of pharmacological interventions that increase catecholamine synthesis in older adults.

Other than in young adults, previous studies on the consequences of changes in catecholamine transmission on working memory performance in older adults have yielded inconsistent results: Administration of amphetamine increased BOLD response variability during N-back task performance in older adults who, compared with young adults, had low response variability during a placebo session (Garrett et al., 2015). However, performance was not altered by amphetamine or methylphenidate when assessed with the N-back task (Garrett et al., 2015), digit span, spatial working memory or spatial span task (Turner et al., 2003). Furthermore, a recent study has revealed impaired working memory performance after the administration of a catecholamine precursor: Acute administration of high doses of tyrosine to older adults resulted in poorer instead of better N-back performance, despite drug-induced increase in plasma tyrosine concentrations (van de Rest et al., 2017). In contrast, higher habitual dietary tyrosine intake has been shown in a large sample to be positively associated with working memory capacity in young and older adults (Kühn et al., 2017).

We propose that this variability in (or lack of) drug effects on working memory might be accounted for by variation in specific working memory task demands. This is based on prior evidence for contrasting effects of dopaminergic drugs depending on task demands and associated neural systems. While prefrontal dopamine has been theorized to increase the signal-to-noise ratio of neuronal firing in the PFC, leading to increased robustness of working memory representations (Durstewitz and Seamans, 2008; Durstewitz et al., 2000; Seamans and Yang, 2004; Servan-

schreiber et al., 1990), dopamine in the basal ganglia (BG) has been proposed to be involved in the flexible gating of new representations into the PFC (Hazy et al., 2007)(see *Cognitive stability versus flexibility*). Thus, depending on the locus of effect, catecholaminergic interventions can shift the balance towards or away from cognitive stability (Braver and Cohen, 2000; Cools and D'Esposito, 2011; Fallon and Cools, 2014; Fallon et al., 2016), thereby improving and impairing working memory performance depending on specific demand. To test the hypothesis that catecholamine effects in older adults depend on specific task demands, we characterized in the current study the behavioral and neural effects of tyrosine administration on distinct processes of working memory: cognitive stability (i.e. distractor inhibition) versus cognitive flexibility (i.e. updating of working memory representations).

Cognitive stability versus flexibility

Adaptive behavior relies on an arbitration between focus and flexibility (Cools, 2016; D'Ardenne et al., 2012). The PFC has been reliably implicated in the active online maintenance of goal-relevant representations (Baddeley et al., 1986) by increasing the activity of brain regions that process goal-relevant representations (Fuster and Alexander, 1971; Gazzaley et al., 2007b; Jha et al., 2004; Miller et al., 1996; Toepper et al., 2010; Yoon et al., 2006). In healthy young adults, amphetamine and methylphenidate have been found to increase BOLD signal during working memory tasks, especially in the PFC (Fallon et al., 2016; Mattay et al., 2000). The increase in prefrontal activation was accompanied by increased distractor inhibition (Fallon et al., 2016). Note that there are also reports on L-DOPA-induced improvements in working memory performance that were accompanied by decreases in prefrontal signal, suggesting that dopamine might alter the recruitment but also physiological efficiency (Cools et al., 2002b; Mattay et al., 2002). BOLD-changes might reflect dopamine-induced changes in the signal-to-noise ratio of neuronal firing in the PFC, leading to increased robustness of currently goal-relevant representations in the face of intervening distractors (Durstewitz and Seamans, 2008; Durstewitz et al., 2000; Seamans and Yang, 2004; Servan-schreiber et al., 1990). According to the dual state theory of prefrontal cortex dopamine, robust online maintenance of information is facilitated by enhanced D1 relative D2 receptor stimulation in the prefrontal cortex (Durstewitz and Seamans, 2008).

However, accumulating evidence indicates that dopamine is also implicated in flexible updating by modulating BG processing with the use of a gating mechanism that regulates the inputs to PFC (Bhandari and Badre, 2018; Braver and Cohen,

2000; Chatham and Badre, 2015; Chatham et al., 2014; Rougier et al., 2005). In line with this proposal, BOLD signals in the BG have been found to increase during processes that require the flexible updating of current goal representations (Cools et al., 2002a; Fallon and Cools, 2014; Fallon et al., 2016; Leber et al., 2008). As such, similar to the role of the basal ganglia in action selection (Gerfen and Surmeier, 2011; Mink, 1996), it has a 'gating-like' function in working memory: more 'Go' activity, which is triggered by dopamine release due to expected reward or drug treatment, stimulates update of WM representations in the PFC (Hazy et al., 2007). This is in line with the observation that the administration of D2 receptor stimulation bromocriptine, which has abundant receptors in the BG, impaired distractor resistance in humans (Bloemendaal et al., 2015) and modulated BG signals during cognitive switching (Cools et al., 2007).

Aging has been primarily associated with impairments in cognitive stability and greater flexibility (Dunnett et al., 1988; Lindenberger and Mayr, 2014; Wang et al., 2011), in line with animal studies pointing at a specific decline in dopamine level within the prefrontal cortex (Goldman-Rakic, 1997; Goldman-Rakic and Brown, 1981).

Tyrosine administration

Tyrosine is a precursor of dopamine and noradrenaline and the administration of tyrosine stimulates synthesis and release of catecholamines (Growdon et al., 1982; Scally et al., 1977; Tam and Roth, 1997). The main source of tyrosine is protein-rich food, but tyrosine has also been administered selectively as a powder for study purposes and has been shown to alter cognition (Jongkees et al., 2015). In young adults, similar to beneficial effects of dietary tyrosine intake (Kühn et al., 2017), tyrosine administration has been shown to improve cognitive control functions that are commonly associated with catecholamine transmission, such as working memory, response inhibition, and task switching (see Deijen, 2005; Jongkees et al., 2015 for reviews).

As is the case for other dopaminergic drugs, effects of tyrosine administration have been shown to depend on the baseline state of the system. For example, tyrosine was shown to be particularly effective in enhancing catecholamine metabolism under stress or high cognitive demand, while having disruptive effects in conditions where baseline catecholamine levels are thought to be higher (Jongkees et al., 2015; Tam and Roth, 1997). We administered tyrosine to older adults, aged 60-75, who we anticipated would be more sensitive to tyrosine administration than young adults for two reasons. First, healthy aging

is accompanied by a decline in dopamine transmission (Bäckman et al., 2006). Second, older adults suffer from an impairment in working memory performance (Abdulrahman et al., 2017; Bloemendaal et al., 2016; Kray et al., 2002; van de Laar et al., 2011; Mitchell et al., 2000; Onur et al., 2011).

Hypothesis

Our hypothesis is grounded in prior observations suggesting that manipulation of brain dopamine modulates distinct cognitive functions, i.e. flexible updating and distractor-inhibition, by acting on dissociable brain regions, i.e. the BG and the PFC respectively (Cools and D'Esposito, 2011).

Given that older adults show greatest deficits in cognitive stability and given the proposal that tyrosine improves dopamine-dependent functions with greater cognitive demand (Colzato et al., 2013), we hypothesize that tyrosine improves distractor inhibition by increasing the signal-to-noise ratio of task-relevant representations in the PFC. This change in distractor inhibition, however, is anticipated to be accompanied by a change in the degree to which working memory representations can be updated, thus leading to improved distractor inhibition and increase in prefrontal BOLD signal, but reduced flexibility. To test this hypothesis we used a modified version of a classic delayed match-to-sample test of working memory, which has previously been shown to be sensitive to the administration of methylphenidate, a catecholamine transporter blocker (Fallon et al., 2016). In line with our current prediction, methylphenidate increased performance and prefrontal BOLD signal when cognitive stability was required, but impaired cognitive flexibility. Using this task, we assess tyrosine effects on the critical intervening phase in which stimuli either needed to be protected against distraction (i.e. ignore condition) or used to update working memory representations (i.e. update).

While our study was set up to assess the hypothesis that tyrosine administration would alter update/ignore balance, we also explored whether tyrosine altered working memory in a manner that depended on either of two well-known dopamine proxy measures: trait impulsivity (Buckholtz et al., 2010) and working memory capacity (Cools et al., 2008; Landau et al., 2009). This exploratory analysis was motivated by the observations that the effects of manipulating catecholamine transmission on cognitive control are well established to depend on (a proxy of) baseline levels of dopamine (Cools and D'Esposito, 2011; Swart et al., 2017) and that effects of tyrosine in older adults have been shown to be baseline-dependent (Bloemendaal et al., 2018; van de Rest et al., 2017).

METHODS

Participants

Exclusion criteria for this study were a history of clinically significant psychiatric, neurological or cardiovascular disorder, abuse of drugs or alcohol, abnormal blood pressure (< 90/60 mmHg or > 160/90 mmHg), medication use that can interfere with tyrosine's action, blindness or colorblindness, smoking > 1 pack of cigarettes per week, or contra-indications for MRI. For a complete list of exclusion criteria, see Supplemental Material 4.1.

After a screening session, 33 healthy, right-handed adults were initially included for participation. However, 4 additional participants were excluded or decided to discontinue during or after the first experimental session, due to blood pressure exceeding our inclusion criteria (n = 1) and fMRI-intolerance (anxiety: n = 1; nausea: n = 1, headache: n = 1), leaving a sample of 29 participants (age: M = 66.7, range = 61-71, 16 males) who completed both experimental sessions. For the fMRI analysis we excluded one additional participant, due to a high frequency of signal intensity spikes (>20 spikes per session) in one session, resulting in a final sample of 28 participants (see Statistical analyses section).

We report questionnaire and neuropsychological assessment data for the complete sample (n = 29) in Table 4.1. Note that this is an exact replication of Table 4.1, because the same participants completed multiple experiments in the context of the same study. All procedures were in accordance with the local ethical guidelines approved by the local ethics committee (CMO protocol NL49758.091.14) and in line with the Helsinki Declaration of 1975.

General procedure

A within-subjects, placebo-controlled, double-blind, cross-over design was employed. Participants visited the institute three times: once for a screening and twice for experimental sessions of around 4.5 hours (Figure 5.1). The general procedure was identical to the procedure presented in chapter 4.

The screening session started with a provision of additional information about the study, informed consent and a check for medical exclusion criteria. To assess exclusion criteria, we administered the Hospital Anxiety and Depression scale (HADS, Bjelland et al., 2002), Mini Mental State Examination (MMSE, Folstein et al., 1975) and the Dutch reading test for an estimate of verbal intelligence (NLV, Schmand et al., 1991). In addition, participants' trait impulsivity (BIS-11, Patton

et al., 1995) and Need for Cognition (NCS scale, Cacioppo and Petty, 1982; Cacioppo et al., 1984) were assessed. We assessed trait impulsivity to explore how individual variation in impulsiveness were associated with drug-effects (Statistical analyses section). The Need for Cognition scale was administered to assess the relationship with cognitive effort discounting, reported elsewhere (Chapter 4). Scores of these self-report questionnaires are presented in Table 4.1. In case of an inclusion, participants were familiarized with the cognitive test battery that was administered during the experimental sessions. This consisted of practicing a response inhibition task (Bloemendaal et al., 2018), the update/ignore working memory task described here (see Update/ignore working memory task section based on Fallon and Cools, 2014; Fallon et al., 2016) and an N-back task (Chapter 4). Afterwards, participants were escorted to the fMRI facility and their weight was assessed for adequate dosage calculation (see Tyrosine administration section).

The two experimental sessions were identical, except that participants received placebo on one day and tyrosine on the other day in counter-balanced order. Participants were asked to come to the lab in the morning (at 8am or 10am) after overnight fasting: they refrained from eating, drinking except from water and taking any medication from 10PM of the previous day. The overnight fast prevents large variability in large neutral amino acid levels in plasma between participants caused by the previous meal (Fernstrom and Wurtman, 1979). A similar fasting procedure has been adopted in other research using tyrosine supplementation (Banderet and Lieberman, 1989; Colzato et al., 2014; Lieberman et al., 1985; Mahoney et al., 2007; Shurtleff et al., 1994). Sessions started approximately at the same time of the day (maximal deviation was 90 minutes), with an interval of one week to a max of 17 weeks between testing days. After signing an informed consent form, participants practiced the response-inhibition task (see Bloemendaal et al., 2018), and right after drug administration (see Tyrosine administration section), the N-back task and update/ignore working memory task (see Update/ignore working memory task section) were rehearsed. The cognitive test battery consisted in total of 3 paradigms (Figure 5.1). The order of practice and paradigms was constant across sessions and participants. After a break of 90 minutes, the response inhibition task (Bloemendaal et al., 2018) and update/ignore working memory task were administered in the fMRI scanner. After fMRI (duration ~90 minutes), we administered a cognitive effort discounting task (Chapter 4) and different neuropsychological tests, including immediate and delayed story recall (Wilson et al., 1989), digit span forward and backward (Groth-Marnat, 2001), Stroop cards (Stroop, 1935), verbal fluency (Tombaugh

et al., 1999), box completion (Salthouse, 1996) and number cancellation (Lewis and Kupke, 1977). Summary scores are presented in Table 4.1.

For safety reasons, blood pressure and heart rate were measured three times throughout the days (start of testing day, before task battery, after task battery). At the same time points, participants' mood was assessed using the Bond and Lader Visual Analogue Scales (calmness, contentedness, alertness; (Bond and Lader, 1974). For exploratory purposes, assessing tyrosine's effect on dopamine metabolites, urine was collected on both testing sessions off drug (i.e. before drug administration) and around the peak of tyrosine concentration (i.e. right after the fMRI part). Drug effects on mood, blood pressure and urine data (all T1-T0 due to peak level of intervention) are reported in Table 4.1. Supplemental Material 4.2 reports mood and blood pressure data for T2-T0.

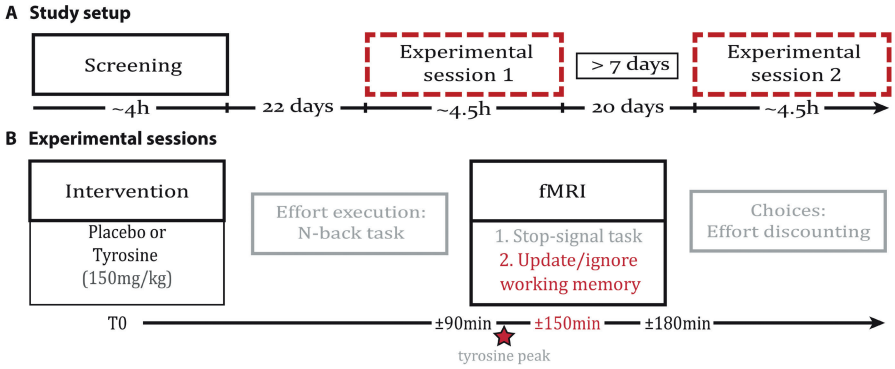


FIGURE 5.1 | Schema of study setup **(A)** and experimental sessions **(B)**. **A** An initial screening was followed by two identical (except for placebo versus tyrosine intervention) experimental sessions. Duration between screening and session 1 was on average 22 days, between the two experimental sessions on average 20 days. To prevent any carry-over effects of pharmacological interventions, the experimental sessions were separated by at least 7 days. **B** During the experimental sessions, participants received yoghurt containing placebo or tyrosine and conducted a test battery (see General Procedure section). The update/ignore working memory task was administered during fMRI and took place around 150 minutes after the intervention. Plasma levels of tyrosine have been shown to peak 90-120 minutes after the administration.

Tyrosine administration

As also described in earlier publications of the same study (Bloemendaal et al., 2018) and chapter 4, participants received tyrosine on one and a placebo substance on the other day, both adjusted to body weight as determined during the screening session (see General procedure section). Following multiple previous

studies in young volunteers (Mahoney et al., 2007; but see e.g. Colzato et al., 2013), we administered 150 mg/kg L-tyrosine powder (BulkpowdersTM, Sports Supplements Ltd. Colchester, Essex, United Kingdom). The placebo product was a mixture of 54 mg/kg dextrine-maltose (Fantomalt by Nutricia) with 110 mg/kg maizena (ratio Fantomalt/cornstarch = ~½). The ratio of Fantomalt to cornstarch was adjusted to ensure that placebo and tyrosine mixture have an equal energy level, similar structure and aftertaste. Tyrosine and placebo powders were mixed with 200 g of banana-flavored yoghurt (Arla Foods Nederland, Nijkerk, The Netherlands) to ensure comfortable ingestion. Weighting of the doses and preparing and coding the samples were performed by staff members who were not involved in the study, ensuring double-blind administration.

Tyrosine is a precursor of the catecholamines: When tyrosine enters the brain via the blood-brain barrier, it is converted into levodopa through the rate-limiting enzyme tyrosine-hydroxylase (TH; Daubner et al., 2011) and then further converted into dopamine through the enzyme aromatic l-amino acid decarboxylase (AADC), resulting in an increase in dopamine levels. In turn, dopamine can be converted into noradrenaline through the enzyme dopamine beta-hydroxylase (DBH; Jongkees et al., 2015; Kaufman & Friedman, 1965). The oral administration of tyrosine significantly enhances central catecholamine synthesis in rodents (Cuche et al., 1985; Fernstrom, 1983; Gibson and Wurtman, 1976; Scally et al., 1977; Sved et al., 1979; Tam et al., 1990) and humans (Growdon et al., 1982). Plasma concentrations peak ~2 hours after administration and remain significantly elevated up to 8h (Glaeser et al., 1979). The administration of 150 mg/kg body weight tyrosine has been shown to significantly increase plasma tyrosine concentrations also in older adults (van de Rest et al., 2017). To test participants at maximal plasma levels, participants underwent the cognitive test battery starting ~90 minutes after drug intake. The delay between drug administration and the update/ignore working memory task (described in Update/ignore working memory task section), the paradigm of primary interest for our research question, was on average 148 (SD = 8.9) minutes (after tyrosine M = 147.7, SD = 6.6; after placebo M = 149.0, SD = 10.9).

Update/ignore working memory task

The task design of the update/ignore working memory task was based on earlier work by Fallon and colleagues (Fallon and Cools, 2014; Fallon et al., 2016). The task was programmed and administered using Psychophysics toolbox (Brainard, 1997; Pelli, 1997) in MATLAB 2013a (Mathworks, Natick, MA, USA).

Participants completed the update/ignore working memory task on three different occasions: they completed a shorter practice version of the task (24 trials) during the screening and both experimental sessions. And, to address our research questions, they completed a longer version (96 trials) of the task twice in the fMRI scanner, once after placebo and once after tyrosine administration.

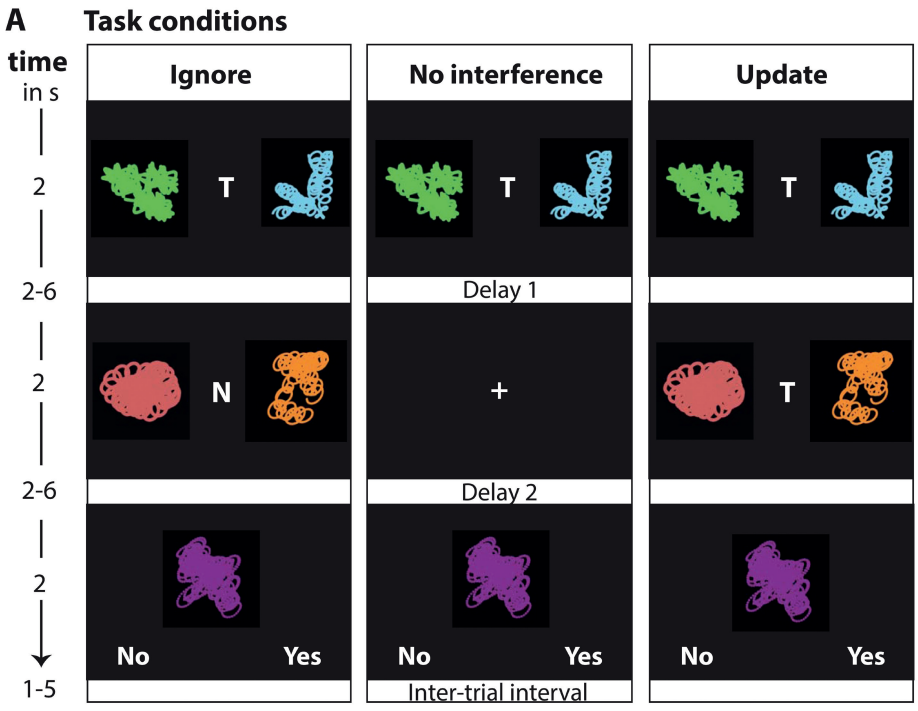
The task is an adapted delayed match-to-sample task (Figure 5.2A). Participants encode stimuli and need to indicate after some delay whether a probe matches one of the two stimuli that have previously been presented. In this task, as in earlier versions (Fallon and Cools, 2014; Fallon et al., 2016), we added an extra phase during the delay, which allowed us to distinguish cognitive stability from cognitive flexibility: the intervening phase. During the intervening phase, participants were required to ignore (i.e. ignore condition) or update (i.e. update condition) stimuli that were presented on the screen. In the ignore condition, participants needed to inhibit distraction by stimuli that are presented on-screen and keep in mind only the stimuli presented during encoding. In the update condition, they had to flexibly update/over-write the encoded stimuli and only remember the newly presented stimuli. We also included control trials, in which no intervening stimuli were presented (no-interference condition), very similar to a standard delayed match-to-sample task. Thus, these trials were identical to the ignore condition regarding the delay between relevant stimuli (i.e. encoding) and target presentation, but lacked distraction.

Stimuli in this task were computer-generated "spirographs," which were composed of different RGB elements. Every trial started with the encoding phase, in which two distinct stimuli were presented on the left and right side of the centre (centered at ¼ of the screen width and ½ of the screen height) on a black background for 2 seconds. During encoding, a white letter 'T' (Times New Roman, font size = 64) was presented in the centre of the screen, indicating that these were target stimuli relevant for encoding. Then, after a delay consisting of a blank screen, during the intervening phase, two new distinct stimuli were presented for 2 seconds on the left and right side from the centre. If the white letter presented in the centre was an 'N', participants had to ignore the stimuli, if the letter was a 'T', then these were the new target shapes and needed to replace the previously encoded stimuli. In case of the no-interference condition, only a white fixation cross was presented. Then, after another delay, the probe screen was presented: one single stimulus was presented in the centre of the screen with the word 'yes' (Dutch: 'ja') and 'no' (Dutch: 'nee') printed below the stimulus on the left and right side. Here, participants were supposed to indicate by a click on the button box with their right index or middle finger, whether they were supposed to remember this probe. They

were supposed to click 'yes' for a match and 'no' for a non-match. In the ignore and no-interference condition, the probe is a match when it is identical to one of the two stimuli presented during the encoding phase; in the update condition, a probe is a match if it is identical to one of the two stimuli presented during the intervening phase. Participants had 2 seconds to respond to the probes before the next trial started after an inter-trial-interval. In contrast to earlier versions of the task, here, the 3 conditions (ignore, no-interference and ignore) were randomized instead of blocked. There was an equal probability of the probe being a match or non-match stimulus, such that participants, if responding correctly, were supposed to respond 'yes' and 'no' in 50% of the trials. Of the non-match trials, half were novel stimuli, the other half were lures. Lures were defined as stimuli that featured as distractors in the ignore condition and initially encoded stimuli in the update condition (Figure 5.2B). We refer to the lures as distractor probes.

The practice version was administered in behavioral labs with participants sitting comfortably in front of the screen, hands positioned on the keyboard. Participants completed 48 trials which were split in 2 blocks of 24 trials (8 trials per condition: ignore, no-interference, update). Delays between encoding, intervening and probe phase were fixed to last 3 seconds each. Inter-trial-interval (ITI) was 2 seconds. After each block, participants were provided with feedback (% correct across conditions). Responses were given with index and middle finger on the keyboard.

The main version of the task was administered while participants were lying in the fMRI scanner. The task was projected via a mirror and the button box was located on the right leg for comfortable access with the right hand (see MRI acquisition section). In the fMRI, participants completed 96 trials, distributed across 4 blocks. Each block contained 24 trials (8 trials per condition). After each block, participants had a break and were provided with feedback (% correct across conditions) for 10 seconds. Delay periods and ITIs were jittered to last respectively 2-6 seconds with a mean of 3 and 1-5 seconds with a mean of 2 seconds. To optimize design efficiency of hemodynamic response estimation, we extracted 4 out of 100 randomizations containing trial order and timings that had minimal correlations between regressors of interest. Each participant conducted 2 of these 4 sequences, one at each experimental session.



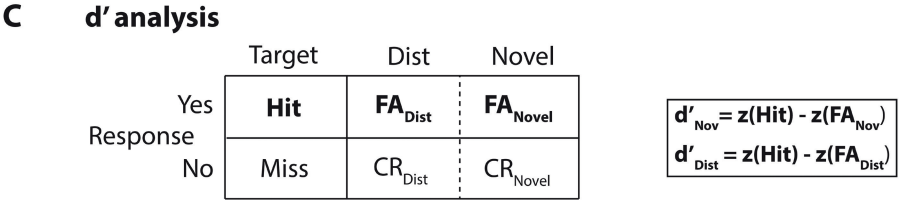


FIGURE 5.2 | A An illustration of the modified delay match-to-sample task. Participants were presented with two stimuli for 2 s that always had to be encoded. After a variable delay period (2–6 s), participants were presented with novel stimuli (2 s) that had to be ignored (in the case of 'N') or used for working memory updating (in the case of 'T'). A no-interference condition, in which only a fixation cross appeared (also for 2 s), was included as a control condition. After another variable delay period (2-6 s), participants were presented with a probe item. Participants had to respond according to whether the presented item matched or did not match one of the relevant stimuli depending on the task condition. In the present example, the correct answer would be 'No' in all conditions,

because it is a non-match (novel stimulus). Participants had a maximum of 2 s to respond before the variable inter-trial-interval (ITI; 1-5 s). Order of task conditions was randomized. Note that for illustration purposes, stimuli are presented larger in this figure than in the real experiment. See Update/ignore working memory task section for details on size. **B** Half of the probes were matches (Target) and half non-matches (distractors (Dist) or Novel). Targets for ignore and no-interference trials were the stimuli presented during encoding (here: blue shape). In the update condition, the target shapes are presented during the intervening phase (here: red 'circle'). Distractors are stimuli that were presented during the trial, but they needed to be displaced (in the update condition) or ignored (in the ignore condition). Novel probes are shapes that were never presented during encoding or intervening phase (pink shape presented in A and B). **C** Following signal detection theory, we calculated, for each drug session and for each condition, participants' sensitivity to discriminate target from non-target (d') based on the hit and false alarm rates.

Questionnaires and digit span

A series of questionnaires and neuropsychological tests were completed by participants during the screening and experimental sessions. The trait impulsivity, the digit span, and need for cognition scales were key to our exploratory research questions and will be described in more detail below. Scores on other acquired measures are presented in Table 4.1.

Trait impulsivity

The Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995) was administered to assess participants' degree of trait impulsivity. The scale is a self-report questionnaire, consisting of 30 statements that participants rate on a 4-point Likert scale ("never" to "almost always"). Examples are "I buy things on impulse" or "I am future oriented". Scores on this questionnaire can range from 30 to 120. The total Barratt score has been found to be associated with reduced dopamine D2/D3 receptor availability in the midbrain, and enhanced dopamine release in the striatum (Buckholtz et al., 2010; Lee et al., 2009) and has been shown to predict effects of MPH on learning (Clatworthy et al., 2009). This measure serves as a second putative proxy of baseline dopamine function for predicting effects of MPH.

Digit span

Baseline working memory capacity was assessed with a recorded version of the digit span (Groth-Marnat, 2001) at the end of both experimental sessions. The digit span consists of two parts: forward and backward digit span. In the first part, participants' task was to repeat series of numbers that are presented via headphones in the same order as presented (forward). Series start with three numbers and increase up to 9 numbers. Participants complete two trials for each

span and their score is identical to the maximum of digits repeated without any error in one of the two trials. The second part is almost identical, except that participants have to repeat the span backwards, beginning with the last digit of the span. The lowest span contains two and the highest eight digits. Here too, the score is equal to the maximum of digits repeated correctly. Forward and backward scores are added to obtain a total score, such that scores can range from 0 to 17. In the absence of tyrosine effect on this measure, as in earlier studies (van der Schaaf et al., 2013), the average total digit span across two days was selected, because it was thought to provide a more reliable estimate of working memory capacity. The total scores were averaged across the assessments and used as a covariate of interest in the analysis (see Statistical analyses section).

MRI acquisition

MRI data were acquired on two different days. Each MRI session lasted ~90 minutes. Working memory task data were collected in the last run (of ~ 30 minutes) of each session after the anatomical scan. Visual stimuli were projected on a screen and were viewed on a mirror attached to the head coil. Responses were given on a MR-compatible button-box located with comfortable access of the right hand (index and middle finger).

Whole-brain imaging was performed on a 3.0 T MRI scanner (Magnetom Skyra, Siemens Medical Systems, Erlangen, Germany) equipped with a 32-channel head coil. During task performance, a total of 900 images with blood-oxygen level-dependent (BOLD) contrast were acquired using a whole-brain T2*-weighted gradient echo multi-echo echo planar imaging (EPI) sequence (34 axial slices per functional volume in ascending order; repetition time, 2070 ms; echo-times, 9.0, 19.3, 30.0, and 40.0 ms; field of view, 224 x 224 mm; flip angle, 90°; 64 x 64 matrix; 3.5 mm in-plane resolution; 3 mm slice thickness; 0.5 mm slice gap). This is a method that uses accelerated parallel imaging to reduce image artifacts and acquires images at multiple echo times following a single excitation (Poser et al., 2006). Before the task, 30 images with the same pulse sequence as used for the task were acquired during resting-state, to determine optimal weighting of echo times for each voxel. For within-subject registration purposes, a whole-brain structural image was made before the task run, using a T1-weighted magnetization prepared, rapid-acquisition gradient echo (MP-RAGE) sequence (192 sagittal slices; repetition time, 2300 ms; echo time, 3.03 ms; field of view, 256 x 256 mm; flip angle, 8°; 256 x 256 matrix; 1.0 mm in-plane resolution; 1.0 mm slice).

Statistical analyses

Behavioral analysis

Behavioral analyses were performed on response times (RT) and d'. Following signal detection theory (Green and Swets, 1966), behavior on a Yes/No task can be broken down into the sensitivity to discriminate target from non-target (d') and an estimate for the overall tendency to judge stimuli as targets (criterion). As our research question concerned working memory performance instead of an overall response tendency, we report d' in the main text and criterion in Supplemental Material 5.1. In line with the standard approach to calculate d' values, we subtracted the z-score that corresponds to the false-alarm rate from the z-score that corresponds to the hit rate (Stanislaw and Todorov, 1999) per task condition per drug (see Figure 5.2C). As outlined in the methods section, half of the non-matches were distractors. To be able to take into account probe type in the analyses, we calculated two separate d' values: once correcting target responses for false alarms after novel probes (FA_{nov}) and once correcting for false alarm rate after distractor probes (FA_{dis})(see Figure 5.2B and 5.2C).

Mean RTs and d' data were normally distributed (Shapiro-Wilk test of normality: $p > 0.1$) and therefore analyzed with 2 separate repeated measures ANOVA using SPSS 23 (IBM Corp., Armonk, N.Y., USA). We included as within-subject factors drug (2 levels: tyrosine vs. placebo), condition (2 levels: Ignore vs. Update) and probe type (3 levels for RT: Target, Novel, Distractor; 2 levels for d': hit rate corrected for Novel vs Distractors). Effects were considered statistically significant if the p-value was smaller than 0.05. Given that our hypothesis concerned the direct contrast between ignore and update conditions, we report analyses in the main text that contrast directly the two levels (Update versus Ignore). However, for completeness, we report in Supplemental Material 5.2 identical analyses, but then including three condition types (Ignore, No interference, Update).

MRI analysis

Preprocessing

Preprocessing was performed using Statistical Parametric Mapping 8 (SPM8; Wellcome Trust Center for Cognitive Neuroimaging, UK; http://www.fil.ion.ucl.ac.uk/spm) running in MATLAB and proceeded in four steps. First, multiecho images were combined based on the parallel acquired inhomogeneity desensitized algorithm (Poser et al., 2006), using in-house built MATLAB software. Using the resting-state scans that were collected before the start of the task, the software

computed the optimal weighting of echo times for each voxel (after applying a smoothing kernel of 3mm full-width at half-maximum) by calculating the contrast-to-noise ratio for each echo per scan. Next, for head motion correction, the software estimated the iterative rigid body realignment that minimizes the residual sum of squares between the first echo of the first scan and all other scans. These estimated parameters were then applied to all other echos, realigning all echos to the first echo of the first scan. Finally, the four echo images of each scan were combined into single images using the computed optimal echo time weightings. Second, after checking data quality (i.e., for signal intensity spikes: see below), the combined and realigned functional images were corrected for differences in acquisition times across slices, resampling all slices in time relative to the middle (i.e. 17th) slice using Fourier interpolation. Third, for the purpose of normalization, i) functional and anatomical data were first co-registered to standardized stereotactic space (Montreal Neurological Institute, MNI) templates (spm8/templates/EPI.nii and spm8/templates/T1.nii), using the mutual information criteria method (Studholme et al., 1999), ii) the anatomical image was segmented and normalized to the International Consortium for Brain Mapping space template for European brains using linear and non-linear deformations (Ashburner and Friston, 1999, 2005), iii) the bias-corrected structural image (output from segmentation) was spatially co-registered to the (mean) functional images using the mutual information criteria method (Studholme et al., 1999) and, finally, iv) the transformation matrix resulting from segmentation was used to normalize the functional images (resampled at voxel size 2×2×2 mm) and anatomical image. Lastly, functional images were spatially smoothed using an 8-mm full-width half-maximum Gaussian kernel.

The data quality check for signal intensity spikes indicated that out of 58 sessions, 53 sessions did not contain any spikes, as defined by a fractional deviation in of the slice mean activity in a certain volume of larger than 0.3 compared to the average signal. Four sessions evidenced spikes in one (n = 3) or two (n =1) slices, which we removed and replaced by an average signal of the identical slice in the previous and next volume in time. However, we excluded one participant from further analyses, because the number of spikes was disproportionally high (25) and we refrained from correcting raw data to such a great extent.

First-level modeling

First-level statistical analysis involved a mass-univariate approach based on general linear models (GLM) in SPM12, comprising three steps. First, each subject's whole-brain BOLD data were modeled with a GLM, including both experimental

sessions. For each session, the following 13 task-related regressors were modeled: initial encoding stimuli, task conditions (Update, No interference, Ignore), probe type per condition (target and novel for all 3 conditions, distractor for ignore and update only) and end of block feedback. Task-related regressors were created by convolving box-car functions (initiated at the onset of the event) with a canonical hemodynamic response function. The box-car function spanned the fixed duration of stimulus presentation of 2 s for the first four predictors (i.e. constant epoch model); for probe regressors, it spanned the length of subject's response time (i.e. variable epoch model). Following the approach of (Lund et al., 2005), 24 nuisance regressors were included in the model: the six realignment parameters used to realign each image, the square of these realignment parameters, the first derivative of these realignment parameters, and the realignment parameters used to realign the previous volume (to account for spin-history effect; (Friston et al., 1996). In addition, we took into account CSF signal based on each individuals' segmented T1 scan to account for movement-related intensity changes and physiological noise. Low frequency drifts were controlled using a discrete cosine transform with cutoff of 128 s. Serial correlations in the fMRI signal were estimated using restricted maximum likelihood estimates of variance components using a first-order autoregressive model. The resulting non-sphericity was used to form maximum-likelihood estimates of the activations. Microtime onsets were adjusted to take into account the earlier slice-timing correction. Second, we performed time series statistical analysis using restricted maximum likelihood estimation (i.e. model estimation). Third, to assess task and intervention effects, we generated for each participant the contrast images of Ignore > Update and Update > Ignore across experimental sessions. Of special interest, given our research question of demand-specific tyrosine effects, was the interaction of drug (tyrosine vs. placebo) and task condition (Ignore vs. Update). These contrasts were also generated per participant on the first level.

Second-level modeling

First-level contrasts were then used for the second level analyses to test consistent effects across participants. One-sample t-tests were calculated based on these contrasts. Group statistical maps were tested for significance using cluster level inference (cluster-defining threshold, $P<0.001$; cluster probability of $P<0.05$, family wise error-corrected for multiple comparisons). Reported local maxima correspond to Montreal Neurological Institute (MNI) space. Activations were localized with the aid of multi-atlas labeling of human brain structures (Landman et al., 2012). Maximum probability tissue labels were provided by Neuromorphometrics, Inc. (http://www.neuromorphometrics.com/) under academic subscription and were

based on 30 MRI scans originating from the OASIS project (http://www.oasis-brains.org/).

Control analyses

We performed a number of control analyses, in which we assessed 1) whether the main finding (Drug x Condition x Probe in d') remains significant when including, one at a time, the perhaps confounding factors in the repeated measures ANOVA: order of drug administration, gender, age, and NLV scores (as a measure of verbal intelligence) and 2) whether the effect of interest interacts with these factors. Age and NLV scores were mean-centered and added as covariates. Order of drug administration and gender were added as between subject factors.

fMRI-behavior association

To assess a relationship between the tyrosine-effects that we observe in the fMRI signal with behavior, we extracted contrast estimates of the interaction of drug (tyrosine vs. placebo) and task condition (Ignore vs. Update) for each participant of significant clusters (using MarsBaR, Brett, Anton, Valabregue, Poline, 2002). We then calculated (non-parametric) correlations between extracted beta values with according behavioral effects in RT and d'.

Exploratory analyses

In addition to our primary, planned analyses, we conducted several exploratory analyses. Since these analyses were data-driven or an *a priori* hypothesis was lacking, we base our conclusions primarily on descriptive statistics (e.g. effect sizes) and not inferential statistics (e.g. test statistics and p-values; Wagenmakers et al., 2012).

Individual differences in putative proxy measures of dopamine

Given the earlier observations that effects of manipulating catecholamine transmission on cognitive control depended on (a proxy of) baseline levels of dopamine (Cools and D'Esposito, 2011; Swart et al., 2017), we included participants' mean-centered trait impulsivity (BIS-11) and working memory capacity (digit span average) scores as covariates in the repeated measures analyses. Likewise, we included these putative proxy measures in two separate 2nd level t-tests in the fMRI analyses to assess baseline-dependent tyrosine effects. Due to missing data for one participant of the trait impulsivity measure, the

sample for the behavioral analysis consisted of 28 participants and for the fMRI analysis 27 (one exclusion due to signal spikes, see Statistical analyses section).

Link with subjective value of cognitive effort

Given recent theorizing about a link between the subjective value (or cost) of cognitive effort and cognitive flexibility versus stability (Inzlicht et al., 2014; Musslick et al., 2018) and given the finding that the effects of tyrosine during this working memory task depend on impulsivity, we assessed whether the tyrosine-induced changes in distractor inhibition in d' (see Results section; Figure 5.3C-D) related to tyrosine-effects on an independent task that was administered in the same session in the same participants: the cognitive effort discounting task (Chapter 4). We therefore calculated parametric correlations between tyrosine-induced changes in subjective value and tyrosine-induced changes in the condition–by-probe interaction on d'.

RESULTS

Behavior - task effects

Participants performed above chance on the update/ignore working memory task, evidenced by an overall proportion of 0.80 (SD = 0.09) and 0.79 (SD = 0.08) correct responses on the placebo and tyrosine session, respectively. Summary scores of the behavioral performance in terms of response times (RTs), hit and false alarm rates and d' are presented in Table 5.1. Statistical analyses were performed of RTs and d'

In line with earlier work (Fallon et al., 2016), performance was sensitive to the task manipulation: There was a main effect of condition on d', the estimate of participants' sensitivity to targets corrected for the propensity to make a target response (false alarms; condition effect: $F(1, 28 = 79.9$, $p < 0.001$; Figure 5.2A). Specifically, participants performed better in the update versus ignore condition. The same effect was found on response times (condition effect: $F(1, 28) = 24.5$, $p < 0.001$; Figure 5.2B), due to shorter response latencies in the update relative to the ignore condition.

Probes consisted of targets and non-targets, of which the non-targets could either be novel shapes or distractors. A distractor or lure in the update condition was a shape that was presented during encoding; in the ignore condition the distractor was presented during the intervening phase. Probe analysis showed that response times were faster and d' was higher for novel probes compared

with distractor probes (probe effect in RT: $F(2, 56) = 2.5$, $p = 0.090$, novel versus distractor probe: $F(1, 28) = 7.9$, $p = 0.009$; probe effect in d': $F(1, 28) = 9.2$, $p = 0.005$). The effects of task condition on d' and RT were not statistically significant (condition x probe for d': $F(1, 28) < 0.1$, $p = 0.918$; for RT: $F(2, 56) = 1.1$, $p = 0.354$).

One might argue that participants could close their eyes during ignore trials to reduce distraction. However, this in unlikely for multiple reasons. First, distracting stimuli were presented at the same time as the condition cue, hence strategically closing eyes would lead to an overall performance decline. Second, there is evidence that distraction in the ignore trials impaired performance, which would not be the case if the eyes were closed: within the ignore condition, participants performed more poorly when distractors were probed compared with novel probes (d' distractor vs novel probes: $F(1, 28) = 9.2$, $p = 0.005$) and participants performed more poorly on ignore trials compared with no interference trials, indicating that distractors were actually processed (see Supplemental Material 5.2: d' ignore vs. no interference: $F(1, 28) = 14.8$, $p = 0.001$).

TABLE 5.1 | Task performance

Drug	*Cond.*	*Probe*	*RTs*	*d'*	*Hit*	*False alarm*
TYR	**Ignore**	**Target**	1226 (153)	-	0.66 (0.20)	-
		Distract	1183 (189)	1.21 (0.73)	-	0.25 (0.11)
		Novel	1157 (166)	1.54 (0.74)	-	0.17 (0.12)
	Update	**Target**	1129 (176)	-	0.80 (0.15)	-
		Distract	1118 (183)	2.02 (0.62)	-	0.16 (0.10)
		Novel	1125 (197)	2.06 (0.59)	-	0.16 (0.10)
PLA	**Ignore**	**Target**	1208 (158)	-	0.68 (0.20)	-
		Distract	1194 (170)	1.38 (0.70)	-	0.21 (0.12)
		Novel	1163 (159)	1.38 (0.57)	-	0.21 (0.11)
	Update	**Target**	1138 (162)	-	0.80 (0.15)	-
		Distract	1153 (190)	1.95 (0.73)	-	0.19 (0.14)
		Nov	1080 (195)	2.25 (0.64)	-	0.12 (0.09)

Summary scores (mean, standard deviation in parentheses) of task performance reported per drug, task condition and probe type. RTs are presented in ms. Analyses were performed on response times and d', which corresponds to the z-scored difference between hit and false alarm rates per probe-type (novel versus distractor). Hit and false alarm rates are presented for intuitive interpretation.

Behavior – tyrosine effects

Contrary to our prediction, the effect of tyrosine administration on performance did not reach statistical significance, also not as a function of the task conditions update versus ignore (for d': drug x IG vs UP: $F(1, 28) = 0.1$, $p = 0.724$; for RTs drug x IG vs UP: $F(1, 28) < 0.1$, $p = 0.990$), nor as a main effect (drug effect for d': $F(1, 28) = 0.1$, $p = 0.753$; for RT: $F(1, 28) < 0.1$, $p = 0.986$),

We assessed tyrosine effects as a function of probe types: including the factor probe-type revealed a significant modulation by tyrosine in d' (drug x condition x probe: $F(1, 28) = 9.0$, $p = 0.006$), but the effect on RTs was not significant (drug x condition x probe: $F(2, 56) = 1.5$, $p = 0.242$). A post-hoc test indicated that tyrosine significantly impaired distractor inhibition on ignore trials, evidenced by an increase in the degree to which a distractor versus novel probe impaired performance (drug x probe: $F(1, 28) = 6.6$, $p = 0.016$). Tyrosine numerically improved distractor inhibition on update trials, yet the effect was not statistically significant ($F(1, 28) = 3.2$, $p = 0.084$; Figure 5.2C-D). Further break-down of these interactions indicate that on placebo, participants exhibited a significant distractor cost (novel – distractor) on update trials, but the effect was not statistically

significant on ignore trials (probe: $F(1, 28) = 7.9$, $p = 0.009$; probe effect in ignore: $F(1, 28) < 0.1$, $p = 0.992$). The pattern reversed under tyrosine, where the distractor cost was only significant on the ignore trials (probe: $F(1, 28) = 10.1$, $p = 0.004$; probe effect in update: $F(1, 28) = 0.1$, $p = 0.748$). A summary of statistical effects is presented in Supplemental Material 5.3.

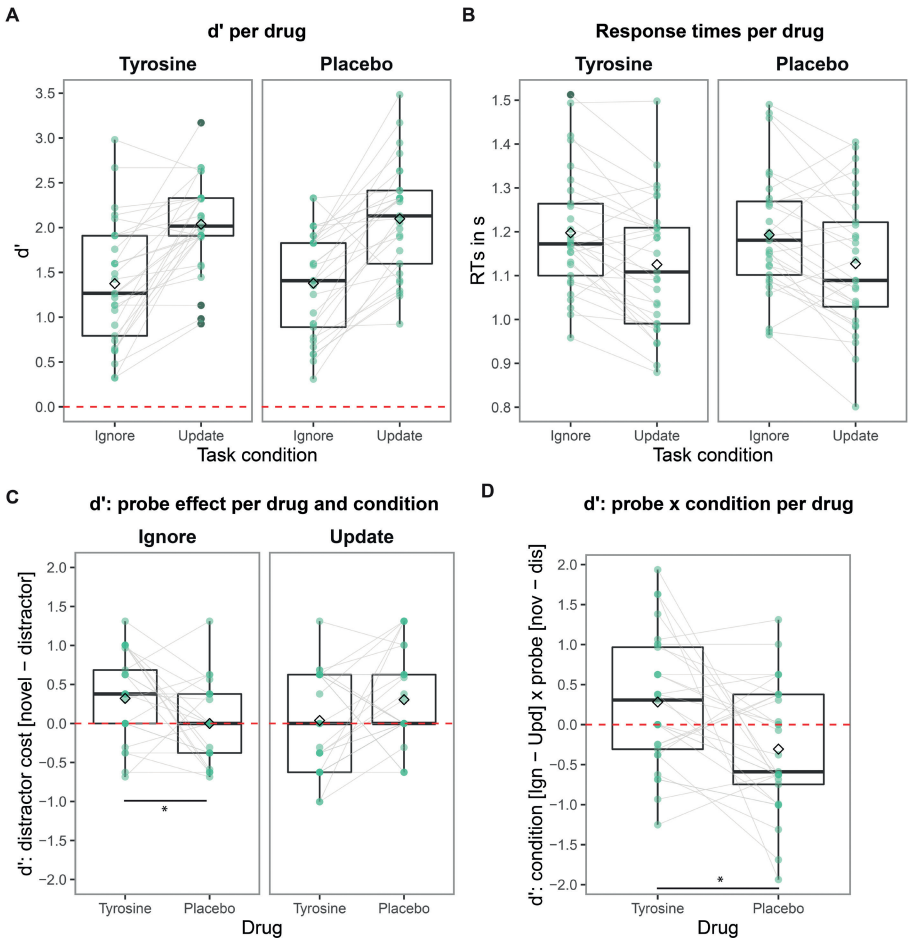


FIGURE 5.3 | Performance on the update/ignore working memory task as a function of task conditions and drug (tyrosine and placebo). Performance did not differ between drug sessions. The horizontal lines in the boxplots represent the median, the diamond represents the mean and green dots are the subject-specific mean, gray lines connect within-subject data points. Outliers are marked by gray dots. **A** d′, the estimate of participants' sensitivity to targets corrected for the propensity to make a target response (false alarms) is significantly lower for ignore than update trials across drug sessions. **B** Response times are

longer for ignore than update trials. **C & D** Tyrosine-effects as a function of probe type (novel versus distractor) in d' (drug x condition x probe). Tyrosine increases the distractor cost in ignore relative to update trials, compared with placebo. * indicates significance at $p < 0.05$. **C** Distractor costs in d' (novel probe – distractor probe) as a function of drug and condition. **D** Condition effects of distractor costs as a function of drug.

fMRI – task results

Consistent with two previous studies using a similar version of this task (Fallon and Cools, 2014; Fallon et al., 2016), intervening stimuli that had to be ignored elicited differential BOLD responses than when they had to be used to update working memory. Ignoring distracting stimuli significantly ($p < 0.05$, whole-brain FWE-corrected) increased BOLD signal in bilateral middle frontal gyri, bilateral angular gyri, right medial/superior frontal gyrus and left precuneus. The reverse contrasts (Update > Ignore) revealed significant clusters of BOLD signal in bilateral supplementary motor cortex, bilateral precentral gyri and left fusiform gyrus (Figure 5.4A). Significant effects observed in whole-brain analyses are displayed in Table 5.2.

fMRI – tyrosine effects

The administration of tyrosine significantly increased update- (versus ignore-) related activity in the right anterior cingulate gyrus/ medial frontal gyrus relative to placebo ($P_{cluster\_FWE} = 0.035$, cluster size = 128 voxels, T = 5.6, peak x, y, z = 12, 42, 4; Figure 5.4B) in a whole-brain analysis. The reverse contrast did not reveal any significant effects. In addition, we assessed tyrosine effects in regions of interest, which were defined by the task-effects across drug sessions (Figure 5.4B). This analysis did not show any significant tyrosine effects.

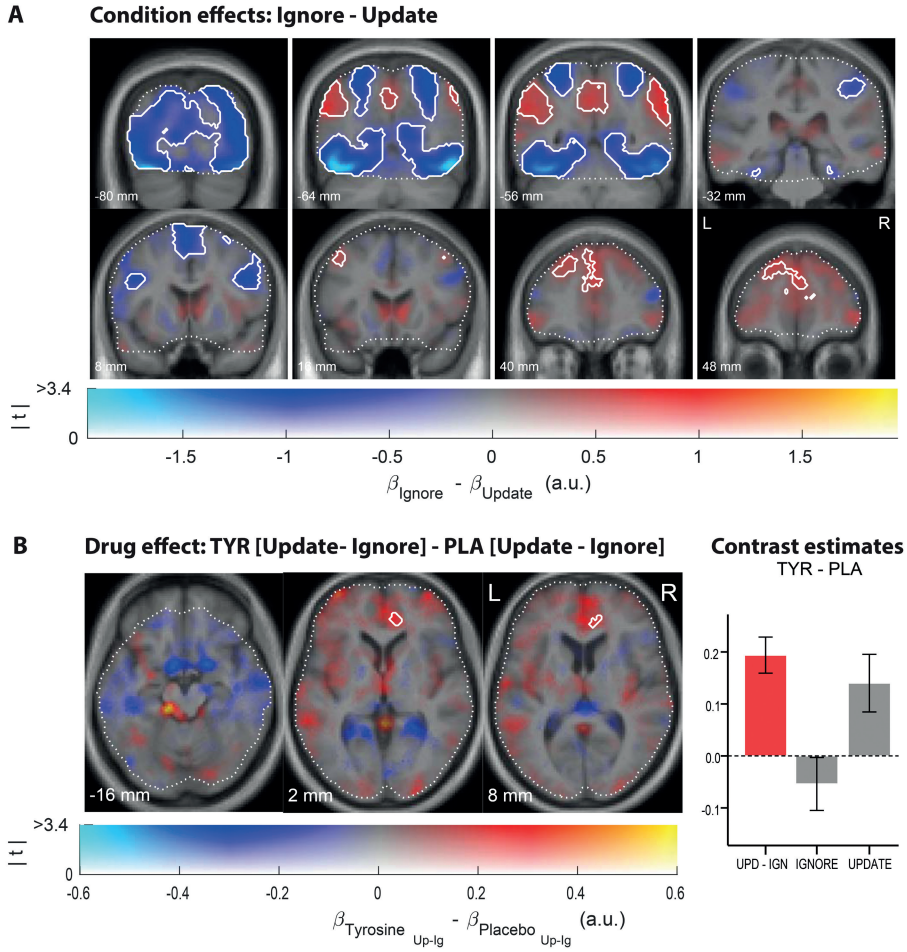


FIGURE 5.4 | A Main effect of task conditions across drug sessions. Maps are dual-coded and simultaneously display the contrast estimate (x-axis) and un-thresholded values for the task contrast (y-axis) in blue for Update (- Ignore) and in red for Ignore (- Update) conditions. Thus, the hue indicates the size of the contrast estimate, and the opacity indicates the height of the t-value. Significant clusters (cluster-level corrected, FWE < p 0.05) are encircled in white. Voxels that were included in the analysis (whole-brain) are marked by a dotted line. The coordinates correspond to the standard MNI brain. **B** Drug effects on the contrast between task conditions: update and ignore. Setup of this figure is identical to A. Analyses reveal a significant interaction between drug [tyrosine > placebo] and task condition [update > ignore] in the right anterior cingulate / medial frontal gyrus. Extraction of contrast estimates from the significant clusters for ignore and update condition separately (gray bars) suggests that the effect is primarily driven by a tyrosine-induced increase in activity in update condition. Neuroimaging data are plotted using a procedure introduced by Allen et al. (2012) and implemented by Zandbelt (2017).

Control analyses

We performed a number of control analyses, where we assessed whether the main finding (Drug x Condition x Probe in d') was affected by any of the following, perhaps confounding, factors: order of drug administration, gender, age, and NLV scores (as a measure of verbal intelligence). Results of these control analyses confirm that 1) the effect was still significant when including these factors, one at a time as covariates (for continuous) or between-subject factors and 2) the variables did not interact with the effect of interest (for all details, see Supplemental Material 5.5).

fMRI – behavior correlations

We extracted beta estimates for the drug-by-condition interaction from the cluster that showed significant tyrosine effects: the right ACC / medial OFC. The extracted activity did not significantly correlate with tyrosine-induced condition effects in d' ($r = 0.09$, $p = 0.634$) or RT ($r = -0.09$, $p = 0.653$).

TABLE 5.2 | Results of fMRI analyses

Contrast name	**Cluster size**	**t-value**	**p-value *(FWE, cluster)***	**p-value *(FWE, voxel)***	**Peak MNI coordinate (x, y, z)**
Tyrosine > Placebo	None				
Placebo > Tyrosine					
L/R suppl. motor cortex / R superior frontal gyrus	142	4.72	0.022	0.665	-4, 14, 64
Update > Ignore					
L fusiform gyrus	20983	10.89	< 0.001	< 0.001	-40, -62, -12
L/R suppl motor cortex	952	8.68	< 0.001	< 0.001	-4, 2, 64
L precentral gyrus	838	7.38	< 0.001	0.004	-50, -4, 44
R precentral gyrus	1034	6.76	< 0.001	0.016	50, 8, 36
Ignore > Update					
L angular gyrus	1005	8.70	< 0.001	< 0.001	-54, -58, 34
L precuneus	1067	6.48	< 0.001	0.029	-4, -52, 38
R angular gyrus	930	6.26	< 0.001	0.046	58, -48, 34
L middle frontal gyrus	968	5.71	< 0.001	0.143	-38, 22,38
R middle frontal gyrus	153	5.31	0.024	0.300	38, 24, 44

Table 5.2 Continued

Contrast name	Cluster size	t-value	p-value *(FWE, cluster)*	p-value *(FWE, voxel)*	Peak MNI coordinate (x, y, z)
R medial/ superior frontal gyrus	159	4.74	0.020	<0.001	12, 60, 16
Tyr > Pla for Ign > Up	None				
Tyr > Pla for Upd > Ign					
R anterior cingulate gyrus / R medial superior frontal gyrus	128	5.58	0.036	0.198	12, 42, 4
Exploration: Drug x Condi x Imp					
L ant. insula/ L putamen/ L postcentral gyrus	900	5.99	< 0.001	0.120	-36, 18, -4
R post. orbital gyrus / R ant. insula	124	4.67	0.037	0.894	32, 16, -18

This table shows all areas that were significant at cluster-level $P_{FWE} < 0.05$ in whole-brain analyses during the intervening phase of the update/ignore working memory task. We present cluster-corrected and voxel-level p-values.

Results of exploratory analyses: individual differences

Given the observation that drug effects vary across individuals as a function of baseline dopamine levels (Cools and D'Esposito, 2011), we assessed whether in this sample tyrosine effects depended on individual differences in putative proxy measures of dopamine: participants' trait impulsivity scores and digit span. We entered the between-subject proxy variables as covariates in two separate repeated measures ANOVAs. Due to missing BIS-scores of one participant, individual differences analyses are conducted in N = 27.

Trait impulsivity

As reported above, tyrosine reduced distractor inhibition on ignore relative to update trials in terms of d'. Entering the between-subject proxy variables as covariates in the primary analyses suggests that the effect of tyrosine on distractor cost on the ignore versus update condition depended on participants' trait impulsivity scores ($F(1, 26) = 9.1$, $p = 0.003$; $r = 0.51$, Figure 5.5A): for more impulsive participants tyrosine decreased the distractor cost on update trials (i.e. cost of letting go initial stimulus: $r = 0.56$) to a greater degree than on ignore trials ($r = 0.13$), thus improving cognitive flexibility.

Paralleling these behavioral analyses, we also assessed in the fMRI data whether tyrosine effects on BOLD signal depended on impulsivity scores. This whole-brain simple regression analysis showed that tyrosine increased update-(versus ignore-) related activity in a cluster containing left anterior insula, putamen and postcentral gyrus ($P_{cluster\_FWE} < 0.001$, cluster size = 900 voxels, T = 6.0, peak x, y, z = -36, 18, -4; Figure 5.5C). The opposite contrast revealed a cluster containing right posterior orbital gyrus / right anterior insula ($P_{cluster\_FWE} = 0.037$, cluster size = 124 voxels, T = 4.7, peak x, y, z = 32, 16, -18). Further exploration showed that the behavioral effect of tyrosine on distractor-inhibition in the update versus ignore condition correlated positively with the neural effect of tyrosine on the left insula/putamen/postcentral gyrus (r = 0.31), but negatively with the neural effect on the right posterior orbital gyrus/insula (r = -0.23). The significant cluster including left anterior insula, putamen and postcentral gyrus shows great overlap with update-(versus ignore-) related task networks when overlaying effects on a lower threshold (see Supplemental Material 5.4).

Trait impulsivity and cognitive effort

Incidentally, the finding that the effects of tyrosine during this working memory task depend on impulsivity is reminiscent of a finding from a different experiment, conducted in the context of the same study, for which the same participants completed a cognitive effort discounting paradigm (COGED) after they came out of the scanner (Chapter 4). This COGED paradigm enabled us to quantify per participant the tyrosine effect on the subjective value of conducting a demanding working memory task: the N-back task (Chapter 4). Exploratory analyses suggested that tyrosine reduced subjective value to a greater degree in more impulsive participants (Chapter 4). Given these results, we assess here the relationship between tyrosine effects on the update/ignore working memory task and tyrosine effects on the subjective value. The probe-dependent tyrosine effect described in 3.2.1 correlates negatively with the tyrosine-effect on subjective value of cognitive effort (medium effect size: r = -0.48): Those participants, who exhibited greater tyrosine-related reduced of subjective value of effort also suffer from stronger tyrosine-induced decreases in distractor-inhibition (Figure 5.5B). These exploratory analyses invite hypothesis-testing in future studies on the link between motivation (i.e. subjective value) and the cognitive flexibility/stability tradeoff. This is of interest in particular given recent suggestions that cognitive effort cost might serve as a motivational signal to bias the system towards greater cognitive flexibility (Cools, 2016; Musslick et al., 2018). There was no evidence for a correlation between tyrosine effects on subjective value and tyrosine effects on

the BOLD signal extracted from the left anterior insula / putamen / postcentral gyrus cluster (r = 0.25, p = 0.295) or on a whole-brain level.

Digit span

Entering the between-subject proxy variables as covariates revealed no significant interactions of digit span scores in behavior (drug x IG vs UP x digit span: F(1,24) = 4.0, p = 0.057; drug x IG vs UP x probe x digit span: F(1, 24) = 3.8, p = 0.064). Including digit span as a covariate in the fMRI analysis did not reveal any significant modulations by tyrosine neither.

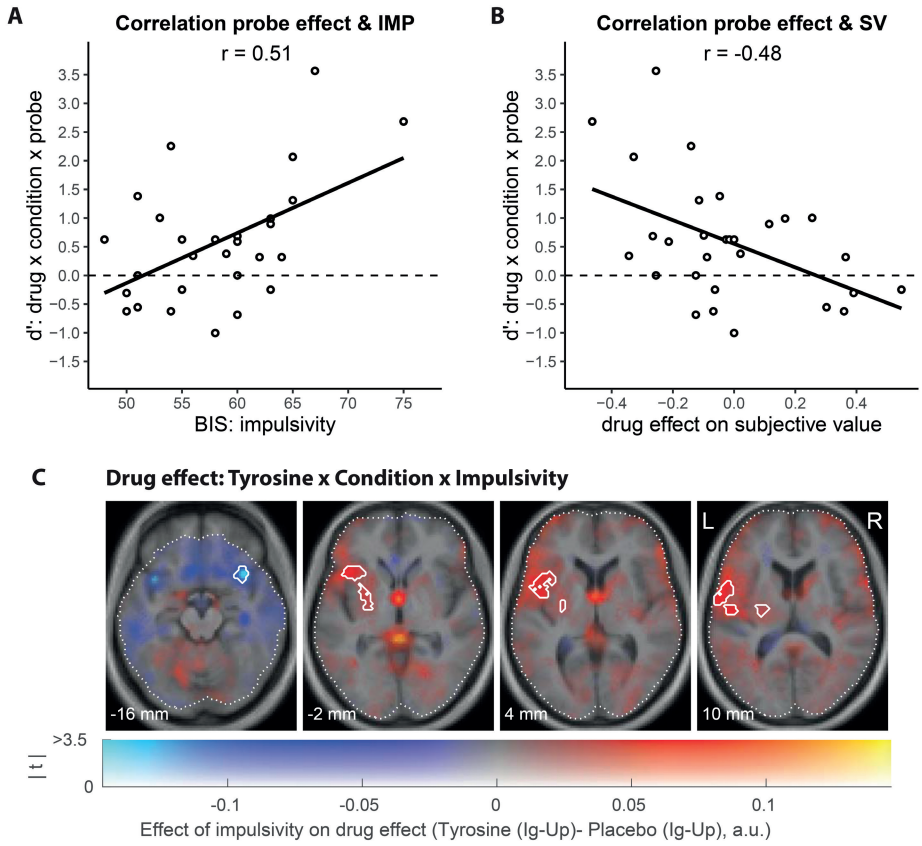


Figure 5.5 | A Positive correlation with large effect size between impulsivity scores and tyrosine-induced condition-dependent effects on distractor cost. **B** Tyrosine effect on condition-dependent distractor cost correlates negatively (medium effect size) with tyrosine-effects on subjective value acquired in a separate cognitive effort discounting

task (see Chapter 4). Dots represent difference scores to visualize the drug x condition x probe-effect: drug effect (tyrosine - placebo) of the condition effect (ignore – update) in distractor cost (novel – distractor). Positive scores on the y-axis reflect larger impairment in distractor inhibition on tyrosine relative to placebo in ignore relative to update trials. The black line represents conditional means given the linear model. **C** The figure displays the significant interaction between drug [tyrosine > placebo] and task condition [update > ignore] as a function of trait impulsivity scores in a cluster containing left anterior insula, left putamen and left postcentral gyrus in red and right posterior central gyrus / anterior insula in blue. Setup of this figure is identical to Figure 5.4.

DISCUSSION

In this study we set out to assess whether the administration of a catecholamine precursor to older participants alters performance on a working memory task with distinct demands for cognitive stability and flexibility. We hypothesized that administering the precursor tyrosine to older adults (age 60-75 years) would improve distractor inhibition, but would impair flexible updating. This hypothesis follows from a range of studies highlighting a role for the PFC and its modulation by dopamine in active maintenance of representations (Brozoski et al., 1979; Durstewitz and Seamans, 2008) and the observation that older adults suffer primarily from impairments in active maintenance (Dunnett et al., 1988) and prefrontal dopamine depletion (Karrer et al., 2017). Thus, we predicted that tyrosine might improve distractor inhibition by acting in the PFC to improve the stabilization and distractor resistance of task-relevant representations. To test our hypothesis, we employed an adapted delayed match-to-sample task, the update/ignore working memory task, that has previously been shown to 1) implicate distinct neural regions when implementing cognitive stability and flexibility, and 2) to be sensitive to neural and behavioral modulations by a catecholamine challenge (Fallon et al., 2016). Specifically, administration of methylphenidate to young adults increased prefrontal activity and improved distractor inhibition at the cost of flexible updating (Fallon et al., 2016).

Task effects

In line with earlier reports, we observed that, across sessions, participants performed well on the task and their performance was sensitive to the task condition: They performed best (i.e. faster and more accurate), when they were required to update their working memory representation, both compared with a control condition in which they remembered certain stimuli without any intervening information and compared with the ignore trials. This difference between update and ignore trials might be a consequence of the timing of the task rather than an index of enhanced flexibility. On update trials the delay between relevant stimuli and the probe is on average 3s shorter than in ignore trials. On ignore trials, in

which distracting stimuli needed to be inhibited, performance was poorest, also compared with the control trials. This shows that the need to inhibit a distractor impairs performance even when timings are matched. As previously observed, ignore and update trials implicated distinct neural regions: Ignoring distracting stimuli increased BOLD signal in bilateral middle frontal and angular gyri, right medial/superior frontal gyrus and left precuneus. Updating was accompanied by bilateral supplementary motor cortex, precentral gyri and left fusiform gyrus activity. While these neural task effects are very similar to those observed in earlier studies using this task (Fallon and Cools, 2014; Fallon et al., 2016), we were surprised to find that updating of working memory representations was not significantly accompanied by activity in the striatum. In earlier versions, updating increased BOLD activity in the putamen (Fallon and Cools, 2014; Fallon et al., 2016). It might be noted that Figure 5.3A suggests that the putamen was implicated in update versus ignore trials, although this signal did not reach statistical significance (only significant on uncorrected voxel level), perhaps due to a lower number of trials or studying an older sample compared with young adults recruited in earlier studies.

Tyrosine effects

Contrary to our prediction, we did not observe a tyrosine-induced shift in overall performance between trials requiring cognitive stability (i.e. ignore) and cognitive flexibility (i.e. update). However, tyrosine had opposite effects on target detection in ignore and update trials as a function of probe type (novel versus distractor). This effect can be summarized as a decrease in cognitive stability: Tyrosine (significantly) increased the distractor cost (distractor – novel) on ignore trials relative to update trials. In the update condition tyrosine numerically improved letting go of initially relevant stimuli, such that the impact of the distractor (i.e. initially encoded stimuli) relative to a novel probe was reduced. These behavioral results suggest that, in older adults, tyrosine enhanced the gating of both relevant and irrelevant information into working memory. Furthermore, while prior work has implicated the striatum in the effects of catecholamine transmission on the gating of working memory representations (Chatham and Badre, 2015; Collins and Frank, 2014), we demonstrate a tyrosine-induced increase in update-related signal in the dorsal medial frontal cortex. While the dorsal medial frontal cortex, including the anterior cingulate cortex, is implicated in many control functions, its activity has also been associated with signaling the value of disengaging in a foraging context (i.e. foraging value (Kolling et al., 2016). As such, an increase in ACC activity has been shown to promote disengagement from a current patch.

There is also strong evidence from work with human volunteers and animals for the involvement of the medial frontal cortex in promoting flexible behavior, including set shifting (Buchsbaum et al., 2005; Floresco et al., 2008b; Stefani et al., 2003) and task-switching (Aarts et al., 2009; Rushworth et al., 2013). In the light of earlier theories of working memory updating, the basal ganglia (BG) is thought to provide a gating signal for controlling updating in the frontal cortex (Hazy et al., 2007). An extension of the model ascribes a key role to the medial frontal cortex for supporting flexible decision-making when environmental contingencies change (Pauli et al., 2011). Due to interconnections between BG and orbitofrontal cortex, gating is enabled by phasic dopamine release in the ventral striatum by neurons in the midbrain. Thus, tyrosine might have impaired distractor inhibition via an increase in phasic dopamine release-dependent gating. In this context, we note that tyrosine also elicited a (sub-threshold) increase in midbrain BOLD signal during update trials (see Figure 5.3B), but this finding should be treated with great caution, because it did not reach significance according to our statistical criteria.

The present finding that tyrosine reduced distractor inhibition in a working memory task concurs generally with a previous observation that the same dose of tyrosine (150 mg/kg), relative to a lower dose, impaired N-back performance in older adults (van de Rest et al., 2017). In addition, those participants with more excessive plasma tyrosine increases showed stronger performance impairments (van de Rest et al., 2017). While the N-back task relies on a mixture of working memory demands, our current study allowed to distinguish flexibility from cognitive stability. Our results suggest that earlier reports on detrimental effects of tyrosine administration might be a result of impairments in specifically the resistance to distraction due to excessive gating of goal-relevant and irrelevant representations. Interestingly, in the current task, we observe that under placebo older adults exhibit rigid rather than flexible behavior, contrasting the idea that aging is associated with greater flexibility (Dunnett et al., 1988; Lindenberger and Mayr, 2014; Wang et al., 2011): probe-type analyses revealed that participants had trouble 'letting go' of the initially encoded stimuli when they needed to update the representation, while there was no significant distractor cost in the ignore condition. This evidence of inflexible cognition concurs with earlier reports on perseverative errors in set-shifting (Gamboz et al., 2009; Ridderinkhof et al., 2002), failed reversals in a reversal learning task (Weiler et al., 2008) and increased task-switching costs (Kray & Li, 2002) in healthy older adults. Tyrosine altered this pattern of 'rigidity': it increased distractor cost in ignore trials, but tended to improve letting go of initially encoded stimuli.

Tyrosine effects – individual differences

The present observation that catecholaminergic drug administration decreases (aspects of) working memory performance is in line with an inverted-U shaped interpretation which suggests that too little but also excessive dopamine in the prefrontal cortex is detrimental for cognitive performance (Cools and D'Esposito, 2011). To account for individual variability, we conducted exploratory analyses including impulsivity and digit span scores, which have previously been associated with dopamine transmission (Buckholtz et al., 2010; Cools et al., 2008; Landau et al., 2009). These exploratory analyses suggest that the behavioral tyrosine effects depend on individual differences in trait impulsivity. This was evidenced by a correlation with a large effect size: tyrosine reduced the cost of 'letting go' of an initially encoded stimulus to a greater degree in more impulsive participants. Thus trait impulsivity was associated with greater tyrosine-induced biases away from cognitive stability towards flexibility. Moreover, trait impulsivity was also associated with tyrosine-induced increases in flexible update-related BOLD signal in a cluster containing left insula, putamen and postcentral gyrus. An increase in cognitive flexibility and activity in a cluster containing putamen might be consistent with a striatal role in excessive gating of working memory representations resulting in lower cost of a distractor in more impulsive participants. This pattern of better relative updating and increased frontostriatal BOLD signal parallels earlier observations in young adults, where bromocriptine improved flexible updating (i.e. switching) and increased switch-related striatal activity in high, but not low impulsive participants (Cools et al., 2007). Also, irrespective of impulsivity, bromocriptine has been reported to increase switch-related BOLD signal in the striatum (Stelzel et al., 2013). Note that in earlier versions of this update/ignore working memory task, updating had also been accompanied by activity in the putamen (Fallon et al., 2016). Overlaying the impulsivity-dependent cluster with task-related BOLD signal suggested stronger overlap with an update-related than ignore-related network. The tyrosine-induced shift towards more cognitive flexibility and less stability was also accompanied by a reduction in right frontal signaling (insula / posterior orbital gyrus), mainly in more impulsive participants. This effect of a reduction in right frontal activity in combination with impaired inhibition has been described before with respect to response inhibition, but also inhibition in working memory paradigms in ADHD patients and patients with right frontal lesions (Aron et al., 2014; Clark et al., 2007).

Finally, we observed, in exploratory (post-hoc) analyses, a positive correlation (of medium effect size) across participants between tyrosine-induced decreases in distractor-inhibition and tyrosine-induced decreases in the subjective value of

cognitive effort (Chapter 4). The (high-impulsive) individuals who exhibited the greatest shift away from stability towards flexibility with tyrosine also expressed the greatest increase in cognitive effort costs. While in need of replication, this observation might be understood in terms of recent resource allocation accounts of cognitive control costs according to which the (subjective) cost of cognitive effort serves as a motivational signal to prevent over-fixation on a current ongoing task and to promote cognitive flexibility and switching to alternative tasks (Cools, 2016; Inzlicht et al., 2014; Kool et al., 2010; Kurzban et al., 2013). Specifically, the present preliminary finding raises the hypothesis, to be tested in future studies, that changes in catecholamine transmission elicit a shift in flexibility/stability tradeoff in working memory by altering the subjective cost of mental effort.

LIMITATIONS

We observed that tyrosine altered cognitive control in a demand-specific manner. However, the effect was subtler than anticipated and only surfaced when taking probe-type into account. Thus rather than changing hit rates, tyrosine modulated false alarm rates for novel versus distractor trials. A second note of caution pertains to our assumption that tyrosine increased central catecholamine synthesis. While peripheral blood plasma levels of DOPAC, a dopamine metabolite, were increased after tyrosine relative to placebo, we cannot ensure that central catecholamine levels were affected. In this context, we highlight that tyrosine does not selectively alter dopamine: oral administration in young adults has also been shown to affect plasma noradrenaline levels (Kishore et al., 2013). Lastly, given that we only tested older adults in a within-subject design, our study does not speak to age-related changes in working memory processes or BOLD signal. Future studies are needed to assess whether our findings are specific to older adults by comparing task and intervention effects to younger participants.

CONCLUSION

In this pharmacological fMRI study, we have shown that the administration of the catecholamine precursor tyrosine to older adults (60-75 years) altered working memory processes in a demand-specific manner. Contrary to our prediction, tyrosine reduced rather than enhanced cognitive stability (i.e. distractor resistance), evidenced by a larger distractor cost on trials requiring stabilization compared with flexible updating. This effect was accompanied by a tyrosine-induced increase of update- versus ignore-related activity in right anterior cingulate cortex / medial orbitofrontal cortex. These findings support the idea that

effects of a catecholamine intervention depend on the type of cognitive demand required and further suggest that, instead of increasing stability, tyrosine in fact increased distractibility in older adults, perhaps by promoting gating of relevant and irrelevant information into working memory.

SUPPLEMENTAL MATERIALS OF CHAPTER 5

SUPPLEMENTAL MATERIAL 5.1 | Criterion

Following the signal detection theory, behavior can be broken down into the sensitivity to discriminate target from non-target (see d' analysis above) and an estimate for the overall tendency to judge stimuli as targets. The latter is referred to as criterion (c) (Stanislaw and Todorov, 1999). A value of 0 means that participants maximize hits and false alarms. Negative values represent a response bias towards 'yes', and positive values a bias toward responding 'no'. The mean criterion in our sample was 0.23 (0.41), indicating that participants had a conservative criterion of judging a stimulus as a target (i.e. miss-oriented). Taking into account task condition, we observe a trending effect (condition: $F(1,28) = 3.9$, $p = 0.052$). The criterion is lowest in update (0.12, SD = 0.40), then ignore (0.22, SD = 0.40), and highest in no interference (0.35, SD = 0.41) trials. Participants' criterion was not altered by tyrosine (drug: $F(1, 28) = 0.1$, $p = 0.830$) or tyrosine as a function of condition (drug x condition: $F(1, 28) = 0.4$, $p = 0.520$).

SUPPLEMENTAL MATERIAL 5.2 | Behavioral results including No interference trials

There was a main effect of condition on d' (condition effect: $F(2, 56 = 29.4$, $p < 0.001$). Specifically, participants performed best in the update condition (vs. no interference: $F(1, 28) = 11.7$, $p = 0.002$; vs. ignore: $F(1, 28) = 79.9$, $p < 0.001$), and had the lowest d' values when they were distracted, i.e. in the ignore condition (vs. no interference: $F(1, 28) = 14.8$, $p = 0.001$). The same effect was found on response times (condition effect: $F(2, 56) = 9.8$, $p < 0.001$), due to the shortest response times in the update condition (vs. no interference: $F(1, 28) = 5.6$, $p = 0.025$; vs. ignore: $F(1, 28) = 24.9$, $p < 0.001$). Response times did not differ significantly between the ignore condition and no interference ($F(1, 28) = 2.9$, $p = 0.103$).

The administration of tyrosine did not significantly alter overall performance, also not as a function of the three task condition (for d': drug: $F(1, 28) = 0.5$, $p = 0.496$; drug x condition: $F(1, 28) = 0.2$, $p = 0.670$; for RTs: drug: $F(1, 28) < 0.0$, $p = 0.877$, drug x condition: $F(1, 28) = 0.1$, $p = 0.829$). There were no significant probe-dependent modulations by drug in response times (drug x probe: $F(1,28) < 0.1$, $p = 0.990$; drug x probe x condition: $F(1,28) = 2.2$, $p = 0.150$), or d' (drug x probe: $F(1,28) < 0.1$, $p = 0.973$; drug x probe x condition: $F(1,28) = 3.0$, $p = 0.092$).

Entering the between-subject proxy variables (BIS impulsiveness and digit span) as covariates in the model did not show significant interactions with drug and/or task conditions in behavior (all $p > 0.05$).

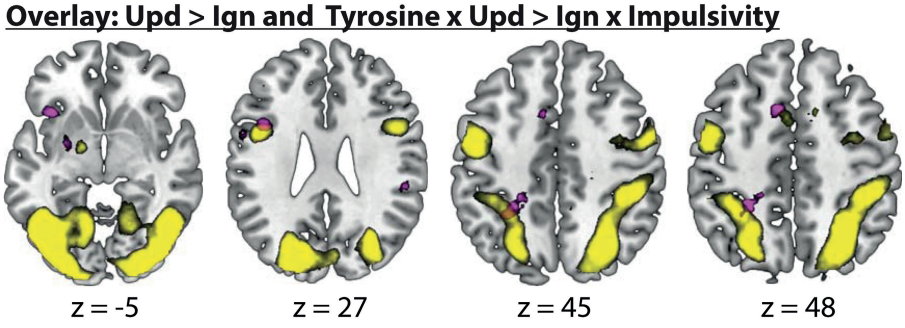
SUPPLEMENTAL MATERIAL 5.3 | Statistical effects

Statistical effects of a priori repeated measures ANOVAs of performance data (d' and RT). In these models, ignore and update conditions were directly contrasted. Drug, condition and probe types were within-subject factors. Bold p-values denote significance at $p < 0.05$.

Effects	Model 1: d'	Model 2: RT
Condition	**F(1,28) = 79.9, p < 0.001**	**F(1,28) = 24.5, p < 0.001**
Drug	F(1,28) = 0.1, p = 0.753	F(1,28) < 0.1, p = 0.986
Drug x Condition	F(1,28) = 0.1, p = 0.724	F(1,28) < 0.1, p = 0.990
Probe	**F(1,28) = 9.2, p = 0.005**	F(2,56) = 2.5, p = 0.090
Probe x Condi	F(1,28) < 0.1, p = 0.918	F(2,56) = 1.1, p = 0.354
Probe x Drug	F(1,28) = 0.1, p = 0.777	F(2,56) = 1.5, p = 0.223
Drug x Condi x Probe	**F(1,28) = 9.0, p = 0.006**	F(2,56) = 1.5, p = 0.242

SUPPLEMENTAL MATERIAL 5.4 | Overlay

Overlay of update-(versus ignore-) related task effects (yellow) and impulsivity-dependent tyrosine effect (violet). Results are displayed at $p < 0.001$, uncorrected, which corresponds to $t > 3.4$. See Table 5.2 and the main text for whole-brain FWE-corrected results.



SUPPLEMENTAL MATERIAL 5.5 | Control models

ANOVA of basic models including putative confounding factors as covariates in d'. Bold p-values denote significance at $p < 0.05$.

*Due to missing NLV scores of 3 participants, this ANOVA contains N = 26 (df = 1, 24).

Effect		NLV*	Order	Age	Gender
Effect of interest:	F(1,27)	**6.7**	**8.6**	**8.6**	**8.9**
Drug x Condi x Probe	p	**0.016**	**0.007**	**0.007**	**0.006**
Effect of interest x confound	F(1,27)	0.3	0.3	<0.1	0.2
	p	0.612	0.589	0.914	0.642

5

CHAPTER 6

Quantifying the cost of cognitive stability and flexibility

This chapter is under review for publication as:

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ABSTRACT

Exerting cognitive control is well known to be accompanied by a subjective effort cost and people are generally biased to avoid it. However, the nature of cognitive control costs is currently unclear. Recent theorizing suggests that the cost of cognitive effort serves as a motivational signal to bias the system away from cognitive stability towards more cognitive flexibility. We asked whether the effort cost of cognitive stability is higher than that of cognitive flexibility. Specifically, we tested this prediction in the domain of working memory by using (i) a delayed response paradigm that allows us to manipulate demands for stability (distractor resistance) and flexibility (flexible updating) of working memory representations, as well as (ii) a subsequent cognitive effort discounting paradigm that allows us to quantify the subjective effort costs assigned to performing the delayed response paradigm. We show strong evidence, in two different samples (28 and 62 participants respectively) that subjective value decreases as a function of demand. Moreover, we demonstrate that the subjective cost of performing a task requiring cognitive stability (distractor resistance) is higher than that requiring flexible updating, supporting the hypothesis that subjective effort cost of cognitive stability is higher than that of flexibility.

INTRODUCTION

Cognitive control often refers to the set of mechanisms required to focus on and pursue a goal, especially in the face of distraction, temptation or conflict. Succeeding to exert cognitive control and focusing on the task at hand is highly valued in our industrialized society, as it allows us to complete our tasks and achieve our long-term goals. Despite its importance, failures of cognitive control are very common. Procrastinating, failing to meet deadlines and performance decrements after fatigue are familiar to most of us.

Why do people fail to exert cognitive control? Focusing on a task carries an effort cost, making people avoid it (Kool et al., 2010), even if such avoidance implies forgoing rewards (Massar et al., 2016; Westbrook et al., 2013). The mechanisms underlying these cognitive effort costs remain elusive. While poor performance on cognitive control tasks has often been explained as limitations in cognitive capacity, more recent accounts shift the focus from capacity to motivation (Botvinick and Braver, 2015). These accounts are supported by experiments that show that performance decrements (caused by effort) can be overcome by increases in incentive motivation, for example as a function of the promise of monetary rewards (Padmala and Pessoa, 2011). According to some such resource allocation accounts, the subjective cost of cognitive effort represents a motivational signal to remain open to alternative opportunities, thus promoting flexibility at the expense of reduced engagement in a current ongoing task (Cools, 2015; Inzlicht et al., 2014; Kool et al., 2010; Kurzban et al., 2013). As our attentional resources are limited (Botvinick and Cohen, 2014; Shenhav et al., 2017), focusing on a given task means that we have to give up on other tasks that require the same set of mechanisms, thus evoking an opportunity cost (Kurzban et al., 2013). Hence, failures of cognitive control can be viewed as stemming not just from failures in *implementation*, but also as a *choice* to pursue alternative tasks that may be more rewarding.

Such a motivational mechanism would be adaptive, given that our constantly changing environment requires a dynamic balance between the cognitive states of focus and flexibility (Cools, 2015, 2016). Focusing is crucial for completing our goals, but flexibility is essential when goals change. Flexibility also allows us to explore alternative ways to solve a problem and come up with new ideas, i.e. to be innovative and creative. According to current theorizing the stability/flexibility tradeoff in working memory is moderated by the strength of current task representations. Strong representations facilitate focusing on a current

task-set at the cost of reduced flexibility, required for e.g. task-switching. Weak representations in contrast allow flexible adaptation but reduce focused intensity.

How do we decide when to be focused and when to relax constraints in order to be flexible? We have previously argued that we arbitrate between a focused (closed) state versus a flexible (open) one, based on a cost-benefit analysis in which the value of cognitive effort corresponds to increased focus and is weighted against its (e.g. opportunity) cost, corresponding to reduced flexibility (Cools, 2016). We thus reasoned that the cost of cognitive stability is higher than that of cognitive flexibility. Here, we investigate this hypothesis by using a novel version of cognitive effort discounting (COGED) paradigm (Westbrook et al., 2013). that allowed us to measure the value that people assign to performing tasks requiring cognitive stability or flexibility. Specifically, rather than asking participants to discount monetary offers to perform the N-back task, which requires both focusing and flexibility at the same time, we asked participants to discount offers to perform a working memory task requiring either maintenance and distractor resistance or updating. This design allowed us to separately quantify the subjective costs of a task with demands for greater stability or flexibility, respectively. We obtained two independent datasets to replicate, and robustly establish the predicted differences between the costs of focus and flexibility.

As in the case of the original COGED paradigm, our paradigm consisted of two stages. In the first stage, subjects performed variants of a well-established color wheel working memory task (Zhang and Luck, 2008). Participants experienced different demands (set sizes 1 to 4) of two conditions of the task. One condition required flexible updating; the other condition required focused distractor resistance. In the second stage, participants made a series of choices about whether or not to repeat one of the task conditions in return for monetary reward. Some trials required choices between either one of the (update or ignore) task conditions versus taking a break. Other trials required direct comparisons between the two (update versus ignore) task conditions.

RESULTS

Working memory task performance

We investigated the effect of demands for working memory stability versus flexibility using a modified color wheel task (Figure 6.1A, see Methods section for more details). Participants were exposed to conditions requiring either distractor resistance (i.e. ignore condition) or flexible updating (i.e. update condition). Every

trial of the paradigm consisted of three phases that were separated by two delay periods. In the first phase (*encoding*), participants saw colored squares, which they always had to memorize. Then after a delay of two seconds, participants saw new colors in the same square locations. In the ignore condition, participants were instructed to maintain in their memory the colors from the encoding phase and not be distracted by the new interfering colors. In the update condition, participants had to let go of their initial representations and update the new stimuli into their working memory. We manipulated the working memory demand by varying the number of stimuli that needed to be remembered. During the response phase, participants had to match the color of one of the relevant squares by clicking with the mouse on a color wheel.

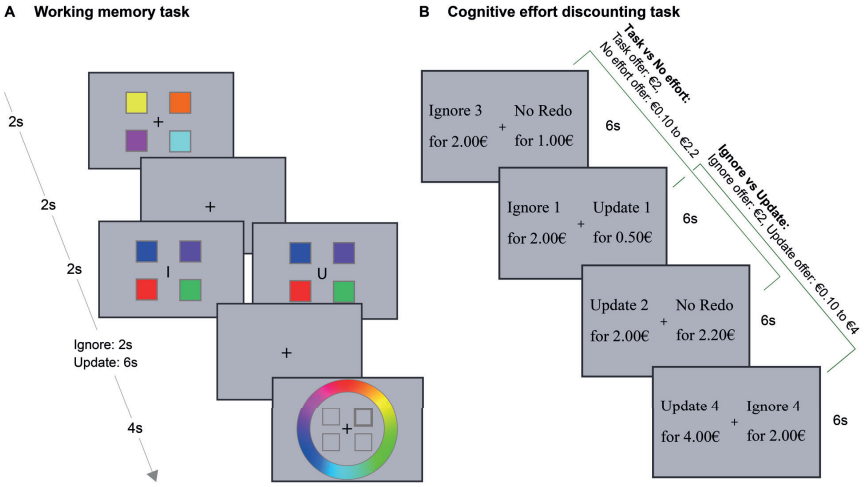


Figure 6.1 | A An illustration of the color wheel working memory task. Every trial of the task consists of three phases. In the encoding phase (2 s), participants need to memorize colored squares. After a delay of 2 s, during the interference phase (2 s), a letter indicates if it is an Ignore (I for ignore) or an updating (U for update) trial. In ignore trials, participants need to maintain in their memory the colors from the encoding phase and not be distracted by the new intervening stimuli. In update trials, participants have to let go of their previous representations and update into their memory the stimuli from the interference phase. Another delay separates interference from the response phase. This delay is 2 s for ignore and 6 s for update trials to match the time that the target stimuli are maintained between conditions. During response phase, participants see a color wheel and black frames of the same squares; they have 4 s to click on the target color for the highlighted square. Demand is manipulated by varying the number of squares from one to four. The example displayed here is of the highest demand. **B** Example trials of the COGED task. Participants perform two versions of choices. In the "task vs no effort" version participants have to choose between repeating a level of ignore or update and not repeating the color wheel task at all ("No Redo"). The task option offer remains fixed at €2 and the no effort "No Redo" option varies from €0.1 to €2.2. In the "Ignore vs Update" trials, participants have to choose between repeating either the ignore or update

condition of the same demand. Ignore offers are always fixed at €2 and update offers vary from €0.1 to €4. Trial duration is 6 s. The trials are intermixed.

Accuracy

Figure 6.2A&B shows accuracy (absolute deviance in degrees from target color) in the color wheel working memory task as a function of set size and task condition (Supplemental Table 6.1 for descriptive statistics and Supplemental Figure 6.1 for precision indices). Performance was sensitive to the demand (i.e. set size) manipulation and, in line with earlier studies contrasting ignore and update trials, participants performed more poorly in the ignore compared with the than update condition (Fallon and Cools, 2014; Fallon et al., 2016). This observation was supported by Bayesian model comparison (Table 6.1), showing strongest support for the model including set size and condition in both studies (BF_{10} =24876 & BF_{10} =5.5e+12). The runner-up model was the one including both main effects and their interaction, which was ~2.3 and ~2 times less likely than the model with the main effects only for experiment 1 and 2 respectively. The effects analysis confirmed the conclusion based on model comparison, showing that accuracy decreased with increasing set size (Experiment 1: $F_{1.52,39.6}$=6.510, p=0.007, BF_{INC}=83; Experiment 2: $F_{1.63,97.7}$=16.998, p=2.8e-6, BF_{INC}=1.6e+10) and that participants performed better on update compared with ignore trials (Experiment 1: $F_{1,26}$=11.068, p=0.003, BF_{INC}=448; Experiment 2: $F_{1,60}$=24.095, p=7.4e-6, BF_{INC}=939) (Table 6.2). Evidence for an interaction effect was not conclusive (Experiment 1: $F_{2.14,78}$=2.205, p=0.116, BF_{INC}=1.3; Experiment 2: $F_{2.32,139.3}$=3.238, p=0.035, BF_{INC}=1.9). We conclude that accuracy decreased as a function of set size and, across set sizes, was worse on ignore relative to update trials.

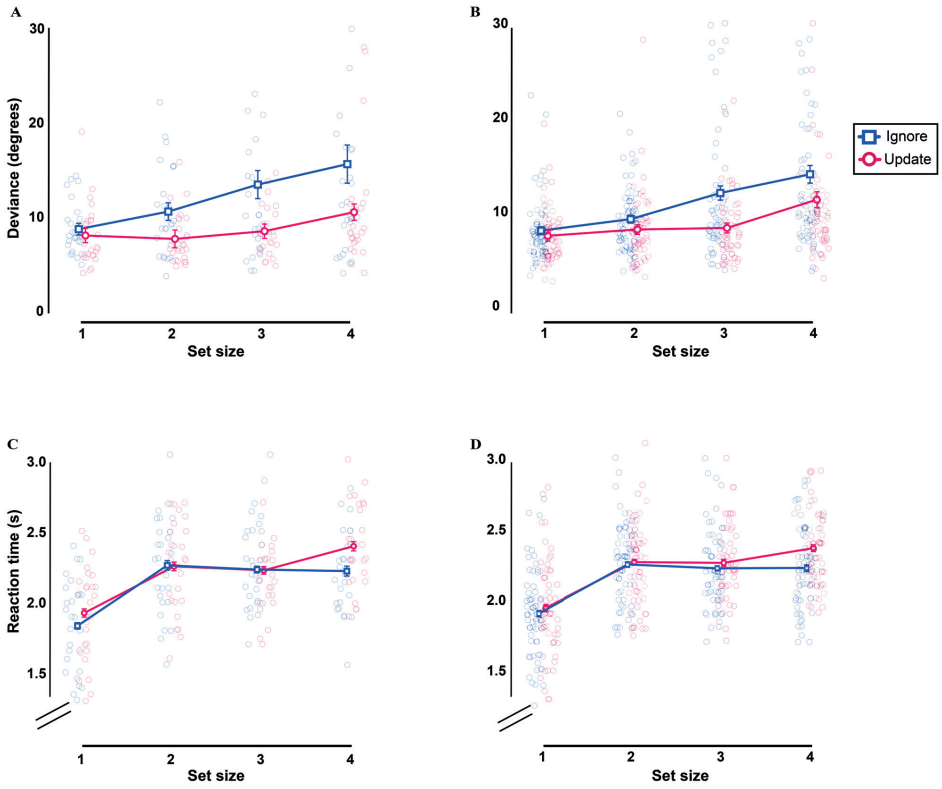


FIGURE 6.2 | Performance on the color wheel working memory task. **A** Median deviance for experiment 1 (27 participants). **B** Median deviance for replication experiment 2 (61 participants). Deviance in degrees from the correct color is displayed here as a function of set size for ignore and update trials. **C, D** Median reaction times as a function of set size for ignore and update conditions. **C** Experiment 1 (27 participants). **D** Experiment 2 (61 participants). Error bars indicate within-participant SEM (Cousineau, 2005; Morey, 2008).

TABLE 6.1 | Model comparison: deviance

Models	BF_{10}	
	Experiment 1	Experiment 2
Condition+ Set size	24875.5	5.5e +12
Condition+ Set size+ Condition* Set size	8023.0	2.7e +12
Set size	48.3	5.8e +9
Condition	263.2	346.2

Model comparison relative to a null model for deviance on the working memory task

TABLE 6.2 | Effects analysis: deviance

Effects	$BF_{inclusion}$		P_{value}	
	Experiment 1	Experiment 2	Experiment 1	Experiment 2
Condition	448.2	939.4	0.003	7.4e-6
Set size	83.2	1.6e+10	0.007	2.8e-6
Condition* Set size	1.3	1.9	0.116	0.035

Effects analysis for deviance in the working memory task

Reaction times

Figure 6.2C&D depicts reaction times (RTs) as a function of set size and condition (Supplemental Table 6.2 for descriptive statistics). Statistical analyses suggest that RTs varied as a function of demand and task condition; participants were responding faster on trials that presented fewer squares (i.e. lower set size) and in the ignore (versus update) condition. In the first experiment, Bayesian model comparison (Table 6.3) showed that the best model was the one including condition, set size and the interaction between the two (BF_{10} =4.8e+31, ~ 1.4 times better than the one also including the interaction). Effects analyses (Table 6.4) confirmed that participants were faster on ignore compared with update trials ($F_{1,26}$=16.436, p=4.1e-4, BF_{INC}=44.6), a very strong set size effect ($F_{3,78}$=64.739, p=4.1e-21, BF_{INC}=∞) and an interaction effect ($F_{2.41,62.7}$=5.643, p=0.003, BF_{INC}=26). In the second experiment, the main effects were in the same direction (set size: $F_{2.4,141}$=90.386, p=1.6e-28, BF_{INC}=∞, condition: $F_{1,60}$=16.179, p=1.6e-4, BF_{INC}=88), but the evidence for an interaction was weaker ($F_{2.7,165}$=4.405, p=0.007, BF_{INC}=3.8). The model that only involves condition and set size was marginally better than the one including the interaction. Thus, the dependence of the set size effect on task demand is not clear.

TABLE 6.3 | Model comparison: RTs

Models	BF_{10}	
	Experiment 1	Experiment 2
Condition+ Set size	6.7e+30	1.4e+53
Condition+ Set size+ Condition* Set size	4.8e+31	1.3e+53
Set size	8.2e+29	2.0e+51
Condition	0.84	3.5

Model comparison relative to the null model for RTs in the working memory task

TABLE 6.4 | Effects analysis: RTs

Effects	$BF_{inclusion}$		P_{value}	
	Experiment 1	Experiment 2	Experiment 1	Experiment 2
Condition	44.6	87.8	4.1e-4	1.6e-4
Set size	∞	∞	4.1e-21	1.6e-28
Condition* Set size	25.5	3.8	0.003	0.007

Effects analysis for RTs in the working memory task

Cognitive effort discounting: To repeat or to avoid?

Next, we quantified the subjective value participants assigned to performing the update and ignore trials. The design of this task was inspired by the temporal and cognitive effort discounting literature (Kable and Glimcher, 2007; Westbrook et al., 2013). To assess subjective value, participants made choices about repeating a level of the color wheel task for a monetary reward (effort option) or not repeating it for a usually smaller reward (no effort option) (Figure 6.1B). The task offer was fixed at €2 and the "no effort" offer varied from €0.1 to €2.2. Every choice was sampled three times to account for response variability. Participants were instructed that after all choices were completed, one of them would be randomly selected and they would repeat a few blocks of that set size and mostly that condition (to reduce predictability). If the "no effort" option was selected they were instructed that they should remain in the testing room for the same amount of time, but they could use their time as they pleased, e.g. make use of their phone or lab computer. They were also informed that receiving the monetary reward would not be contingent on their performance, as long as they put effort into doing the task.

We computed participants' indifference points (IPs) to estimate subjective value. Indifference points reflect the monetary amount offered for the presumably less effortful option at which participants are equally likely to choose one or the other, thus the probability of accepting either option would be 0.5. We calculated the probabilities of accepting the presumably easier offer using binomial logistic regression analysis.

Figure 6.3A&B depicts the logistic regression curves of an example participant for whom it was possible to estimate indifference points (the participant selected both the task and no effort options enough times to fit a logistic regression, see Methods section) for both update (A) and ignore (B) conditions. The indifference point (IP) represents the degree of discounting of the high-effort offer, where an IP

of 2 corresponds to subjective equivalence (given that the offer of the discounted task was always €2, IP = €2 implies that the participant finds the task and the no effort option equally costly). IPs smaller than €2 represent greater discounting (the participant finds the redo option to be more costly than the no-redo option) and thus reduced subjective value.

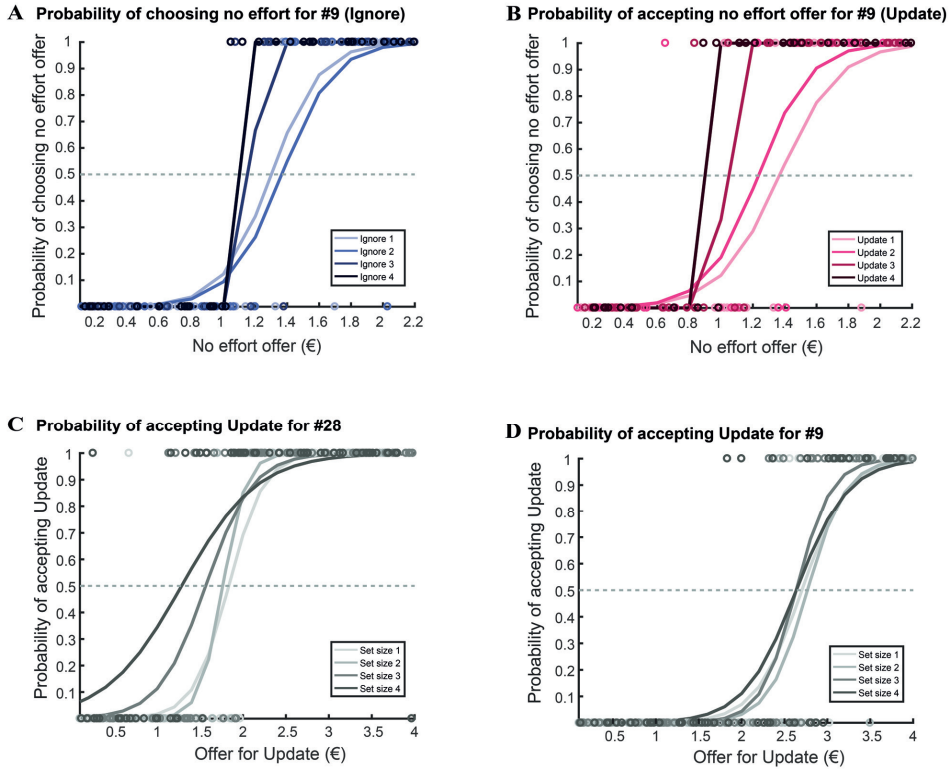


FIGURE 6.3 | Example participant logistic regression curves. **A, B** Logistic regression curves for "task vs no effort" choices of one participant for update (A) and ignore (B) condition. The probability of accepting the "no effort" (i.e. no task) offer (y-axis) is plotted as a function of the amount of money offered for "no effort" (x-axis). Task offer was always €2 for both conditions and all set sizes and the "no effort" offer varied from €0.10 to €2.20. The estimated indifference point is the offer for "no effort" where the probability of choosing to do the task or the "no effort" option is equal (i.e. 0.5). Indifference points decreased with increasing set size. **C, D** Example logistic regression curves for "ignore vs update" indifference points. Presented is the probability of choosing the update offer as a function of the amount of money offered for update. Ignore offer was always €2 for both conditions and all set sizes, while the update offer varied from €0.10 to €4. The indifference point is the update offer for which the acceptance probability is 0.5, i.e. subjective equivalence. **C** Example participant who discounted rewards in order to avoid ignore trials (preference for update). **D** Example participant who discounted rewards in order to avoid the more demanding levels of update trials (preference for ignore).

Next, we analyzed IPs using Bayesian and classical 2x4 repeated measures ANOVAs to assess whether the subjective value of an offer decreased with demand. Indifference points are displayed as a function of set size and experiment in Figure 6.4A&B (Supplemental Table 6.3 for descriptive statistics). Overall, the results show that participants significantly discounted the working memory task as the subjective value decreased as a function of task difficulty (i.e. set size). Moreover, in line with our hypothesis, the subjective cost of performing the ignore condition is higher than that of the update condition (Figure 6.4). On average, participants found the no effort option less costly than the task option, for both conditions. Analyses of data from Experiment 1 (Table 6.5) showed that the winning model, which included set size and condition (BF_{10}=5006) was four times more likely than the runner-up model which included set size alone (BF_{10} =1229). Our second experiment replicated this finding, with the same winning model (BF_{10}=9.7e+19) being ~19 times more likely than the runner up (Table 6.5). Individual effects analyses (Table 6.6) strengthened these model comparison-based inferences: They provide very strong evidence for a set size effect (Experiment 1: $F_{1.3,31}$=5.666, p=0.016, BF_{INC}=1246; Experiment 2: $F_{1.57,77}$=22.230, p=2.8e-7, BF_{INC}=6.0e+15), indicating that participants find higher set sizes to be increasingly costly. In Experiment 1, there was anecdotal evidence that the subjective value of the ignore condition was lower than that of the update condition ($F_{1,23}$=10.924, p=0.003, BF_{10}=3.1). The more powerful replication study showed extreme evidence for a lower subjective value of ignore versus update ($F_{1,49}$=18.216, p=9.0e-5, BF_{10}=1684), indicating that participants found the ignore condition subjectively more costly than the update condition. Finally, there is limited evidence against an interaction effect (Experiment 1: $F_{3,69}$=1.798, p=0.168, BF_{INC}=0.2; Experiment 2: $F_{2.66,130}$=2.167, p=0.102, BF_{10}=0.5).

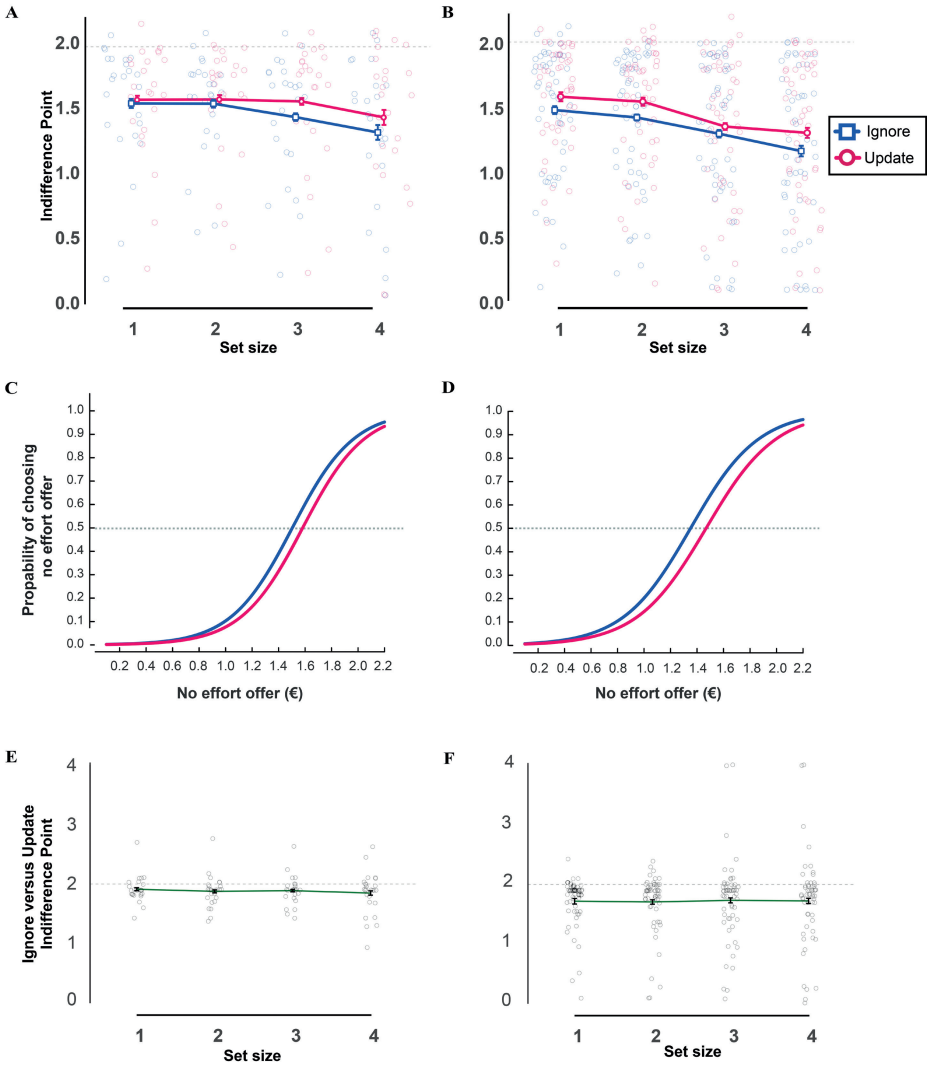


FIGURE 6.4 | A, B "Task vs no effort" indifference points as a function of set size. **A** Experiment 1 (24 participants). **B** Experiment 2 (50 participants). The more the indifference points deviate from 2, the more participants discounted the task option (the task offer was fixed at €2). **C, D**: Logistic regression curves for "task vs no effort" choices per condition across set size. The probability of accepting the "no effort" (i.e. no task) offer (y-axis) is plotted as a function of the amount of money offered for "no effort" (x-axis). Logistic curves estimated using the lmer package (Bates et al., 2015) in R (R Core Team, 2014). **C** Experiment 1 (24 participants). **D** Experiment 2 (50 participants). **E, F** Indifference points for "ignore versus update" choices as a function of set size. **E** Data from experiment 1 (26 participants). **F** Data from experiment 2 (58 participants). Indifference points smaller than 2 indicate a preference for update over ignore (offer for ignore was fixed at €2). Error bars indicate within- participant SEM (Cousineau, 2005; Morey, 2008).

TABLE 6.5 | Model comparison: indifference points

Models	BF_{10}	
	Experiment 1	Experiment 2
Condition+ Set size	5002.7	9.7e +19
Condition+ Set size+ Condition* Set size	722.8	5.2e +18
Set size	1229.2	4.0e +16
Condition	2.7	243.7

Model comparison relative to the null model for "task vs no effort" indifference points

TABLE 6.6 | Effects analysis: indifference points

Effects	$BF_{inclusion}$		P_{value}	
	Experiment 1	Experiment 2	Experiment 1	Experiment 2
Condition	3.1	1683.9	0.03	9.0e-3
Set size	1241.0	6.0e +15	0.016	2.8e-7
Condition* Set size	0.5	0.2	0.168	0.102

Effects analysis for "task vs no effort" indifference points

Cognitive effort discounting: To Ignore or to Update?

Next, we assessed choices that involved direct comparison between performing the ignore and the update trials. The offer for ignore was fixed at €2 and the offer for update varied from €0.1 to €4. Accordingly, an IP < 2 indicates a preference for (increased subjective value of) update vs ignore, while an IP > 2 represents a preference for ignore vs update (see Methods section for more details). Figure 6.3C&D depicts logistic regression curves of two example participants, one preferring the update condition and exhibiting an effect of set size (left panel) and the other preferring the ignore condition and not exhibiting an effect of set size (right panel).

Descriptive statistics are presented in Supplemental Table 6.4 and one-sample t-test output in Table 6.7. In Figure 6.4E&F, we report the average indifference points per set size. In accordance with our second hypothesis, the overall average subjective value of ignore versus update choices was less than 2 (1.88), indicating a preference for update over ignore. The support in the data for this hypothesis is ~4.8 times higher than the null (T-test (IP<2) t_{25}=-2.440, p=0.011, BF_{-0}= 4.8). In Experiment 2, the average subjective value was 1.73 and a preference for update over ignore was ~65 times more supported by the data than no preference

(T-test (IP<2): t_{57}=-3.535, p=4.1e-6, BF_{-0}= 65). The output of the one-way repeated-measures ANOVA shows very strong evidence for the data under the null hypothesis that subjective value is not influenced by set size (Experiment 1: $F_{1.8,45}$=0.961 p=0.382, BF_{10}=0.149; Experiment 2: $F_{1.2,69}$=0.069, p=0.840, BF_{10}=0.023). Our results provide confidence in our second hypothesis that participants discount rewards in order to repeat flexible updating trials over distractor resistance and this does not vary with set size.

TABLE 6.7 | Ignore versus update analysis

Set size	BF_{-o}		P_{value}	
	Experiment 1	**Experiment 2**	**Experiment 1**	**Experiment 2**
Across	4.8	64.9	0.011	4.1e-4
1	2.4	6698.0	0.026	2.6e-6
2	4.3	1105.0	0.013	1.8e-5
3	4.2	13.2	0.013	0.002
4	3.0	10.9	0.02	0.003

One-sample t-test that "ignore vs update" IPs are smaller than 2

Exploratory analyses

Having established that ignore is both more difficult and perceived as more costly for most participants, we next asked whether variability in preference for update varies with variability in task performance. A plot of deviance for ignore versus update against preference for ignore versus update reveals little correlation (Figure 6.5). We also assessed a relationship between preference and performance using mixed effects logistic regression (see Methods section). We compared the models with and without the main effect of performance (deviance). For both experiments, adding deviance did not improve model fit significantly (Experiment 1: model without deviance: BIC: 4474.3, AIC: 4376.5; full model: BIC: 4482.5, AIC: 4377.9, p(pr>Chisq)=0.430; Experiment 2: model without deviance: BIC: 10535, AIC: 10426; full model: BIC: 10544, AIC: 10427, p(pr>Chisq)=0.463). Additionally, in the full model, which includes deviance, the effect of condition is still present in Experiment 2 (p=0.061 for Experiment 1; p=0.0001 for Experiment 2). The above suggest that variability in performance does not explain away differences in preference for update versus ignore.

FIGURE 6.5 | Relationship between reported, measured preference and performance in the color wheel task. The y axis represents the difference in performance between ignore and update across demand. Measured preference: indifference points in the direct comparison across demand being higher or lower than 2 (preference for update or ignore respectively). Reported preference: participants written report of which task condition they prefer. Performance on update versus ignore trials does not covary with a preference for update versus ignore. There is a correlation measured (indifference points) and reported (questionnaire) preference for update versus ignore. Depicted data from Experiment 2 (60 participants).

DISCUSSION

In this project, we set out to quantify the subjective value of cognitive stability and cognitive flexibility in the domain of working memory. We asked not only whether these working memory processes are associated with higher subjective costs when demand increases, but also whether tasks requiring cognitive stability carry a lower subjective cost than do tasks requiring cognitive stability. In keeping with prior work (Apps et al., 2015; Chong et al., 2017; Massar et al., 2016; Westbrook et al., 2013), we demonstrate highly robust and monotonic discounting of delayed response task value with parametrically increasing working memory load (i.e. set size). Most critically, the results provide strong evidence that the ignore condition of the task with high stability demands is more costly than is the update version of the task with high flexibility demands: Participants are willing to forego higher monetary offers in order to avoid repeating performing ignore compared with

update trials. This finding is evident both indirectly when participants had to choose between the task and a break, but also directly when they had to choose between ignore and update. This result was replicated in the second independent sample and concurs with our primary prediction that the cognitive effort cost of cognitive stability is higher than that of cognitive flexibility.

Depending on one's perspective, this effect of condition on effort cost might be very intuitive or surprising. We might be surprised, because the update trials were longer, and required the encoding and gating into working memory of twice the number of stimuli compared with the ignore trials. Moreover, many studies have shown that tasks with high demands for cognitive flexibility, like task switching and set-shifting, are accompanied by robust (residual) costs (Rogers and Monsell, 1995; Rubinstein et al., 2001). However, the effect might be considered intuitive, if we recognize that reorienting to salient stimuli can be considered a bottom-up process. In this task, updating is a relatively automatic process, while ignoring requires the withholding of intervening stimuli and thus resolution of conflict, that is, the core function of cognitive control (Botvinick and Cohen, 2014; Corbetta and Shulman, 2002; Ernst et al., 2011; Feng et al., 2014). This then brings us back to the original question: What makes cognitive control costly?

What makes cognitive control costly?

One possibility is that this effect reflects a difference in opportunity costs. In our task, the more subjectively costly ignore trials were 4 seconds shorter than were the cheaper update trials, thus opportunity costs are unlikely to map directly to time costs (Niv et al., 2007). However, we speculate that the effect of task demands on subjective cost reflects an opportunity cost of focusing: the cognitive strategy required for accurate ignore versus update performance differs in the degree to which it allows novel input and thus, alternative opportunities, to impinge on current processing. More generally, it is possible that the brain is more strongly biased against tasks that demand stable focusing compared with flexible opening given that focusing will incur higher opportunity costs across environments.

The observation that the subjective cost of repeating the ignore task is higher than that of the update task is in line with the finding that participants perform more poorly on ignore compared with update trials. This finding concurs with previous results from studies using an analogous task with ignore and update conditions (Fallon and Cools, 2014; Fallon et al., 2016, 2017). In those prior studies, however, the task-relevant delay between the to-be-remembered items and the probe was shorter in the update than ignore condition, rendering inference about

the cognitive mechanism underlying the performance difference difficult. Here, we show that the ignore condition is accompanied by worse performance than the update condition, even if task-relevant delay is matched between conditions.

A key question that is raised by the performance difference between task conditions is whether the condition effect on subjective effort cost reflects differences in the degree of (aversion to) anticipated performance error. We argue, however, that an increase in the anticipated performance error is unlikely to account fully for the increase in subjective effort cost of the ignore versus update condition, for the following three reasons. First, while instructing participants, we highlighted that monetary rewards would not be contingent on performance during the 'redo session', so that performance error should not have influenced participants' choices in our design. Second, in a statistical mixed-effects model that took into account accuracy, the effect of condition was still present, as a trend in Experiment 1 and highly significant in the more powerful Experiment 2. Third, there was no evidence for a clear association between performance error and measured preference (Figure 6.5). In future studies, we might consider matching performance between the two conditions or provide "fake" feedback to influence participants' beliefs about their performance. Notably, participants responded not only more accurately, but also more slowly on the update than the ignore trials. We are puzzled by this finding, and consider it possible that this response time effect is a consequence of a differential delay between the presentation of the intervening stimulus and the probe in the two conditions. For example, it might reflect changes in an orienting response to the intervening stimulus (Loveless and Sanford, 1975). We also consider an alternative explanation, namely that the effect of condition on reaction times reflects a modulation of a decision threshold rather than of attentional orienting, trading off time for higher accuracy (Bogacz et al., 2010) in the update condition in which the memory is more robustly maintained and such a strategy would be beneficial. Here we should note that in both experiments, the time of the mouse click was used as an index of reaction time. However, a clearer picture could be formed if we also had data on initial response times (mouse move) and decision times (move to click). This is a limitation that should be addressed in future studies.

Benefits of current task design

In addition to disentangling the subjective value of distractor resistance and flexible updating task performance, the present results strengthen and extend previous studies on the value of cognitive engagement. First, we confirm that, on average, people are averse to cognitive demand, are 'cognitive misers', willing to decline

rewards in order to avoid demanding tasks. This strengthens earlier work showing that participants prefer to avoid more demanding N-back tasks (Westbrook et al., 2013), detection tasks (Chong et al., 2017) or sustained attention tasks (Massar et al., 2016). Our results further extend these conclusions to the most classic of working memory tasks: the delayed response task. A distinct strength of our design is the fact that our implementation of the discounting procedure takes into account the observation that choices are probabilistic. Unlike prior studies on cognitive effort which used staircase procedures sampling every choice option only once (Massar et al., 2016; Westbrook et al., 2013), we sampled the full discounting curve and every choice option multiple times. Furthermore, unlike prior studies, in which on the first trial a lower monetary offer was made for the low effort option than for the high effort option, we avoided (potential) anchor effects by presenting, on the first trial the same offer for both options. Finally, unlike previous discounting studies we gave participants the opportunity to choose the effortful option for less money. As expected, most participants declined this offer, but the subjective value of four participants (total in both samples) was higher than 2 for at least one of the two working memory processes, indicating a preference for repeating the working memory task, suggestive of effort seeking. These various features of our design likely allowed us to obtain more precise and unbiased estimates of the subjective value of cognitive work than previous designs.

CONCLUSION

In conclusion, this study provides new insights to the novel and growing fields of cognitive effort discounting and value-based decision- making. Specifically, we showed that with increasing demand on working memory processes, the subjective valuation decreased, both for the process of distractor resistance and flexible updating. We also show strong evidence that distractor resistance is perceived as relatively costlier than flexible updating.

METHODS

Participants

For Experiment 1, 32 participants (22 women), aged between 18-29 years old were tested in total. Participants had normal or corrected-to-normal vision. Colorblind participants were excluded. Four data sets were lost during data transfer, so we ended up with 28 data sets (20 women, 18-33 years old, mean: 24). For Experiment 2, we estimated the number of participants required to reach a Bayes factor of 10 for either the null or the alternative hypothesis that update is

more costly than ignore given the effect size estimated from Experiment 1 using the BFDA (Schönbrodt, 2016) package in R. Based on the results of the power calculation we collected 62 data sets (37 women, 20-44 years old, mean: 25.6, standard deviation: 4.3). The study was approved by the local ethics committee (CMO region Arnhem/Nijmegen, The Netherlands, CMO2001/095) and all participants provided written informed consent, according to the declaration of Helsinki.

Exclusion criteria

We excluded participants based on four rules: 1) Failing to pass the color sensitivity test twice. 2) Striking evidence that they did not understand or will to perform the tasks. 3) Their mean deviating further than 3 standard deviations from average for at least one of our main conditions (across demand). 4) In the effort discounting tasks analyses we excluded people whose indifference points we could not estimate for at least one condition (across demand levels).

Based on our criteria, one outlier was excluded from performance analysis of Experiment 1 for deviating more than 3 standard deviations from the mean for ignore (~3SD) and one from Experiment 2 for deviating more than 3 standard deviations from the mean of both conditions (~5.4SD from Ignore and ~6.6SD from Update mean). Four people were excluded from the analysis of task vs no effort indifference points in Experiment 1 and twelve in Experiment 2. In Experiment 1, all four were excluded because we could not estimate indifference points for at least one of the two conditions (ignore/update). Among the four that were excluded, one always chose the no task option, one of them always chose the task option and one of them always chose no task for update trials and task for ignore trials. In Experiment 2, eleven participants were excluded due to inadequate response variability and one because he was not performing the task. Out of the eleven whose IPs we could not estimate, one almost always chose the task option and the rest always preferred the no effort option. The other participant always responded using one of the two response buttons. This is a clear indication that he was not trying to perform the task because easy and hard offer presentation was counterbalanced across response buttons. We excluded two participants from the analysis of "ignore vs update" indifference points in Experiment 1 analysis; one because we could not estimate any indifference points (always chose ignore) and another because they deviated more than 3 standard deviations from the mean. Four participants were excluded in Experiment 2 for the same analysis. One always chose ignore, two always chose update and one did not do the task (see above).

Task design

All paradigms were entirely programmed in MATLAB (Mathworks, Natick, MA, USA)(release 2013a) using the Psychophysics Toolbox extensions (Brainard, 1997) (version 3.0.12) on a Windows 7 operating system. The screen resolution was 1920x1080 pixels. The background color for all paradigms was grey (R: 200 G:200 B:200).

The experiment lasted about 130 minutes and consisted of four tasks performed at a computer and questionnaires that participants filled in at the end. The first task (~7min) was a color sensitivity test aiming to check whether participants were sensitive to the colorful stimuli used in the color wheel memory task. Participants then proceeded with the color wheel working memory task to acquire experience with varying demand of the two working memory processes of interest (~10min practice and 30min task). The third task (~5min practice and 55min task) was a cognitive effort discounting paradigm that was used to estimate subjective value and address our research questions. The last computer-based task was a redo of the color wheel task (~10min). Finally, participants filled in some experiment-related questionnaires (~5min).

Color sensitivity task

For our working memory task, we used color stimuli and a color wheel, so it was crucial that our participants' color vision was not impaired. To test their sensitivity to our manipulation we developed a version of the color wheel task without a working memory component. In this task participants viewed a colored square in the middle of the screen and the same color wheel used in the memory task. Their goal was to click on the color of the wheel that matched the colored square.

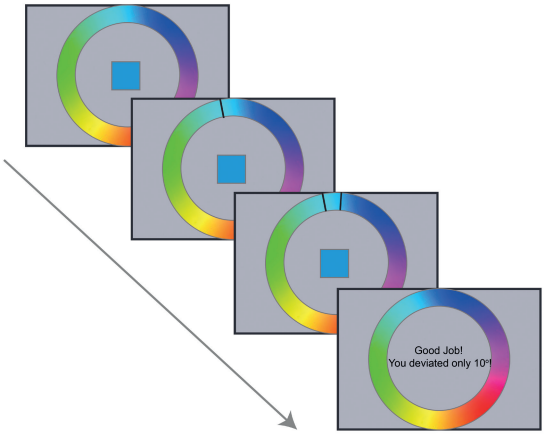


FIGURE 6.6 | Two example trials of the color sensitivity task. Participants viewed a colored square in the middle of the screen and they had to click with a mouse on the corresponding color on the color wheel. A black line indicated the selected color and a successive line the correct color. If the selected color deviated 10° or less from the correct color they received feedback that they performed well. The task was self-paced (24 trials total). They successfully completed the task if their average deviance was less than 15°.

The stimuli used for the color sensitivity task were a color wheel, black lines and colored squares. The color wheel was created by 512 successive colored arcs of equal angle (512/360° = 1.42°), each arc carrying a different color. The radius of the wheel was 486 pixels. To form the wheel into a ring, a smaller circle was superimposed, whose radius was ~362 pixels. The centre of both the wheel and the circle coincided with the centre of the screen. The 512 colors of the color wheel arcs were generated using the hsv MATLAB colormap. The black lines were 0.4° black arcs.

In every trial of this task, participants viewed the color wheel and a colored square in the middle of the screen (Figure 6.7). They were instructed to look at the color of the square and use the mouse to click on the corresponding shade on the color wheel. To indicate that their response was recorded a black line appeared on the color wheel and successively another black line appeared designating the location of the correct color. Feedback consisted of the actual deviance plus a positive message ('Good job! You deviated only __ degrees.') and was provided only when responses deviated less than 10°.

To test a representative sample of the color wheel we split the wheel in 12 main arcs. Participants were tested in two different shades from each of the 12 color categories. So, they performed in total 24 trials of this task. The presentation

of the trials as well as the orientation of the color wheel were randomized. The responses were self-paced and total task duration was approximately 7min. The main dependent variable in this task was deviance in degrees from the correct color. If their average deviance was less than 15° by the end of the task, the experiment continued. Otherwise, they had one more chance to perform the color sensitivity task, but if failed again they would be excluded.

All participants from both experiments completed 24 trials of the color sensitivity task and they all met the criterion (average deviance from correct color below 15 degrees) to continue to the main paradigm. For Experiment 1, the average deviance from the target color was 6.63 degrees (SD = 1.23; median = 4.72, SD = 0.85) and for Experiment 2 mean deviance was 6.27 degrees (SD=1.4; median=4.85, SD=1.08). We also reported the median for easy comparison with the color wheel working memory task results.

Color wheel working memory task

After successfully completing the color sensitivity task, participants proceeded with the color wheel working memory task. In this part, participants experienced varying demands of distractor resistance and flexible updating. This task was based on a short-recall task (Zhang and Luck, 2008) and delayed-match-to-sample tasks (Fallon and Cools, 2014) that have previously been used to disentangle between the two working memory processes of interest.

The stimuli displayed during this paradigm were a color wheel, colored squares, black frames of squares, a fixation cross, black lines and central letter cues. The color wheel was generated as described in the color sensitivity section. The number of squares varied from one to four and they could be located in four different positions. The centres of the squares formed a rectangle with dimensions 248x384 pixels. Each of the four squares was 100x100 pixels in size. To choose the colors of the squares, we split the color wheel into 12 main arcs of 42 colors each and only used the 15 central colors of each arc. The arcs from which the colors would be sampled per trial were defined manually, but the exact shade (RGB values) was randomly selected. The letter cues were “I” and “U”, colored black and presented at the centre of the screen.

Every trial of the task consisted of three phases separated by two delay periods (Figure 6.1A). During the ***encoding*** phase, participants viewed the fixation cross and one to four colored squares for two seconds. The number of squares displayed (set size 1-4) represented the demand of the trial. A delay of two

seconds followed, during which only the fixation cross was displayed. Then the ***interference*** phase followed. In this phase, participants viewed the same number of squares as during encoding, at the same locations, but with different colors. Instead of a fixation cross, one of the two letter cues were presented during interference in the middle of the screen. The cue indicated the condition of the trial: "I" for distractor resistance trials and "U" for flexible updating. The second delay duration depended on trial condition, and was two seconds for distractor resistance and six seconds for updating trials. Finally, during the ***response*** phase participants saw black frames of the same squares, one of which was highlighted, in addition to the color wheel and the fixation cross. If the participant responded within four seconds, a black line appeared on the color wheel, otherwise, they were instructed to respond faster ('Please respond faster!). The total duration of the response phase was five seconds.

For the encoding phase, participants were instructed to always memorize the colors and locations of all presented squares. The instructions for the interference phase differed based on the condition as indicated by the letter cue. In distractor resistance trials, participants needed to maintain in their memory the colors from the encoding phase and not be distracted by the new intervening stimuli. In flexible updating trials, participants had to let go of their previous representations and update into their memory the stimuli from the interference phase. Thus, the colors that needed to be remembered for distractor resistance were the ones from the encoding phase, while on updating trials they were the ones from the interference phase. To match the time that the relevant stimuli were maintained in memory for both conditions, the second delay was 4 seconds longer for update trials. Participants were to indicate the color for only the highlighted square. They had to identify the target color on the color wheel and click using a mouse, within four seconds. Only the first response counted. A black line indicated their response. Only during practice trials, a second line appeared at the correct color and positive feedback was displayed if they were performing well (as in color sensitivity section). During the task, no feedback was provided. We instructed participants to fixate in the middle of the screen throughout the task in order to dissuade them from adopting the strategy of closing their eyes during ignore trials in order to avoid being distracted.

Participants first underwent a practice session of 16 trials and then performed two blocks of the task. A block consisted of 64 trials, resulting from repeating each combination of difficulty (four levels: set size 1 – 4) and condition (two levels: ignore and update) eight times. Depending on the difficulty level of the trial, a group of two to eight colors was used to create the trial stimuli, each color coming

from one of the 12 arcs. Colors of the same arc never appeared more than once in the same trial. To make sure that ignore and update trials were as similar and counterbalanced as possible, the color stimuli sets displayed and the target colors were the same for both conditions. Because the relevant colors appeared during encoding for Ignore and during interference for update, we made sure that the same group of stimuli also appeared in reverse order between these two phases. So, the same groups of colored squares were presented four times per set size and in total 32 groups of colors were used. To decrease learning effects due to repetition, we split the same stimuli groups between the two blocks. To control for differences between the two hemispheres in representation of color(Gilbert et al., 2006), target locations (left/right) were counterbalanced across conditions. Moreover, the same colors were highlighted for all four set sizes.

Cognitive effort discounting task

After participants gained experience with all four difficulty levels of update and ignore conditions of the color wheel working memory task, they proceeded with the third part of the experiment: the effort discounting task (Figure 6.1B). The aim of this paradigm was to quantify the subjective value that participants assigned to color wheel task performance. There were two versions of choice trials to address our two research questions. In both versions, two options were accompanied by an amount of money and the options defined what participants would do in the last part of the experiment.

In every trial of the task participants saw a rectangle containing two options and a fixation cross. The options could be "No Redo" or any set size of ignore or update, for example "Ignore 2", corresponding to the ignore condition of the task and set size of 2. Below each option, a monetary reward was displayed, for example "for 2€". Participants could choose the left or right option by pressing 1 or 2 on the keyboard and they had six seconds to respond. When participants made a choice, a black square surrounding the selected offer appeared to indicate that their response was recorded.

At this stage, participants were instructed that there were two more parts in the experiment. In the last part, they would have the opportunity to earn a bonus monetary reward by redoing one to three blocks of the color wheel task. However, the amount of the bonus and the type of trials they would repeat would be based on the choices they made on the choice task. To highlight the importance of every choice, we instructed them that of all the choices they made (of both versions) the computer would select only one randomly and the bonus and redo

would be based on that single choice. To minimize effects of error avoidance on choices, we informed participants that accuracy during the redo part would not influence whether they receive the monetary reward, as long as their performance was comparable with the first time that they did the color wheel task (part 2 of experiment). Both the rewards and the redo were real and not hypothetical.

Task vs No effort: Choices between working memory task and no task

These trials addressed the first research question: whether the subjective value of distractor resistance and flexible updating subjective values decreases as a function of task demand. Here, participants had to choose between repeating a level of ignore or update (task offer) and not redoing the color wheel task at all (no effort offer). If they chose the no task option ("No Redo") they were instructed that they would be able to use their time as they pleased (e.g. by using their phones or lab computer) but they would still have to stay in the testing lab so that time spent on the experiment was the same for both options. Otherwise, if the option to repeat the task was selected, the redo trials would consist of mostly the selected choice condition and level. "Mostly" is important because if they always did the same condition during the redo, they would be able to predict whether they had to update or ignore. We emphasized that they should take their time to respond, consider both the money and their experience while doing the color wheel task as well as the importance of choosing their true preference and not try to please us.

Ignore vs Update: Choices between distractor resistance and flexible updating

This trial type aimed to investigate whether distractor resistance is perceived as costlier than flexible updating by directly contrasting them. In these trials, participants had to choose between doing the same level of either ignore or update.

The amount they were offered for the no effort "No Redo" option varied from €0.10 to €2.20 in €0.20 steps (except the first step, which was €0.10), while the task option (effort offer) was always fixed at €2.00. The €2.20 option for "No Redo" was included to identify whether there were participants who strongly preferred performing the task, even if that meant forgoing rewards. As we hypothesized that ignore would be costlier, in this case ignore (hard offer) was kept steady at €2 and update (easy offer) was varying from €0.10 to €4 in €0.20 steps (as above). There were 96 possible pairs for "task vs no effort" choices

(12 amounts*2 conditions*4 set sizes) and 84 for "ignore vs update" choices (21 amounts*4 set sizes). As there is evidence that choice is probabilistic rather than deterministic (Rieskamp, 2008), every pair of options was sampled three times. We decided on three repetitions of the pairs based on a simulation analysis using pilot data (Supplemental Figure 6.3) in order to optimize the trade-off between indifference point estimation and task duration. Each participant performed three blocks that contained in total 288 trials of "task vs no effort" trials and 255 trials of "ignore vs update". There was a short practice session of 12 trials, where the amounts offered were the same for all options (€2) to avoid anchor effects. The trials of the two versions were interleaved (mixed) and randomized within each block. To avoid location effects, we counterbalanced the left-right presentation of the two options. Total task duration was about 55 minutes.

We decided to use fixed sets of offers and not a titrated staircase procedure to estimate subjective value because staircase procedures do not sample the entire logistic regression curve. Our version of effort discounting task sampled the logistic regression curves adequately because all participants were faced with the entire range of offer options.

Redo

After participants finished three blocks of the discounting choice task, one of their choices was pseudo-randomly selected. Specifically, the computer only sampled from "ignore vs update" choices of level 3 or 4. Participants always did one block of 24 trials of the color wheel task. Two-thirds of these trials were their preferred condition (ignore/update). We decided to never select the no effort option to maintain experimenter credibility, so that participants discussing the task are convinced that the consequences are real. The redo data were not analyzed and participants always received the bonus regardless of their performance.

Debriefing questions

After the end of the experiment we requested participants to complete questionnaires. We explicitly asked them to report their preference by asking "Which trials did you prefer?".

Data analysis

We analyzed our data using both frequentist and Bayesian statistics. All statistical analyses were performed using open source software JASP (version 0.7.5.6)(JASP Team, 2016; Wagenmakers et al., 2016a) on a Windows 7 operating system.

As skepticism against classical statistical tools increases (Ioannidis, 2005), we turned to Bayesian statistics (Wagenmakers et al., 2016b). This allowed us to quantify evidence for our hypotheses instead of forcing an all-or-none decision and an arbitrary cut- off of significance. Bayesian statistics can also provide evidence for the null hypothesis (H_0), thus distinguishing between undiagnostic data ("absence of evidence") and data supporting H_0 ("evidence of absence"). Another important benefit is that we were able to monitor evidence as data accumulate and we can continue sampling without biasing the result. Due to all the above advantages, we decided that our main conclusions would be drawn based on the Bayesian analyses.

However, frequentist statistics are well-established and widely-acknowledged tools, so more scientists are familiar with their rationale and interpretation. To ensure that our results are interpretable for all and to allow comparison with earlier work, we additionally included classical statistics. Bayesian statistics allow model comparison, but also provide evidence for individual effects. When possible, we reported Bayesian model comparison (BF_{10}: Bayes factor of model against the null) as well as Bayesian and frequentist effects analyses ($BF_{INC(LUSION)}$: Bayes factor of Bayesian model averaging). We used the default JASP Cauchy priors for all Bayesian statistics (Wagenmakers et al., 2016a). Regarding frequentist statistics, we considered a p-value of 0.05 or smaller as significant. In the cases where sphericity was violated, we reported the Greenhouse-Geisser corrected p-values.

Color sensitivity task analysis

The data from this task were used only to establish that participants are sensitive enough to our color wheel. We calculated the overall average deviance in degrees.

Color wheel task data analysis

We computed the median deviance and median reaction time for all levels of ignore and update. The rationale behind choosing the median was that it is less sensitive to extreme values. For example, 90° and 180° accuracy scores are both wrong responses, but the latter affects the mean much more strongly. We used the above indices for the statistical analysis using classical and Bayesian 2x4

repeated measures ANOVAs with condition (ignore/update) and set size (levels 1-4) as within-subject factors. All participants in both experiments performed above chance level (mean deviance less than 90°).

Discounting choice task data analysis

As an estimate of subjective value, we computed participants' indifference points. The indifference points can be interpreted as the financial amount offered for the presumably less effortful option (no effort or update) at which participants are equally likely to choose one or the other, thus the probability of accepting either option would be 0.5. With the main dependent variable being choice, a dichotomous variable, we calculated the probabilities of accepting the presumably less effortful offer using binomial logistic regression analysis in MATLAB and extracted the indifference points for the different conditions.

Choices between working memory task and no effort

Having determined the indifference points for all levels of both working memory tasks per participant, we continued with the statistical analysis using classical and Bayesian 2x4 repeated measures ANOVAs to assess our first hypothesis that subjective value decreases with demand for distractor resistance and updating. Confirmation of this hypothesis would require that the model including set size is more likely than the null model, or the presence of a set size effect with p-value smaller than 0.05. We also performed Bayesian and classical one sample t-tests on the indifference points across levels for both conditions to assess whether the subjective value of the working memory functions was overall lower than the no task subjective value. The task offer was always €2, so a subjective value lower than 2 would imply that participants were discounting the task option.

Choices between Update and Ignore

We then computed participants' indifference points collapsing across levels of "ignore vs update" choice trials to evaluate our hypothesis that ignore has a lower subjective value than update using Bayesian and classical one sample t-tests. As ignore offer was set at €2, subjective values lower than 2 indicate that participants were willing to forgo rewards to repeat update instead of ignore trials. Additionally, we calculated indifference points for all levels separately and used a 1x4 ANOVA with set size as a factor to assess if the preference for update varies with demand.

Mixed effects analysis

We tested for a relationship between preference and performance with mixed effects logistic regression analyses, using the lmer package (Bates et al., 2015) in R (R Core Team, 2014). In our model, we regressed preference on fixed effects of set size, condition, the money offered for the "no effort" option and deviance (accuracy index). We also included random intercepts and slopes for the effects of easy offer amount, condition and set size. Continuous variables "easy offer amount" and "deviance" were log-transformed and standardized. We also assessed if the effect of condition remained significant after including deviance in the model. For that analysis, deviance was also added as a random slope. Model fits were compared using likelihood ratio chi- square tests. To estimate the discounting curves across participants (Figure 6.3C&D) we used a mixed effects model per condition with offer amount as fixed factor and participant as a random factor.

SUPPLEMENTAL MATERIALS OF CHAPTER 6

SUPPLEMENTAL TABLE 6.1 | Descriptive statistics for color wheel task deviance

Condition	Set size	Experiment 1		Experiment 2	
		Mean	SD	Mean	SD
Ignore	**1**	8.69	2.71	7.96	3.51
	2	10.55	4.67	9.19	3.49
	3	13.42	10.39	11.96	7.78
	4	15.60	13.47	13.95	9.49
Update	**1**	8.01	3.24	7.41	2.84
	2	7.65	2.70	8.09	3.76
	3	8.47	2.60	8.24	3.51
	4	10.50	6.02	11.25	8.94

SUPPLEMENTAL TABLE 6.2 | Descriptive statistics for color wheel task RTs

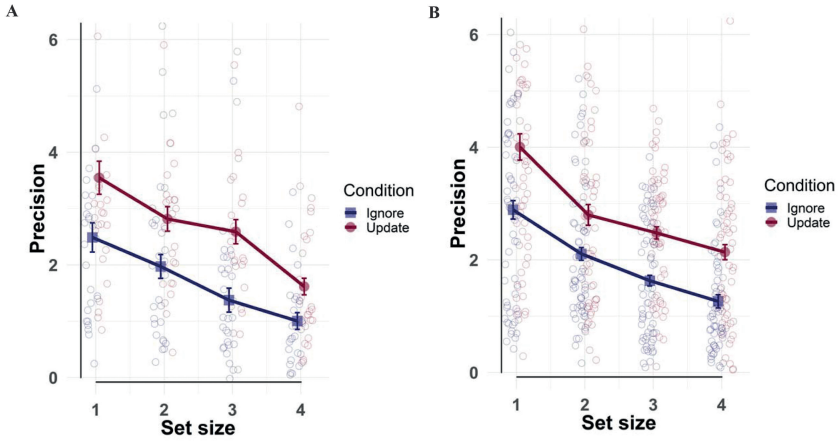
Condition	Set size	Experiment 1		Experiment 2	
		Mean	SD	Mean	SD
Ignore	**1**	1.84	0.32	1.91	0.31
	2	2.27	0.35	2.25	0.28
	3	2.24	0.27	2.23	0.28
	4	2.22	0.29	2.23	0.30
Update	**1**	1.93	0.33	1.94	0.33
	2	2.26	0.32	2.27	0.29
	3	2.23	0.31	2.26	0.26
	4	2.40	0.30	2.37	0.28

SUPPLEMENTAL TABLE 6.3 | Descriptive statistics for "task vs no effort" indifference points

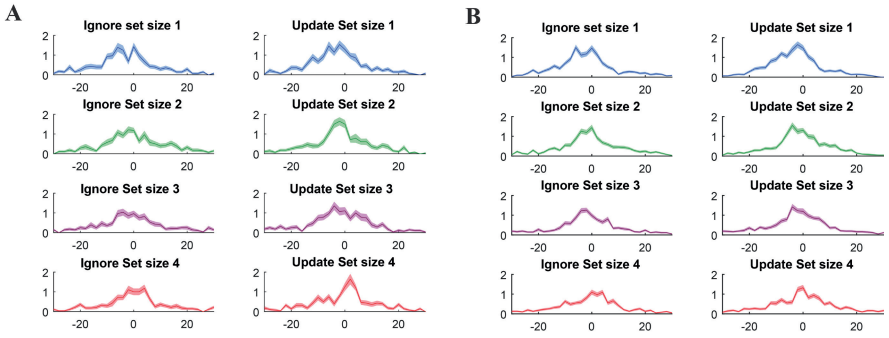
Condition	Set size	Experiment 1		Experiment 2	
		Mean	SD	Mean	SD
Ignore	**Across**	1.48	0.45	1.36	0.52
	1	1.57	0.47	1.48	0.49
	2	1.56	0.39	1.42	0.52
	3	1.46	0.48	1.29	0.58
	4	1.34	0.56	1.16	0.62
Update	**Across**	1.55	0.46	1.48	0.42
	1	1.59	0.44	1.58	0.41
	2	1.60	0.44	1.54	0.45
	3	1.58	0.50	1.35	0.55
	4	1.46	0.57	1.30	0.56

SUPPLEMENTAL TABLE 6.4 | Descriptive statistics for "Ignore vs Update" indifference points

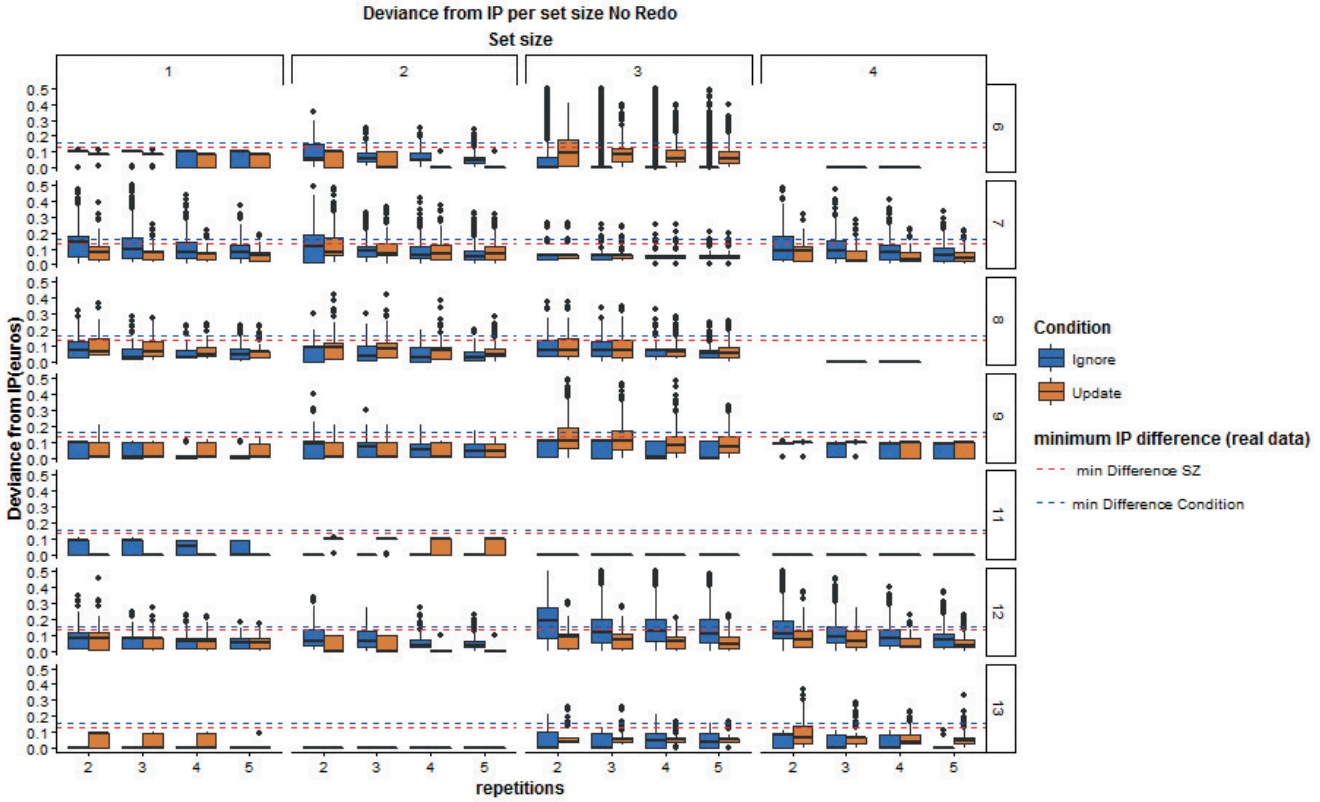
Set size	Experiment 1		Experiment 2	
	Mean	SD	Mean	SD
Across	1.88	0.25	1.73	0.58
1	1.91	0.22	1.72	0.42
2	1.88	0.26	1.71	0.50
3	1.89	0.24	1.73	0.69
4	1.85	0.36	1.73	0.74



SUPPLEMENTAL FIGURE 6.1 | Precision (Bays et al., 2009) in the color wheel task as a function of set size for Experiment 1 (A, 28 participants) and Experiment 2 (B, 62 participants).



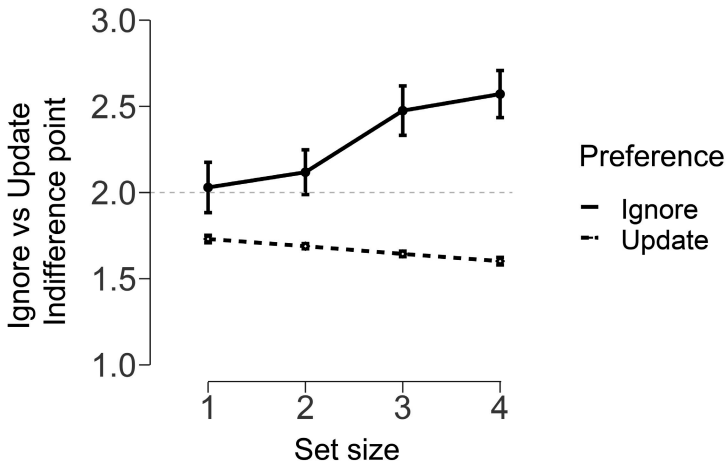
SUPPLEMENTAL FIGURE 6.2 | Distribution of color wheel task responses per condition per set size in Experiment 1 (A, 28 participants) and 2 (B, 61 participants). X axis represents deviance from target color.



SUPPLEMENTAL FIGURE 6.3 | Simulations of cognitive effort discounting task given indifference points derived from pilot participants. The goal was to assess the number of repetitions of choice offer pairs necessary to extract indifference point effects for set size and condition as measured with pilot data. Every column represents a different set size, every row different participant. Every cell has been simulated 1000 times. Red line: minimum significant difference for set size derived from real data. Blue line: minimum significant condition effect difference.

SUPPLEMENTAL RESULTS | Individual differences

In both studies, as well as in previous pilot studies, the majority of participants (83%) preferred update. However, a smaller percentage reported preference for Ignore (17%). Given this observation, we considered the possibility that, on the direct (Update versus Ignore) comparison trials, an effect of set size was in fact present, but masked by relevant individual variation in the overall preference for Update or Ignore. To assess this, we conducted supplementary analysis of Experiment 2 data, in which the effect of set size on IP was stratified by a group factor representing overall preference for Update over Ignore. Specifically, participants from the larger replication Experiment 2 were assigned to one or the other group based on their average IP being larger or smaller than 2. In keeping with our hypothesis, one-way ANOVAs in each group separately revealed effects of set size, both in those preferring Update (70 participants), as well as in those preferring Ignore (14 participants)(Ignore: $p=0.076$, $BF_{10}=4.56$; Update: $p=3.12e\text{-}4$, $BF_{10}=865$).



SUPPLEMENTAL FIGURE 6.4 | "Ignore vs Update" indifference points varying by demand separately for participants who overall preferred distractor resistance (ignore) or flexible updating (update) trials. Participants pooled from both experiments. The update group consists of 70 participants and the ignore group consists of 14. Error bars indicate within- participant SEM (Cousineau, 2005; Morey, 2008).

6

CHAPTER 7

General Discussion

The overarching goal of this thesis was to characterize the role of catecholamines and specific task-demands in shaping our motivation for cognitively demanding processes in the healthy population. To begin to understand the mechanisms of cognitive control and its avoidance, the concrete aims of this thesis were to:

- quantify the willingness (i.e. motivation) to conduct cognitively effortful tasks and assess how motivation is affected by pharmacological interventions that challenge the catecholamine system;
- develop a novel paradigm that allows quantification of the motivation to engage in flexible versus stable cognition;
- study how a catecholamine challenge alters performance on a task probing flexible versus stable cognition in older adults.

KEY FINDINGS

In this section, I summarize the key findings according to the three aims defined above, interpret them in the context of related literature, describe implications and concrete limitations.

Catecholamine challenge alters cognitive control avoidance as a function of impulsivity

(based on Chapters 2-4)

Summary

As introduced in 1.3, accumulating evidence indicates that cognitive control is subjectively costly (Westbrook et al., 2013) and people generally choose to refrain from effortful control (Kool et al., 2010), despite, at times, devastating consequences. However, when increasing the motivation by promising incentives, most people manage to improve cognitive control performance (Botvinick and Braver, 2015), pointing towards limited motivation instead of lack of capacity (Cools, 2016). By understanding the mechanisms that alter motivation for cognitive control, we can develop interventions that promote motivation and achievements in the long-term.

In **chapter 2,** we highlighted in a literature review the potential contribution of the major ascending neuromodulators, in particular catecholamines, to our tendency to avoid cognitive control. We argued that striatal dopamine might alter

choices about cognitive control (avoidance) by modulating (and learning about) the expected value of cognitive task performance. Thus, we hypothesized that increases in (striatal) dopamine lead to an emphasis on the benefits, but reduced weight on the costs of cognitive control. This follows from earlier empirical and neurocomputational work on a role for dopamine in value-based decision-making (Collins and Frank, 2014). Based on further empirical evidence for baseline-dependency of catecholaminergic manipulations (see 1.6), we also hypothesized that excess or supraoptimal levels of dopamine might paradoxically reduce the value of cognitive control (Cools and D'Esposito, 2011). To begin to assess contributions of catecholamines to choices about cognitive demand avoidance, we conducted two pharmacological studies, of which one is also reported in chapter 2.

In **chapter 3,** we administered methylphenidate in a within-subject design to 100 healthy young adults and let them complete the demand selection task (Figure 3.1C) twice, once after a placebo pill and once after 20mg of methylphenidate. In the demand selection task, participants chose between two patches of which one has a low and the other a high demand on task-switching. The proportion of low demand choices was used as an index of demand (i.e. task-switching) avoidance. We recruited a large sample for this study given the earlier reports on baseline-dependency in catecholaminergic interventions. Thus, we were interested in individual differences in drug response and assessed whether putative proxy measures of dopamine transmission modulated drug responses. As proxy measures, we employed working memory capacity (Daneman and Carpenter, 1980) and trait impulsivity (Patton et al., 1995) (Buckholtz et al., 2010; Cools et al., 2008; Landau et al., 2009). In line with our predictions, participants were demand avoidant and methylphenidate altered demand avoidance in a baseline-dependent manner. Methylphenidate increased demand avoidance in more relative to less impulsive participants (Figure 3.3) whereas the effect on task-switching performance was not statistically significant.

In **chapter 4,** we administered the catecholamine precursor tyrosine to 29 healthy older adults (aged 60-75), given that aging has been associated with reductions in dopamine transmission (Karrer et al., 2017) and reduced motivation for cognitive control (Westbrook et al., 2013)(see 1.3). We hypothesized that tyrosine might increase the value of control, as measured by the cognitive effort discounting paradigm (Figure 4.2). Contrary to our prediction, tyrosine administration did not increase the subjective value of conducting an N-back task for reward, as a main effect. Instead, in line with chapter 3, drug effects varied as a function of participants' trait impulsivity scores. Specifically, tyrosine reduced the subjective

value of conducting higher N-back levels in more relative to less impulsive participants. In this task, effort execution (N-back task performance) and choices (effort discounting) were separated in time, of which only the choices were conducted when tyrosine levels were expected to be elevated.

Interpretation

In line with the hypothesis that catecholamines alter choices about cognitive control investment, we observed, for the first time and in two independent studies, that a catecholamine challenge changed participants' motivation to conduct demanding tasks, including task-switching and N-back tasks. Importantly, both studies showed that drug effects were isolated only when taking into account participants' trait impulsivity scores. Even though chapter 4 was not set up to investigate individual differences in older adults, we explored the link with impulsivity based on chapter 3. Results of the two studies converged, showing consistent effects despite differences in drug manipulation, task, and population. Next to this generalization, chapter 4 extends chapter 3 in different ways; Chapter 3 employs the demand selection task, where choices might represent learning of demand costs because demand is manipulated implicitly. In addition, there was no benefit of engaging in demanding choices, thus the value of control was not (parametrically) manipulated. In chapter 4, we observe a modulation of choices by catecholamine manipulation when measuring cost-benefit decision-making. Thus, we could conclude that a pharmacological catecholamine manipulation modulates the subjective value of cognitive effort in the absence of learning about effort costs. This is in line with the proposal that catecholamines alter cognitive control beyond learning by modulating cost/benefit-based decision making (Cools, 2016; Shenhav et al., 2013). It also converges with empirical findings from animal work, showing that dopamine neurons signal cost-discounted reward values when deciding whether to engage in physical effort (Varazzani et al., 2015). Moreover, work with experimental rodents has shown that amphetamine altered the willingness to invest cognitive effort (Cocker et al., 2012).

One important question remains: What is the mechanism that links trait impulsivity and drug effects on the value of cognitive control? In earlier work, higher trait impulsivity scores were accompanied by enhanced baseline levels of striatal dopamine release and lower presynaptic dopamine D2 receptor availability in the midbrain (Buckholtz et al., 2010). In addition, impulsivity scores correlated with greater catecholaminergic drug effects in previous studies (Clatworthy et al., 2009; Cools et al., 2007). We therefore put forward two possible accounts. One possibility is that in high-impulsive participants, a catecholamine challenge

potentiates the demand cost by eliciting supraoptimal levels of dopamine. This might work by acting on (fewer but perhaps more sensitive) pre-synaptic D2 receptors and thereby triggering a self-regulatory mechanism, leading to a net reduction in dopamine release in more impulsive subjects (Grace, 2001; Seeman and Madras, 2002). An alternative account is that greater drug-induced increases in striatal dopamine in more impulsive participants convey higher opportunity costs (Niv et al., 2007) of engaging with effortful cognition (i.e. opportunity cost; Boureau et al., 2015) resulting in disengagement. Indeed, there are recent proposals arguing that subjective cognitive effort costs reflect opportunity costs (Kurzban et al., 2013).

Ongoing studies address the link between dopamine synthesis capacity (instead of D2 receptor binding (Buckholtz et al., 2010) and various measures including trait impulsivity and cognitive demand avoidance in a large sample. This will help interpret impulsivity-dependent effects, as earlier work showed an association of trait impulsivity with D2 receptor density and drug-induced dopamine release, which only indirectly point towards increased baseline synthesis capacity. The conclusion of our studies is that the self-report measure of trait impulsivity was associated with catecholaminergic drug effects on the motivation to engage in effortful cognition, which is informative, also irrespective of its biological correlate.

Implications for a proxy model, smart drug use, and clinical disorders

In line with earlier work, we observed that drug effects were baseline-dependent and might be predicted by non-invasive, self-report measures (e.g. Clatworthy et al., 2009; Cools et al., 2007). The aim of an ongoing large-scale study (https://www.trialregister.nl/trial/5959) is to reveal a proxy model that helps combine various self-report, cognitive and physiological measures to predict baseline-dependent drug effects. This model should offer a non-invasive, cheap alternative for PET measurements and facilitate personalized medicine on the long term. Here, we observed that drug effects depend on impulsivity scores, supporting its relevance in such a model. Alternative or additional candidates are e.g. eye-blink rate (Groman et al., 2014; Müller et al., 2007, but Dang et al., 2017; Sescousse et al., 2018), color vision (Roy et al., 2003), pupil dilation (Joshi, Li, Kalwani, & Gold, 2016, but Costa & Rudebeck, 2016) or performance on different (reward-related) paradigms.

Next to putative implications of such a proxy model for personalized medicine, these findings might have concrete societal implications. More and more healthy

students and academics use "smart drugs" for cognitive enhancement (Maher, 2008). The key implication of our studies for smart drug use is that not everyone benefits and some cognitive processes, such as the motivation to perform challenging tasks, might even be impaired. Also, in older adults, who have been associated with altered dopamine transmission, tyrosine does not remedy a lack of motivation. Based on our finding, an additional, tentative implication is that especially more impulsive people should not use e.g. methylphenidate when aiming to boost their motivation for studying. This is interesting in part because i) ADHD patients are highly impulsive and commonly treated with methylphenidate, and ii) it is usually the more impulsive students who are more tempted or at risk to try out (smart) drugs (de Wit, 2009). It might be true that other cognitive functions that we did not quantify here do improve in more impulsive participants. Indeed, earlier work evidenced that methylphenidate improves reversal learning in more relative to less impulsive participants (Clatworthy et al., 2009). Here, we observed that methylphenidate and tyrosine speeded up overall responding in the tasks. This illustrates that we cannot conclude (yet) on an individual level who would benefit in which context and emphasizes the need for careful dissemination of research findings to the public. We do not in any way intend to encourage smart drug use or increase pressure on parents or students to do so, as its use is accompanied by risks and side effects (Lakhan and Kirchgessner, 2012), though primarily in chronic use. Researchers who administer drugs that are known as 'smart drugs' in the general population, should be aware of ethical considerations. These have been acknowledged in interesting editorials (Farah et al., 2014; Greely et al., 2009; Partridge et al., 2011; Sahakian and Morein-Zamir, 2011) and thoughtful proposals for the 'responsible use of cognitive-enhancing drugs' (e.g. in a special report by the American Academy of Neurology, September 2009 in Neurology).

Our findings might have clinical implications, because catecholaminergic drugs are the first-choice treatment in several neuropsychiatric disorders that are also characterized by high trait impulsivity (Iacobucci, 2018). It seems paradoxical that methylphenidate enhanced cognitive demand avoidance in more impulsive participants, while in ADHD patients - who are generally highly impulsive - methylphenidate is known to remedy cognitive deficits (Coghill et al., 2013; Faraone and Buitelaar, 2010; Leonard et al., 2004). Our findings highlight the need to i) quantify motivation in addition to execution of cognitive control tasks in patient populations and ii) assess drug-induced changes in the perceived cost of cognitive control to observe whether treatment might actually harm its motivation. A core symptom of ADHD in the DSM-5 diagnosis is "avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort". Thus, there is some progress in taking into account motivational factors in ADHD (diagnosis)

(Mies et al., 2019; Morsink et al., 2017; Sergeant, 2005; Sonuga-Barke et al., 2003), but future work should further assess whether this and more disorders should be described and treated as disorders of the will. Note that our findings were obtained in the lab-context of choices with little alternative opportunity than doing a task (easy versus hard). The question remains whether the effects generalize to real-life environments where high effort choices are compared against taking a break or more rewarding activities.

Limitations

One caveat of our studies is that we do not know how task performance alters effort avoidance and, therefore, whether drug effects on effort avoidance (partly) reflect changes in (perceived) task performance. This is an important limitation, given i) that the more demanding option is usually accompanied by poorer performance (higher error rate, longer response times), ii) drug effects on task execution in addition to choices, and iii) earlier work indicating that performance feedback and the (false) belief about one's capacity altered cognitive control performance, motivation to perform a task (Clarkson et al., 2011; Vallerand and Reid, 1984). For example, in chapter 3, participants made more mistakes when more frequent task-switching was required; in chapter 4, performance decreased as a function of working memory load. We aimed to minimize the impact of performance on choices by refraining from providing any performance feedback in chapter 3 and by splitting performance and choice (i.e. effort discounting) in two separate parts of the experiment in chapter 4. Only the second part took place when tyrosine effects were peaking, thus minimizing drug alterations of performance. To assess whether intervention effects on choice reflect indirect modulations of the capacity to execute a task, we analyzed, in addition to changes in choices, the effect of the intervention on task performance. We observed that in both tasks, accuracy was not different as a function of drug and impulsivity, thus failure avoidance should not have driven the changes in demand avoidance. However, methylphenidate speeded responding in more impulsive participants irrespective of demand (Chapter 3) and tyrosine reduced level-induced slowing on the N-back task as a function of impulsivity (Chapter 4). Thus, more impulsive participants who expressed lower motivation for cognitive control also showed speeding on the cognitive control tasks. This is not in line with an account in which time on task enhances subsequent avoidance or reduces its value. One might argue that the opposite (but not correlating) drug-induced effects on value and response speed can be explained by a drug-induced increase in the capacity of effort allocation which results in faster responding but the enhanced effort

investment was then perceived as more costly. We cannot address this hypothesis with the current data. Future work may employ pupil dilation, as this has been suggested to correlate with effort allocation (Kahneman and Beatty, 1966; Massar et al., 2015) and might be used as an index of effort investment.

One key remaining open question is whether the observed drug effects reflect modulations of dopamine, noradrenaline or both. Our hypotheses were motivated primarily by a robust literature on dopamine's role in physical effort and cost-benefit decision making. However, both our pharmacological interventions do not selectively stimulate dopamine transmission, but also noradrenaline (Kishore et al., 2013; Kuczenski and Segal, 2001; Scheel-Krüger, 1971). The locus-coeruleus-noradrenaline system has been associated with processes closely related to cognitive effort, such as mental fatigue (Berridge and Waterhouse, 2003), task engagement (i.e. exploitation) versus disengagement (i.e. exploration)(Aston-Jones and Cohen, 2005; Gilzenrat et al., 2010), lapses of attention (Van den Brink et al., 2016) and meta-cognitive regulatory functions, including confidence (Hauser et al., 2017). When assessing the distinct contributions of dopaminergic versus noradrenergic neuron activity during effort-based decisions in monkeys, it seems that these systems may play complementary roles in resolving decisions about physical effort investment (Varazzani et al., 2015); dopamine encoded cost-discounted values of rewards, whereas noradrenergic cells modified activity in relation to the amount of effort required to obtain them (Floresco, 2015). In ongoing work, we administer drugs with selective affinity for dopaminergic receptors while quantifying motivation of cognitive control, which will help assess the unique contribution of dopamine in the cognitive domain. The administration of selective drugs has an additional advantage: due to their selectivity to e.g. D2-type receptors, it is possible to draw conclusions about regional effects as D2 receptors are particularly abundant in the striatum.

Cognitive stability is subjectively more costly than cognitive flexibility

(based on chapter 6)

Summary

Exerting cognitive control is perceived as effortful and was suggested to carry an intrinsic cost resulting in its avoidance. However, it is unclear which aspects of cognitive control are accompanied by high effort costs and whether this depends

on the demand for flexible versus stable control. **Chapter 6** presents a novel effort discounting paradigm (see Figure 6.1) that allows to quantify the subjective cost of cognitive processes with specific demands for stable versus flexible control. For this purpose, we merged multiple streams of literature: we added to a well-established working memory task (Zhang and Luck, 2008) an intermediate phase to probe distractor resistance (i.e. cognitive stability) versus flexible updating (i.e. cognitive flexibility) (cf. Fallon and Cools, 2014; Fallon et al., 2016) and a subsequent effort-discounting phase (cf. Westbrook et al., 2013). Based on recent theorizing, the cost of cognitive effort might represent a motivational signal that biases behavior away from focusing on a task towards opening up for new opportunities (Cools, 2016; Kurzban et al., 2013; Musslick et al., 2018). Thus, we predicted that the effort cost of cognitive stability is larger than that of cognitive flexibility. In keeping with prior work (Apps et al., 2015; Massar et al., 2015; Westbrook et al., 2013), we demonstrated in two independent samples (28 and 62 participants respectively) that the subjective cost of conducting cognitive control tasks increased as a function of working memory load . Moreover, the subjective cost of performing a task requiring distractor resistance (i.e. cognitive stability) was higher than that requiring updating (i.e. cognitive flexibility; see Figure 6.4).

Interpretation

Results of this study indicated that our novel task is sensitive to changes in subjective value based on the load manipulation and that both processes carry an effort cost. Based on our research question, we assessed in two ways whether tasks requiring cognitive stability carry a greater subjective cost than do tasks requiring cognitive flexibility; we quantified the cost i) indirectly, by letting participants compare and choose between task engagement (i.e. update or ignore trials) and taking a break ('no redo') and ii) directly by contrasting choices between updating versus ignoring for varying levels of rewards. Both discounting task versions indicated a greater cost of cognitive stability, which is also replicated in the second, larger sample. These internal and independent replications strengthen our confidence that the task is reliable and conclusions are valid.

But why is cognitive stability perceived as more costly or put differently, cognitive flexibility as more valuable? We speculate that the effect of task demands on subjective cost reflects an opportunity cost of focusing: Focusing does not allow novel input and thus, alternative opportunities, to impinge on current processing, aligning with the hypothesis that subjective effort costs bias against stability in favor of flexibility (Musslick et al., 2018). Alternative interpretations of the findings are less likely; in this task version, the delay between target stimuli

and the target response is matched between conditions. This implies that the demand for maintaining the relevant stimulus is identical and cannot explain a value difference. However, by equalizing this relevant delay, the total trial duration differs between conditions; update trials are longer because the target stimuli are only presented during the intervening phase. If effort costs reflect an opportunity cost of time (Niv et al., 2007), we should observe a preference for faster, shorter processes. This account would thus predict the opposite pattern with a preference for the shorter ignore trials. However, a failure-avoidance account makes predictions that are congruent with our findings as participants perform less accurately (i.e. larger deviance from the correct color) in the ignore condition, which is also perceived as more costly. We consider it unlikely that this fully accounts for the change in effort cost, given the absence of performance feedback during effort execution and the fact that 'accuracy' reflects deviance from the target color instead of dichotomous correct/incorrect judgment. On the highest levels, performance on the two conditions differed on average by only 5 degrees. In addition, a statistical model that takes performance into account still revealed the condition effect of interest and we instructed participants that payments are not contingent on performance during a redo.

Implications for cognitive training in young adults and future paradigm application

Focusing is crucial for completing our goals, but flexibility is essential when goals change. Our findings suggest that young healthy adults are better in responding flexibly to environmental triggers and also prefer to do so when contrasted with their inhibition. Sometimes, flexibility is useful as it allows us to explore alternative ways to solve a problem and come up with new ideas, i.e. to be innovative and creative. However, these findings are also worrisome when considering our ever-changing stimulating environment. I aim to finish my thesis instead of responding to Twitter notifications or Pinterest pop-ups. I aim to consume a healthy diet instead of acting on a McDonald's advertisement while driving. Most people manage to engage in effortful focusing when needed and some people even prefer to do so, but it seems that the majority of our healthy student sample prefers flexible cognition. Different interventions, such as mindfulness or meditation training might help to increase the value of focus as assessed with this task. Mindfulness consistently improves inhibition but has mixed effects on updating and shifting, a literature review suggests (Gallant, 2016). Future studies should assess whether it is beneficial to train focus and distractor inhibition (i.e. self-control) in young adults or whether we should consider adaptations in e.g. our educational and

media settings to match an individual's preference for distractibility versus focus (see Future directions).

In the context of this study, we developed and extensively tested a novel paradigm that might offer a quantitative measure of cognitive and motivational deficits in a healthy and patient population. Before we conducted this study, we knew that various cognitive control tasks can be perceived as costly, also in patient populations (Gold et al., 2015). However, many tasks, but also many situations in everyday life rely on a mixture of focus and flexibility. For example, successful completion of the N-back task (Chapter 4) requires participants to keep online in working memory recently presented stimuli (i.e. cognitive stability), but also updating initially relevant ones (i.e. cognitive flexibility). Likewise, the task-switching task (Chapter 3) depends on task set maintenance, distractor inhibition and updating of task sets. Our novel paradigm allows explicit quantification of the motivation for cognitive control with distinct demands for cognitive flexibility versus stability, while many disorders are actually characterized by a shift in the flexibility/stability tradeoff. As mentioned in the introduction, ADHD for example is accompanied by excessive distractibility but perhaps better flexibility and creativity (Boot, Nevicka, & Baas, 2017, but Healey & Rucklidge, 2005). Patients suffering from Parkinson's disease or obsessive-compulsive disorder in contrast suffer from rigid, compulsive cognition with trouble switching to new things (Cools, 2001; Cools et al., 1984; Gu et al., 2008; Lees and Smith, 1983; Meiran et al., 2011). We hypothesize that neuropsychiatric disorders might in fact reflect changes in preference and not (only) an inability to focus or to let go. Using our paradigm, future studies can assess whether ADHD patients or distractible healthy colleagues might rather be unmotivated to focus and prefer to process (also distracting) stimuli. Our paradigm is well suited to be administered in intervention or medication studies to investigate treatment effects on motivation. The main reason why it is suited for acute intervention studies is that task execution and choices are split in time which enables the assessment of drug effects on the motivation only. In addition, baseline task measures and their alteration by chronic treatment might yield more objective guidance in choice of therapeutic drug than subjective (physician) reports. One remaining open question is whether the administration of e.g. methylphenidate or tyrosine would shift the performance versus motivation for flexible and stable cognition in healthy and patient populations. This question is currently investigated in ongoing studies.

Limitations

As described in the previous limitations section (p. 211), we cannot rule out that (perceived) performance failure reduced the value of redoing the task. That is, the 'more costly' ignore condition was again accompanied by poorer performance in terms of accuracy (i.e. deviance from target). We argued above (see Interpretation) that we consider it unlikely that this fully accounts for the change in effort cost, given the absence of performance feedback and performance-contingent rewards and given that control analyses still reveal the condition effect of interest. Future work should address this limitation by matching performance or assess the effect of feedback manipulation on subjective value of control.

There are several practical limitations of this paradigm. First, the task is extensive and takes a long time to complete (~2 h), as participants need to complete the color wheel working memory task probing ignore and update trials of four different levels before conducting the choice task which contains more than 500 choices with 3 repetitions of each choice. Earlier versions employed staircase procedures (see chapter 4) which are more efficient but perhaps less valid; the choice sequence is fixed and every choice pair is sampled only once, assuming that choices are deterministic. However, choices have been shown to be probabilistic (Rieskamp, 2008) which is taken into account in our paradigm by sampling every choice option three times. Future work should compare these approaches to find a powerful, yet efficient design. Second, performance relies on correct perception of colors, thus it cannot be administered in color-blind participants. Intriguingly, color perception has recently been linked to dopamine transmission, as dopamine can be found in high concentration in the retina (Bodis-Wollner and Tzelepi, 1998; Witkovsky, 2004). Accordingly, color discrimination has been shown to be affected in patients suffering from neuropsychiatric conditions implicating dopaminergic functioning, such as ADHD, cocaine use and Parkinson's disease (Hulka et al., 2013; Melun et al., 2001; Paulus et al., 1993; Pieri et al., 2000; Tannock et al., 2006). This practical limitation needs to be taken into account when intending to compare performance between participants or patient groups. Note that we started the experiments with a color sensitivity test to make sure that participants were in principle able to select the distinct color stimuli on the color-wheel. In addition, we were interested in the distinct processes of cognitive stability versus flexibility which were manipulated within subjects and should therefore not be differentially affected by color perception. Future studies should address the link between dopamine transmission and the ability to discriminate colors and assess the suitability of this paradigm for patient populations.

Catecholamine challenge impairs distractor inhibition in older adults

(based on chapter 5)

Summary

Adaptive behavior relies on a dynamic arbitration between focus and flexibility. As introduced in 1.3, dopamine in the prefrontal cortex is thought to support primarily cognitive stability (Braver and Barch, 2006; Koechlin, 2003; Miller, 2000; Seamans and Yang, 2004), while striatal dopamine has been proposed to be involved in cognitive flexibility (Cools, Barker, Sahakian, & Robbins, 2003; Hazy et al., 2007; Rogers et al., 2000; see also Figure 1.1B). It seems that older adults generally perform poorly when tasks put a high load on cognitive stability (Dunnett et al., 1988; Wang et al., 2012), perhaps due to a decline in dopamine in the prefrontal cortex (Goldman-Rakic, 1997; Goldman-Rakic and Brown, 1981; Karrer et al., 2017). In **chapter 5**, we assessed the behavioral and neural effects of administering the catecholamine precursor tyrosine on distinct processes of working memory: distractor inhibition (i.e. cognitive stability) versus updating of working memory representations (i.e. cognitive flexibility)(Figure 5.2). We predicted that tyrosine might improve distractor inhibition by increasing the signal-to-noise ratio of task-relevant representations in the PFC but impair the degree to which working memory representations can be updated, thus reduce flexibility. Contrary to this prediction, we observed that tyrosine reduced distractor inhibition in older adults, evidenced by a larger distractor cost on trials requiring stabilization compared with that on flexible update trials after tyrosine administration (Figure 5.3C-D). This effect was accompanied by a tyrosine-induced increase in update-versus ignore-related activity in a cluster containing the right anterior cingulate cortex and medial frontal cortex (Figure 5.3B). Following impulsivity-dependent effects of methylphenidate (Chapter 3) and tyrosine (Chapter 4) reported above, we also explored in this paradigm whether tyrosine altered neural and behavioral effects in a baseline-dependent manner. Here again, we observe that tyrosine effects depended on trait impulsivity scores. More impulsive participants showed a greater shift towards cognitive flexibility, accompanied by a greater increase in update-related activity in putamen, insula and postcentral gyrus, all relative to less impulsive participants.

Interpretation

In this study we employed a delayed match-to-sample task that has earlier been developed to probe cognitive stability and flexibility in the working memory domain. We show that neural and behavioral task effects align well with earlier administrations of this task (Fallon and Cools, 2014; Fallon et al., 2008). However, in young adults the administration of methylphenidate improved distractor resistance but impaired flexible updating by increasing ignore-related activity in the dorsolateral prefrontal cortex (Fallon et al., 2016). Here, we observed the opposite effects when administering tyrosine: older adults became less resistant to distraction, evidenced by an increased performance cost when the distractor (versus a novel stimulus) was probed. In the update condition, disengagement of the initially encoded stimuli, if anything, improved. We interpret this as a tyrosine-induced increase in the gating of relevant (i.e. in the update condition), but also irrelevant (i.e. in the ignore condition) working memory representations, in line with a key role for striatal dopamine in cognitive flexibility (Cools et al., 2007; Hazy et al., 2007). However, in earlier work in young adults, cognitive flexibility has been associated with an increase in striatal activity. Here, in the older sample, we observed significant update-related increases in anterior cingulate cortex (ACC) and medial frontal cortex. Next to the involvement of the medial frontal cortex in promoting flexible behavior, including set shifting (Buchsbaum et al., 2005; Floresco et al., 2008a; Stefani et al., 2003) and task-switching (Rushworth et al., 2013), the ACC has also been shown to signal the value of disengaging from a current option, in a foraging task in young adults (i.e. foraging value (Kolling et al., 2016). An open question is whether the observed tyrosine effects are specific to older adults due to age-related changes in the catecholamine system or whether this drug would also increase ACC-activity and distractor costs in a young population.

In chapter 6 we propose a link between sensitivity to effort costs and the ability to focus, in line with the idea that the (subjective) cost of cognitive effort serves as a motivational signal to prevent over-fixation on a current ongoing task and to promote cognitive flexibility and switching to alternative tasks (Cools, 2016; Inzlicht et al., 2014; Kool et al., 2010; Kurzban et al., 2013). Here, we speculate about a role for catecholamines in eliciting the shift in flexibility/stability tradeoff in working memory (in part) by altering the subjective cost of mental effort (Cools et al., 2008). This speculation is based on an explorative analysis in which we correlated data from the same participants on the working memory paradigm with the cognitive effort discounting task described in chapter 4 and 7.1.1. We assessed whether tyrosine effects on the effort cost correlated with tyrosine effects

on the update (versus ignore) benefit. Interestingly, the individuals who expressed the greatest increase in cognitive effort costs also exhibited the greatest shift away from stability towards flexibility with tyrosine, evidenced by a correlation of medium effect size. This observation extends the finding described in chapter 6 in suggesting that changes in catecholamine transmission elicit a shift in flexibility/stability tradeoff in working memory by altering the subjective cost of mental effort (Cools, 2016).

Implications for cognitive training, motivation and tyrosine use in older adults

What did this study tell us about flexibility versus stability in aging and the potential role of tyrosine in remedying cognitive deficits? Our study suggests that working memory performance in older adults suffers less from irrelevant distractors than previously hypothesized (Gazzaley et al., 2005) and that tyrosine made them in fact more distractible. We were surprised to observe that under placebo older adults exhibited a distractor cost (i.e. lure effect) only in the update condition. This implies that they had trouble letting go of the initially encoded stimuli, although the distractor cost was not statistically significantly different from zero in the ignore condition. Instead of an age-related increase in flexibility (Lindenberger and Mayr, 2014), this points towards cognitive rigidity in older adults, concurring with earlier reports on perseverative errors in set-shifting (Gamboz et al., 2009; Ridderinkhof et al., 2002), failed reversals in a reversal learning task (Weiler et al., 2008) and increased task-switching costs (Kray et al., 2002) in healthy older adults. Note that in the current paradigm, participants performed better in the flexible updating than in distractor inhibition condition. However, this difference can be a consequence of a shorter delay between relevant stimuli and target presentation in the update condition (see Limitations) and should not be interpreted as an index of a flexibility benefit. When administering tyrosine, the pattern reversed; participants showed distractor effects in the ignore trials but no longer in the update condition. Of course, it depends on the context and environmental demand, whether it is beneficial to be more focused or more flexible. Perhaps the environment of older adults puts a higher weight on stable cognition due to (health) risks of excessive distractibility. For example, being distracted by cell phone conversations while riding a car can have catastrophic consequences. When comparing distractibility in young and older adults in a car-following paradigm in a driving simulator, it seems that older adults were not impaired to a greater degree by multi-tasking (hands-free cell phone conversation) than younger adults (Strayer and Drews, 2004). In this case, it is advantageous to be focused. However, when older

adults are required to flexibly update cues, such as playing Halli Galli with their grandchildren or more seriously, traffic requires them to suddenly brake because a child jumps on the street, tyrosine might improve their performance. Intriguingly, I suggested in 7.1.2 to assess whether mindfulness training could increase the value and ability to focus in younger adults. In older adults, trainings have been developed to delay impairments in or recover cognitive functions. However most cognitive trainings are targeted at reducing distractibility (e.g. Mishra, de Villers-Sidani, Merzenich, & Gazzaley, 2014), improving (working) memory (Berry et al., 2010; Frankenmolen et al., 2018; Mahncke et al., 2006; Vermeij et al., 2016) or speeding of visual processes (Ball et al., 2007; Wolinsky et al., 2015). Few trainings are targeted at improving cognitive flexibility. There is evidence that benefits of task-switching training were transferred to a structurally similar new switching task in older adults (Karbach and Kray, 2009; Minear and Shah, 2008), suggesting that dual task performance can be improved. Future studies should assess dynamic trainings that are tailored towards specific impairments, which can be quantified in several ways; for example, based on performance on cognitive tasks, such as the working memory task employed here (or in chapter 6) or the recruitment of prefrontal cortex during task execution (Vermeij et al., 2017).

Remaining open questions are whether older adults also perceive tasks requiring flexibility as more costly than young adults and, importantly, whether a catecholamine challenge has opposite effects on the subjective cost as a function of age. This might be achieved by administering the novel discounting paradigm (Chapter 6) in young and old adults in future studies. Earlier work using the cognitive effort discounting paradigm (COGED; Figure 4.2) in older and younger adults points towards reduced motivation for conducting an N-back task, but as outlined in 1.3, the N-back task relies on flexible and stable cognitive processes, which can be teased apart in the novel version.

To conclude, would I advice older adults to use tyrosine for cognitive enhancement? Probably not. We observed in chapter 4 that, across the group, tyrosine did not significantly increase motivation for conducting an N-back task and chapter 5 demonstrates significant increases in distractibility. In addition, the same dose of tyrosine has shown to impair N-back performance in older adults (van de Rest et al., 2017) and proactive response inhibition as a function of age (Bloemendaal et al., 2018). Also, the administration of tyrosine in such large amounts (150 mg/kg) increases competition of precursors at the blood brain barrier, thus also reducing precursor availability of other relevant neurotransmitters. The amount of tyrosine that we administered is 4-5 times higher than the advised daily ratio (WHO 1985; Basile-Filho et al., 1998; Food and Nutrition Board of the Institute of Medicine).

A more responsible advice would be to adapt the diet to consume food high in tyrosine concentrations to increase perhaps reduced dopamine transmission in the aging brain (Karrer et al., 2017 but Berry et al., 2016). An increase in daily tyrosine intake has indeed been associated with cognitive benefits in older adults (Kühn et al., 2017).

Limitations

The study design and the interpretation of findings have several caveats, also discussed in chapter 4. First, the performance comparison between update and ignore conditions of e.g. the placebo sessions cannot be used as an index of an age-related shift in the update/ignore tradeoff. This is the case, because these conditions differ not only in terms of the relevant manipulation of distractor resistance versus updating, but also in their demands for working memory maintenance. Unlike the novel paradigm presented in chapter 6, here the task conditions are of identical total duration, but the delay between to-be-matched stimuli and probe is shorter for the update condition than the ignore condition. Note that this limitation does not affect our main interpretations, because these are based on within-subject tyrosine-induced *changes* in performance. For exploring patterns in placebo or tyrosine sessions separately, we looked at probe-dependent effects within update and ignore conditions, which are less sensitive to the timing issue described above. Also, this limitation is less problematic for the fMRI analyses, as we focus on the intervening phase where the process of updating or ignoring took place. Up to that point participants encountered identical visual input (i.e. encoding) and identical demand for maintenance in the two conditions. Yet, it is important to emphasize that any proposal on age-related enhancement in rigidity (see Implications) need to be assessed in future studies comparing performance of older adults with that of younger adults.

Second, there is inconsistency in the literature regarding alterations of catecholamine synthesis in healthy aging with reports on reduced, but also enhanced dopamine and noradrenaline synthesis (Berry et al., 2016; Karrer et al., 2017; Manaye et al., 1995; Wang et al., 2013). This complicates the interpretation of intervention effects. If synthesis is indeed increased, the administration of additional tyrosine might lead the rate-limiting TH enzyme to inhibit further transformation of tyrosine into L-DOPA for homeostatic reasons (Fisone et al., 2001; Grace, 2001). As a consequence, tyrosine administration might decrease instead of increase dopamine synthesis and transmission in older adults. We did not measure central tyrosine levels here, but earlier work shows that an identical tyrosine dose increased peripheral tyrosine levels to a greater degree in older

than in younger participants (van de Rest et al., 2017). It is unclear whether this reflects a higher peripheral need of tyrosine in older adults resulting in less central tyrosine availability. Future work might investigate this mechanism, which is relevant for the interpretation of the tyrosine effects in chapter 3 and chapter 4.

Lastly, in line with the limitations described above (p. 212), one key remaining open question is whether the observed drug effects reflect modulations of dopamine, noradrenaline or both. This is pertinent also because tyrosine has been shown to affect both, dopamine and noradrenaline synthesis (Kishore et al., 2013; Kuczenski and Segal, 2001; Scheel-Krüger, 1971) and both systems were suggested to affect processes related to working memory and cognitive flexibility (Alexander et al., 2007; Sales et al., 2019).

FUTURE DIRECTIONS

The studies presented in this thesis have increased our insight into the catecholaminergic modulation of cognitive control and the motivation to conduct cognitively effortful tasks. However, the findings also raise new questions that may be addressed in future studies. Concrete follow-up studies were mentioned in the limitation and implication paragraphs, such as selective manipulations of dopamine versus noradrenaline or performance-matching on cognitive effort tasks. Here, I want to go beyond concrete follow-up steps and highlight two novel approaches and future directions.

Learning from effort costs versus effort relief?

Effort-based decision-making concerns how we make choices based on the integration of expected effort and reward (Shenhav et al., 2013). Yet, relatively little is known how the cost of a cognitive action, such as a mental effortful task, contributes to the (learning of) choices to engage or avoid effortful control. Striatal dopamine promotes motivated behavior (Berridge and Robinson, 1998) and has been suggested to play a role in overcoming physical and cognitive effort 'costs' (Manohar et al., 2015; Salamone and Correa, 2002). In addition, dopamine influences choices via (reinforcement) learning (Glimcher, 2011; Montague et al., 2004), where phasic dopamine release signals unexpected rewards and reward-predicting cues (Schultz, 1997). In the case of learning about simple states and/or actions, it has previously been shown that increases in dopamine potentiate the impact of benefits (reward) on learning and choice, while undermining the impact of punishment (and other costs) on learning and choice (Collins and Frank, 2014; Cools et al., 2009). Future studies could employ computational modeling of learning task data to disentangle the degree to which the effect of catecholaminergic interventions on demand avoidance reflect learning (or choice) based on reward (i.e. effort relief) or punishment (i.e. effort cost). In one of our studies (Chapter 3), greater methylphenidate effects on demand avoidance in the high-impulsive subjects might represent greater increases in striatal dopamine, thereby potentiating the impact of mental effort relief (i.e., reward) on learning and choice. The present study was not set up (and, given high response stickiness rates, did not allow us) to make this distinction. Critically, as is the case in chapter 3, evidence indicates that there is large individual variability in the direction and extent of the effects of dopaminergic drugs on the learning and choice (van der Schaaf et al., 2013; Swart et al., 2017). Intriguingly, there are also reports on effort being perceived as valuable (Inzlicht et al., 2018) and some participants indicated in chapter 6 that they prefer to do a task instead of taking a break. We

hypothesize that baseline dopamine levels, perhaps reflected in impulsivity scores, might relate to the sensitivity to (learn from) cognitive effort costs versus effort relief, similar to a role of dopamine and impulsivity in reward versus punishment sensitivity (Frank et al., 2004; Potts et al., 2006).

Power of motivation - non-pharmacological interventions to promote motivation

As described above, striatal dopamine promotes motivated behavior (Berridge and Robinson, 1998) and has been suggested to play a role in overcoming physical and cognitive effort 'costs' (Manohar et al., 2015; Salamone and Correa, 2002). Like dopaminergic drugs, the promise of a reward implicates the dopamine system and has been shown to alter cognitive performance and the willingness to engage in physical and cognitive effort (Massar et al., 2016; Padmala and Pessoa, 2011). I suggest to investigate the potential role of feedback and task structure on cognitive motivation beyond the lab settings. In children, academic motivation was primarily measured with self-report questionnaires (e.g. Broussard & Garrison, 2004; Entwistle, 1968) or observational assessments of motivation while solving challenging puzzles in kindergarten (Berhenke et al., 2011). These subjective measures were indicative of academic performance (Entwistle, 1968) and teacher rating of children's academic achievement (Berhenke et al., 2011), emphasizing the key contribution of motivation to academic success. However, employing cognitive tasks in educational settings has two advantages. First, it yields a more objective, rater-independent measure of motivation for cognitive control. Second, it can be easily adapted to quantify the motivation for specific aspects of cognition, such as flexible versus stable cognition (Chapter 6), feedback versus no feedback, and valence of feedback. This information can be implemented in educational programmes tailored to individual preferences. There are several reasons for the need of a tailored approach when intending to promote motivation; for example, it is very striking that adults perceive tasks as more costly that were accompanied by poorer performance (Kool et al., 2010; Westbrook et al., 2013), while effort-discounting in children evidenced demand instead of error avoidance (Chevalier, 2018). However, not everyone avoids effort; also, in adults there are reports on effort being perceived as valuable (Inzlicht et al., 2018) and some participants indicated that they prefer to do a task instead of taking a break (Chapter 4), despite greater risks of failing. Similar individual differences have been reported with respect to the promise of performance-contingent reward; the promise of reward might promote motivation in most students, but actually impair motivation and performance in others (Aarts et al., 2014, Chapter 3, Chapter

4). The development of such task batteries and programmes should happen in close collaboration with educational scientists and teachers to allow successful implementation and realistic goal-setting.

CONCLUSION

The overall goal of this thesis was to characterize the role of catecholamines and specific task-demands in shaping our motivation for cognitively demanding processes in the healthy population. First, we show in two independent studies that a pharmacological challenge of the catecholamine system alters cognitive effort avoidance as a function of trait impulsivity; in more relative to less impulsive participants, methylphenidate increased demand avoidance in a young adult sample and tyrosine increased the cost of conducting an effortful working memory task in older adults (aged 60-75). Second, using a novel effort discounting procedure, we quantified the cost of conducting a working memory task with distinct demands for flexible (i.e. updating) versus stable (i.e. distractor inhibition) cognition. Findings of two studies converge in indicating that distractor inhibition is accompanied by a greater effort cost than flexible control. Third, the administration of tyrosine to older adults impaired the ability to inhibit distractors and tended to improve flexible updating in a working memory task. This was accompanied by update-related increases in anterior cingulate cortex activity.

In sum, the studies presented in this thesis demonstrate that cognitive control is costly and that catecholaminergic drugs do not just alter the ability to perform a task but also the motivation to do so. This is in line with the idea that catecholamines have a double duty in altering cognitive control performance but also decisions about cognitive control investment.

APPENDIX A

References

Summary

Dutch summary

Acknowledgements

About the author

List of publications

Donders Graduate School

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SUMMARY

In this dissertation, I studied the phenomenon of (un-)motivated cognition. The overarching goal was to characterize the role of catecholamines (dopamine and noradrenaline) in shaping the motivation for cognitively demanding processes in the healthy population. The mental couch potato described in the title is a metaphor for someone who enjoys to put his *brain* on a couch and watch Netflix instead of engaging in effortful cognition, such as conducting Sudoku puzzles. Understanding the basis of such cognitive 'laziness' will bring us closer to the long-term goal, which is to promote the motivation in the healthy and clinical population to engage in cognitive control. In this dissertation, I

- quantified the willingness (i.e. motivation) to conduct cognitively effortful tasks and assessed how the motivation is affected by pharmacological interventions that challenge the catecholamine system (chapter 3 and 4);

- developed a novel paradigm that allowed to quantify the motivation to engage in flexible versus stable cognition (chapter 6);

- studied how drugs that challenge the catecholamine system alter performance on a task probing flexible versus stable cognition (chapter 5).

Cognitive control is a broad term that can be defined as the capacity to guide behavior in the service of internally represented goals. As such, it is an umbrella term that refers to the set of cognitive functions that enable us to stabilize our goals by resisting impulses, temptation and distraction. In this thesis, I studied cognitive control from two perspectives: i) the motivation to engage in cognitive control functions and ii) the neural and behavioral mechanisms of cognitive stability and cognitive flexibility.

Motivation to engage in cognitive control

When cognitive control is assessed in the lab or exams are graded, it is often assumed that the performance or grades reflect a person's true and maximal capacity. This implies that we always perform at our best. However, there is a rich body of evidence suggesting that this is not the case. Participants who receive a bonus or monetary incentive for good performance tend to improve their performance. Thus, it seems that people do not always perform at their best and that cognitive control performance is a mixture of (at least) the capacity

to perform to best of one's ability during a certain task and the motivation, or choice, to do so.

In **chapter 2,** we highlighted in a literature review the potential contribution of the major ascending neuromodulators, in particular catecholamines, to the tendency to avoid cognitive control. We argued that striatal dopamine alters choices about cognitive control (avoidance) by modulating the expected value of cognitive task performance. Thus, we hypothesized that increases in striatal dopamine lead to an emphasis on the benefits, but reduced weight on the costs of cognitive control. Based on further empirical evidence for baseline-dependency of catecholaminergic manipulations, we also hypothesized that excess or suboptimal levels of dopamine might paradoxically reduce the value of cognitive control.

To assess contributions of catecholamines to cognitive demand avoidance, we setup two pharmacological experiments. In these studies, we quantified how catecholamine challenges alter value-based decision making about cognitive control investment. In chapter 3, we administered the catecholamine transporter blocker methylphenidate and assessed demand avoidance in a large sample of young adults to probe individual differences in drug effects. Chapter 4 describes how the catecholamine precursor tyrosine altered the subjective value of cognitive effort in older adults.

In **chapter 3,** healthy young adults conducted a demand selection task twice, once with 20 mg intake of methylphenidate and once after taking a placebo pill. In this task, participants chose between two pictures of which one has a low and the other a high demand on task-switching. The proportion of low-demand choices was used as an index of demand (i.e. task-switching) avoidance. Earlier research has shown that there is large individual variability in the direction and extent of catecholaminergic drug effects on human cognition and that the individual differences reflect dependency on baseline levels of dopamine. We therefore included in the study two putative proxy measures of dopamine levels: working memory capacity as assessed with the listening span and trait impulsivity measured by the Barratt Impulsiveness Scale. In line with our predictions, participants preferred the option with lower demand for task-switching (i.e. mental couch potatoes) and methylphenidate altered demand avoidance in a baseline-dependent manner. Methylphenidate intake increased demand avoidance in more relative to less impulsive participants, whereas methylphenidate effects on task-switching performance were not found.

In **chapter 4,** we administered the catecholamine precursor tyrosine to 29 healthy senior adults (aged 60-75), given that aging has been associated with reductions in dopamine transmission and reduced motivation for cognitive control. We hypothesized that tyrosine (relative to placebo) increases the value of control, as measured by the cognitive effort discounting paradigm. Contrary to our prediction, tyrosine administration did not (significantly) increase the subjective value of conducting an N-back task for reward, as a main effect. Instead, in line with chapter 3, drug effects varied as a function of participants' trait impulsivity scores. Specifically, tyrosine reduced the subjective value of conducting higher N-back levels (again) in more relative to less impulsive participants. In this task, effort execution (working memory performance) and choices (effort discounting) were separated in time, of which only the choices were conducted when tyrosine levels were expected to be elevated. Together these studies provide first empirical evidence in humans that catecholaminergic drugs act in part by modulating value-based (learning and/or choice) processes that can boost but also undermine the willingness to exert cognitive control. This leads to re-conceptualize cognitive control as involving cost/benefit choice in addition to ability.

Cognitive flexibility versus stability

The need for an optimal balance between flexible and stable cognition can be illustrated easily by means of the office life: When you share an office with multiple people, it requires you to inhibit incoming distractors, such as office mates running in and out or conversations with students. However, when the fire alarm in the building goes off, you should be able to allow registration of the signal and act on it. Many situations in everyday life and experimental paradigms rely on a mixture of these processes. Performance impairments can therefore be a consequence of reduced stability and/or increased flexibility. In chapter 5 & 6, we studied the opposing functions by administering an adapted delayed match-to-sample task. Like in delayed match-to-sample tasks, participants needed to encode stimuli and judge after a delay whether a probe is a 'match' or 'non-match'. However, during the delay period, we either present distracting stimuli that need to be ignored (i.e. the office mates), or stimuli that need to be processed (i.e. the fire alarm). Many executive functions are known to implicate the cortico-basal ganglia loops that link the prefrontal cortex (PFC) and the striatum and their modulation by dopamine. The prefrontal cortex has been suggested to support the stabilization of goals and distractor resistance while the striatum has been associated with the de-stabilization of goals with the purpose of letting in new environmental stimuli for flexible responses. One hypothesis for how the brain arbitrates between stable

versus flexible states is with the use of a dopamine-dependent gating mechanism that regulates the inputs to PFC.

In **chapter 5**, we assessed the behavioral and neural effects of administering the catecholamine precursor tyrosine on distinct processes of working memory: distractor inhibition (i.e. cognitive stability) versus updating of working memory representations (i.e. cognitive flexibility). We administered this task in 29 senior adults (identical sample as described in chapter 4) given that aging has been associated with reductions in dopamine transmission and a shift in flexibility/stability tradeoff. We predicted that tyrosine (relative to placebo) improves age-related impairments in distractor inhibition by increasing the signal-to-noise ratio of task-relevant representations in the PFC. At the same time, we expected tyrosine administration to impair the degree to which working memory representations can be updated, thus reduce flexibility. Contrary to this prediction, we observed that tyrosine reduced distractor inhibition, evidenced by a larger distractor cost on trials requiring stabilization compared with that on flexible update trials after tyrosine administration. This effect was accompanied by a tyrosine-induced increase in update- versus ignore-related activity in a brain cluster containing the right anterior cingulate cortex and medial frontal cortex.

In the light of motivated cognitive control described above, one might expect that changes in the flexibility/stability tradeoff, as evidenced here, (partly) reflect changes in preference and not just an inability to focus or flexibly update. Distractible colleagues might rather be unmotivated to focus and prefer to process (also distracting) stimuli.

In **chapter 6**, we therefore developed a novel effort discounting paradigm that allowed to quantify the subjective cost of cognitive processes with specific demands for stable versus flexible control. For this purpose, we added to a well-established working memory task an intermediate phase to probe distractor resistance (i.e. cognitive stability) versus flexible updating (i.e. cognitive flexibility) and a subsequent effort-discounting phase. Based on recent theories, the cost of cognitive effort might represent a motivational signal that biases behavior away from focusing on a task towards opening up for new opportunities. We therefore predicted that the (effort) cost is larger when the task requires cognitive stability, compared with cognitive flexibility. In keeping with prior work on cognitive demand avoidance, we demonstrated in two independent samples (28 and 62 participants respectively) that the subjective cost of conducting cognitive control tasks increased as a function of working memory load. Moreover, the subjective cost of performing a task requiring distractor resistance (i.e. cognitive stability)

was higher than that requiring updating (i.e. cognitive flexibility), even after taking into account performance effects.

CONCLUSION

First, we demonstrated in two independent studies that a pharmacological challenge of the catecholamine system altered cognitive demand avoidance as a function of trait impulsivity; in more relative to less impulsive participants methylphenidate increased cognitive demand avoidance in a young adult sample and tyrosine increased the cost of conducting an effortful working memory task in senior adults (aged 60-75). Second, using a novel effort discounting procedure, we quantified the cost of conducting a working memory task with distinct demands for flexible (i.e. updating) versus stable (i.e. distractor inhibition) cognition. The findings of these two studies converge in indicating that distractor inhibition is accompanied by a greater effort cost than flexible control. Third, the administration of tyrosine to older adults impaired the ability to inhibit distractors and tended to improve flexible updating in a working memory task. This was accompanied by update-related increases in anterior cingulate cortex activity. In sum, the studies presented in this thesis demonstrate that task execution with a high demand for cognitive control is perceived as subjectively costly and that catecholaminergic drugs do not just alter the ability to perform a task but also the motivation to do so. This is in line with the general proposal that catecholamines have a double duty in altering cognitive control performance but also decisions about cognitive control investment.

Future studies should further investigate the potential impact of also non-pharmacological interventions (e.g. task- and feedback structure) on cognitive motivation beyond the lab settings to work towards the long-term goal of promoting motivation in the healthy and clinical population.

DUTCH SUMMARY

In dit proefschrift heb ik de invloed van motivatie op cognitieve controle bestudeerd. Het overkoepelende doel was te bepalen hoe dopamine en noradrenaline (samengevat catecholamines) in de gezonde populatie de motivatie beïnvloeden om inspannende denkprocessen uit te voeren. De mentale "couch potato" die in de titel wordt beschreven, is een metafoor voor iemand die graag zijn hersens op een bank legt en Netflix kijkt in plaats van zich bezig te houden met moeilijke denkprocessen, zoals het uitvoeren van Sudoku-puzzels. Als we de basis van cognitieve 'luiheid' begrijpen, komen we dichter bij het lange termijn doel, namelijk de mogelijkheid om motivatie in de gezonde en klinische populatie te bevorderen om moeilijke denkprocessen niet uit de weg te gaan.

In het kader van dit proefschrift, heb ik

- de bereidheid (d.w.z. motivatie) gekwantificeerd om cognitief inspannende taken uit te voeren en beoordeelde ik hoe de motivatie wordt beïnvloed door farmacologische interventies die het catecholaminesysteem manipuleren (hoofdstuk 3 en 4),

- een nieuw paradigma ontwikkeld waarmee de motivatie gekwantificeerd kan worden om flexibele versus stabiele cognitieve processen uit te voeren (hoofdstuk 6) en

- onderzocht hoe een catecholamine-manipulatie de prestatie verandert op een taak die flexibele versus stabiele controle vereist.

Cognitieve controle is een brede term die kan worden gedefinieerd als het vermogen om gedrag te sturen ten dienste van intern gerepresenteerde doelen. Als zodanig is het een overkoepelende term die verwijst naar de set van cognitieve functies die ons in staat stellen onze doelen te realiseren door weerstand te bieden aan impulsen, verleiding en afleiding. In dit proefschrift heb ik cognitieve controle vanuit twee perspectieven bestudeerd: i) de *motivatie* om cognitieve controlefuncties uit te voeren en ii) de neurale en gedragsmechanismen van twee tegenovergestelde functies: cognitieve stabiliteit en cognitieve flexibiliteit.

Motivatie om cognitieve controle uit te oefenen

Wanneer cognitieve controle in het lab wordt gemeten of examens worden getoetst, wordt er vaak van uitgegaan dat de prestatie of het cijfer de ware en maximale capaciteit van een persoon weerspiegelt. Dit betekent dat de aanname

bestaat dat iedereen altijd op zijn best presteert. Het is echter wetenschappelijk aangetoond dat dit niet het geval is. Bijvoorbeeld, deelnemers die een bonus voor goede prestaties ontvangen zijn geneigd om vervolgens beter te presteren. Het lijkt erop dat prestaties op het gebied van cognitieve controle een combinatie zijn van (tenminste) het vermogen om een bepaalde taak uit te voeren en de motivatie of keuze om dit ook daadwerkelijk te doen.

In hoofdstuk 2 benadrukten we in een literatuuroverzicht de mogelijke bijdrage van de belangrijkste oplopende neuromodulatoren, met name catecholamines, aan het vermijden van cognitieve inspanning. We stelden dat (striatale) dopamine een bijdrage levert aan het vermijden van cognitieve inspanning door de verwachte waarde van cognitieve controle te moduleren. Daarom hebben we de hypothese gesteld dat de verhoging van (striatale) dopamine leidt tot een sterkere nadruk op de voordelen en minder gewicht legt op de kosten van cognitieve controle.

Om de bijdragen van catecholamines aan keuzes over cognitieve inspanning te beoordelen, hebben we twee farmacologische experimenten opgezet. In hoofdstuk 3 hebben we de catecholamine transporter blocker methylfenidaat toegediend aan een groot aantal gezonde jonge volwassen. Hoofdstuk 4 beschrijft hoe de catecholamine-voorloper tyrosine de subjectieve waarde van cognitieve inspanning bij oudere volwassenen veranderde ten opzichte van de placebo sessie.

In hoofdstuk 3 voerden gezonde jonge volwassenen tweemaal een keuzetaak uit, eenmaal met 20 mg methylfenidaat en eenmaal na het innemen van een placebo-pil. In deze taak kozen de deelnemers tussen twee afbeeldingen. Het kiezen van de ene afbeelding leidde deelnemers naar een gemakkelijke taak (d.w.z. minder taak-omschakeling) en het kiezen van de andere afbeelding naar een moeilijke taak (d.w.z. meer taak-omschakeling). Het aantal keuzes van de gemakkelijke optie werd gebruikt als een maat van inspannings-vermijding. We verwachtten dat er grote individuele variabiliteit is in de richting en omvang van de effecten van methylfenidaat en dat deze o.a. afhangt van de initiële staat van het catecholamine systeem. Daarom hebben we in het onderzoek twee maten opgenomen om de dopamine-niveaus te schatten: werkgeheugencapaciteit zoals beoordeeld met de luisterspan en impulsiviteit gemeten door de Barratt Impulsiveness Scale. In lijn met onze voorspellingen waren de deelnemers inspannings-vermijdend (d.w.z. mentale “couch potatoes”) en veranderde metylfenidaat de vermijding als functie van impulsiviteit: methylfenidaat-inname

versterkte 'mentale luiheid' bij meer (t. o. v. minder) impulsieve deelnemers, terwijl effecten op taakprestatie niet werden gevonden.

In hoofdstuk 4 hebben we de catecholamine-voorloper tyrosine toegediend aan 29 gezonde senioren (60-75 jaar oud). Dit heben we gedaan omdat veroudering in verband werd gebracht met vermindering van dopamine-overdracht en verminderde motivatie voor cognitieve controle. Onze hypothese was dat tyrosine de aversie tegen het uitvoeren van cognitieve controle zou verlagen, gemeten aan de hand van een cognitieve inspannings-paradigma. Anders dan in hoofdstuk 3, waren hier de taakuitvoering en de keuzes in de tijd gescheiden, waarvan alleen de keuzes werden uitgevoerd wanneer medicatie-effecten te verwachten waren. In tegenstelling tot onze voorspelling, heeft tyrosine-toediening in deze groep niet de motivatie verhoogt om cognitieve controle (d.w.z. een werkgeheugen taak) uit te voeren. In plaats daarvan, en in overeenstemming met hoofdstuk 3, varieerden de tyrosine-effecten als functie van de impulsiviteits-scores: Tyrosine verminderde de motivatie van het uitvoeren van een moeilijke werkgeheugentaak weer meer in hoog (t.o.v. minder) impulsieve deelnemers. Samen leveren deze studies het eerste empirisch bewijs in mensen dat catecholaminerge geneesmiddelen gedeeltelijk werken door processen te moduleren die de motivatie veranderen om cognitieve controle uit te oefenen en deze dus ook kunnen ondermijnen. Dit onderzoek leidt tot een reconceptualisering van de term cognitieve controle, waarbij, naast het vermogen, ook de kosten en baten van cognitieve controle van invloed zijn.

Cognitieve flexibiliteit versus stabiliteit

Een optimale balans tussen flexibele en stabiele cognitieve processen is voordelig. Dit kan eenvoudig worden geïllustreerd aan de hand van het kantoorleven: wanneer je een kantoor deelt met meerdere mensen, moet je afleiding, zoals het in- en uitwandelen van kantoorgenoten of gesprekken met studenten, negeren. Wanneer het brandalarm in het gebouw afgaat, moet het signaal echter geregistreerd worden om erop te kunnen reageren. Veel situaties in het dagelijks leven en experimentele paradigma's zijn afhankelijk van een combinatie van deze processen. Veranderingen in taakprestatie kunnen daarom bijvoorbeeld een gevolg zijn van verminderde stabiliteit en / of verhoogde flexibiliteit. In hoofdstuk 5 en 6 hebben we de tegengestelde functies bestudeerd door een aangepaste uitgestelde match-to-sample-taak af te nemen. Deelnemers moesten twee plaatjes onthouden en na een vertraging beoordelen of een enkel plaatje op het scherm een 'match' of 'non-match' is met wat ze moesten onthouden. Tijdens het onthouden werden ze echter afgeleid door nieuwe plaatjes die ze óf

moesten negeren (d.w.z. de kantoorgenoten), óf moesten onthouden terwijl ze de oude plaatjes vergeten (d.w.z. het brandalarm). Van veel cognitieve functies is bekend dat ze afhankelijk zijn van functionele cortico-basale ganglia-lussen. Deze lussen verbinden de prefrontale cortex (PFC) en het striatum en worden gemoduleerd door dopamine transmissie. De prefrontale cortex speelt een belangrijke rol bij de stabilisatie van doelen en het buitenhouden van afleiding, terwijl het striatum vooral geassocieerd wordt met het binnenlaten van stimuli om flexibele responsen te bevorderen. Het wordt aangenomen dat het brein tussen een stabiele versus flexibele staat wisselt door het gebruik van een dopamine-afhankelijk poortmechanisme dat de invoer naar de PFC regelt.

In hoofdstuk 5 hebben we de gedrags- en neurale effecten van het toedienen van de catecholamine-voorloper tyrosine op verschillende processen van werkgeheugen onderzocht: focus (d.w.z. cognitieve stabiliteit) versus het updaten van representaties van het werkgeheugen (d.w.z. cognitieve flexibiliteit). We hebben deze taak door 29 senioren (identieke steekproef als hoofdstuk 4) laten uitvoeren. Dit hebben we gedaan omdat veroudering in verband is gebracht met vermindering van dopamine-overdracht en achteruitgang in cognitieve functies die focus vereisen. We voorspelden dat tyrosine de leeftijds-gerelateerde achteruitgang van focus zou verbeteren door de signaal-ruisverhouding van werkgeheugen-representaties in de PFC te verhogen. Tegelijkertijd verwachtten we dat tyrosine-toediening de mate waarin nieuwe plaatjes flexibel kunnen worden bijgewerkt nadelig beïnvloedt. In tegenstelling tot deze voorspelling hebben we vastgesteld dat tyrosine (ten opzichte van placebo) de focus juist verminderde, wat blijkt uit sterkere afleidbaarheid in situaties die stabilisatie vereisen in vergelijking met flexibel updaten. Dit effect ging gepaard met een tyrosine-geïnduceerde toename in de activiteit in de prefrontale cortext wanneer flexible gedrag vereist werd (meer specifiek in een cluster in de rechter anterior cingulate cortex en mediale frontale cortex).

In het kader van motivationele invloeden op cognitieve controle die hierboven zijn beschreven, zou men kunnen veronderstellen dat veranderingen in prestatie gedeeltelijk veranderingen in voorkeur weerspiegelen. Afleidbare collega's zijn misschien minder gemotiveerd om zich te concentreren en verwerken dus liever (ook afleidende) stimuli.

In hoofdstuk 6 hebben we daarom een nieuw paradigma ontwikkeld waarbij gekwantificeerd kan worden hoe aversief deelnemers zijn ten opzichte van cognitieve processen met specifieke eisen voor stabiele versus flexibele controle. Voor dit doel hebben we, zoals ook in hoofdstuk 5, aan een bestaande

werkgeheugentaak een tussenfase toegevoegd om de focus (d.w.z. cognitieve stabiliteit) versus flexibiliteit (d.w.z. cognitieve flexibiliteit) te meten. Bovendien hebben we een extra fase toegevoegd waarin keuzes gemaakt worden over het vermijden van inspanning. Volgens recente theorieën, kan het voelen van cognitieve inspanning een motiverend signaal vormen dat het openstellen voor nieuwe kansen bevordert en daardoor het focussen verslecht. We hebben daarom voorspeld dat de het meer moeite kost wanneer de taak cognitieve stabiliteit vereist in vergelijking met cognitieve flexibiliteit. In overeenstemming met eerder onderzoek naar het vermijden van cognitieve inspanning, hebben we in twee onafhankelijke steekproeven (respectievelijk 28 en 62 deelnemers) aangetoond dat de subjectieve kosten van het uitvoeren van cognitieve controletaken toenamen als functie van de moeilijkheid. Bovendien waren de subjectieve kosten van het uitvoeren van een taak die focus vergde (d.w.z. cognitieve stabiliteit) hoger dan wanneer nieuwe informatie moest worden onthouden (d.w.z. cognitieve flexibiliteit). Dit was zelfs het geval wanneer we rekening hielden met verschillen in prestatie tijdens de taakuitvoering. Het lijkt er dus op dat fouten maken alleen niet kan verklaren waarom focus aversiever aanvoelt.

CONCLUSIE

Ten eerste hebben we in twee onafhankelijke onderzoeken aangetoond dat een farmacologische manipulatie van het catecholamine-systeem de vermijding van cognitieve controle heeft veranderd als functie van impulsiviteit; in meer ten opzichte van minder impulsieve deelnemers verlaagde het toedienen van zowel methylfenidaat als tyrosine de motivatie om moeilijke denkprocessen uit te voeren. Ten tweede tonen we aan dat focus en afleiding gepaard gaan met hogere inspannings-kosten dan flexibele controle. Ten derde heeft het toedienen van tyrosine aan oudere volwassenen het vermogen verminderd om afleiding buiten te houden, maar waren deelnemers juist beter in het flexibel updaten van het werkgeheugen. Kortom, de studies in dit proefschrift tonen aan dat cognitieve controle kostbaar is en dat catecholaminerge geneesmiddelen niet alleen het vermogen veranderen om een taak uit te voeren, maar ook de motivatie om dit te doen. Dit is in overeenstemming met het idee dat catecholamines een dubbele taak hebben, namelijk bij het veranderen van de prestaties van cognitieve controle, maar ook bij beslissingen over de investering van cognitieve controle.

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"True friendship isn't about being inseparable, it's being separated and nothing changes."

I sometimes wish I had my close friends as neighbours and just drop by for coffee every now and then, but unfortunately, most of my friends live spread out meaning at least weekend-trips. Still, knowing that you are there and spending weekends with you, has helped this thesis' author tremendously! :)

★ Bielefeld Mädels

Ach, meine lieben Handball-Mädels (**Karen, Maren, Henny, Steffi, Milena, Katta, Katha, Kira, Rena, Laui, Jessi, Mona)**! Wie oft habe ich in den letzten Jahren Geburtstage und Co absagen müssen weil ihr so weit weg seid. Das tut mir leid! Ihr bedeutet mir viel und ich freue mich, dass ich jetzt wieder etwas näher wohne! Manchmal würde ich einfach gerne den Bollerwagen nehmen, Finerau singen und wie in alten Zeiten mit Ghettoblaster durch die Spenger Kurven ziehen… ihr habt mich versaut ;) Das gleiche gilt für **David**. Wir haben uns in den letzten 5 Jahren vielleicht 2-3 Mal gesehen, aber im Herzen bist du mir ganz nahe!

★ Wafelclubje

Mijn hemel wat is er in de laatste 12 jaar veel gebeurd, **Johanna, Charlotte, Nadine, Annika, Lisa, Tini**. Ik weet nog zo goed hoe wij in 2007 allemaal met grote verwachtingen aan de taalcursus in Enschede begonnen. Ik zou nooit meer zonder jullie willen… inmiddels zitten we allemaal in andere steden en zijn hartstikke druk met trouwen, familie stichten en huizen bouwen, maar de Wafelclubje chat is nooit stil. Ik zie ons al als oma's met wafels in de Eifel (of zo) zitten… dank dat jullie er altijd voor me zijn!

★ My dear Nijmegen people

Mao, seit 2007 läuft unsere Karriere quasi parallel: Bachelor in Enschede, Master in Nijmegen, PhD @Donders. Danke, dass du für mich da warst und für die Gespräche über alle Frustrationen der Wissenschaft.

Jana und **Carsten,** ich denke mit viel Vergnügen an unsere Masterzeit zurück. Schade, dass ihr beide nach dem Studium weggegangen seid, das Kickern hat so viel Spaß gemacht.

Iris, wat was het een verrassing om jou bij de Trekvogels op het voetbalveld te zien op dag 1. Ik kijk terug naar een leuke tijd en ben blij dat we elkaar bij **dames 3** hebben ontmoet.

Madelon, het begon als huisgenoot, ging door als huisgenoot èn kantoorgenoot en eindigde met een dikke vriendschap. Wat ben ik blij om jou als vriendin (en zus :)) te hebben. Volgens mij vullen we elkaar goed aan: jij hebt de structuur en ik probeer deze omver te gooien :D

JenSwa, dank dat je er altijd voor me was tijdens de promotie en we eindeloos veel koffie en aardbei croissantjes samen hebben genuttigd. Onze salsa carrière was bijna succesvoller dan de wetenschap huh ;)

Lieneke, onze gezamenlijke tijd in Nijmegen Oost was weliswaar beperkt, maar we hebben er heel veel van gemaakt. Wat een fantastische zomer met veel speciaalbier, hoelahoep en Kaai. Altijd leuk om met jou over lab en leven bij te kletsen. Dank voor de leuke tijd samen in bij de foodies, cools lab en donders.

Naomi, danke, dass du mein Personal Trainer und Sport maatje warst… Pumpen hat mit dir so viel Spaß gemacht! Ich habe dich als Freundin sehr ins Herz geschlossen, hoffentlich sehen wir uns noch oft!

Sandra und Sofia, ihr glaubt gar nicht wie viel ihr mir bedeutet. Sandra, du teilst mit Mama den 1. Platz in der Gutmensch-Kategorie. Ich bin dir so dankbar, dass du den Kartoffelpürree nicht mit Rührstab püriert hast und so lieb warst, meine Schoko-Vorräte zu plündern. Sofia, es macht Spaß sich mit dir über die Scheiß-Augen der Kinder zu unterhalten und zusammen Weinchen + Snacks zu konsumieren. Danke, dass du so ein großes Herz und Sinn für Humor hast. Bald komme ich euch in Hamburg besuchen.

Swinda, ich weiß noch zu gut wie wir in Lent im Supermarkt standen: „Ich bin schwanger", „cool, ich auch". Nach Jahren hatten wir uns wiedergefunden und konnten uns austauschen darüber, wie man nur so bekloppt sein kann, in der Schlussphase der Promotion ein Kind zu bekommen. Danke für alle guten Ratschläge und Spaziergänge um den See.

Julia, beim Schwangerschaftsyoga haben wir festgestellt, dass wir beide aus (der Nähe von) Bielefeld kommen und schon war das Eis gebrochen. Ich werde nie

vergessen, wie wir 3 Tage vor der Geburt montags um 13 Uhr mit unseren dicken Bäuchen alleine im Kino saßen. Ich finde es schade, dass wir weggezogen sind, gerade weil es so viel Spaß gemacht hat mich mit Swinda, Benjamin, Mera und dir zum Kaffee und Spazieren gehen zu treffen. Hoffentlich bald in Düsseldorf.

Martin en Cathy, eigenlijk wilde ik slechts een appartement huren maar wat ik kreeg was veel meer… een huis vol gezelligheid in Nijmegen Oost. Dank voor de etentjes, gezamenlijke picknicks en de brownie-verrassingen.

★ Paranimphs

Jacob, ich bin froh, dass wir uns direkt am Anfang des PhDs kennengelernt haben und nicht nur als Kollegen, sondern auch als Freunde mit der (Social) Science faculty das Fußballturnier gewonnen haben :D Wir ticken in einigen Dingen sehr gleich, was geholfen hat, uns auf persönlicher und fachlicher Ebene gut austauschen zu können. Danke, dass du mir fast täglich über hangouts bei den wichtigen Fragen des Lebens hilfst (wie kann ich die Figure verbessern, gibt es stamppot oder curry bei der Feier…). Ich freue mich, dass du trotz des Abstands und deinem busy schedule mein Paranimph sein willst.

Lieke vL, ik vind je zo fantastisch… we hebben de afgelopen jaren veel koffie en wijn samen gedronken en opgemerkt dat we dezelfde (sarcastische) blik op onze wetenschappelijke omgeving hebben. Dat doet zo goed! Dank dat we samen over Honkie en 2D-Harr kunnen lachen en dat je mijn paranimf wilt zijn!

Liebe Familie,

ihr glaubt gar nicht wie sehr mich eure bedingungslose Liebe, endlose Unterstützung und Geborgenheit geprägt hat! Durch euch habe ich gelernt die Welt positiv zu betrachten und mich zu trauen (manchmal ;)) gegen den Strom zu schwimmen. Auch wenn wir inzwischen alle unsere eigenen Wege gehen, seid ihr die Basis meiner Person und Persönlichkeit.

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Papa, ich bin genauso verrückt wie du. Komplette Selbstüberschätzung, Perfektionismus, Ehrgeiz und unendliche Energie. Ob ich dir dafür danken soll, weiß ich nicht, aber dieser Wille das Unmögliche möglich zu machen habe ich sicherlich dir zu verdanken. Auch wenn wir völlig unterschiedliche Weltansichten haben und dich meine grüne, andersdenkende Art manchmal zur Weißglut treibt, genieße ich unsere Gespräche und Zeit zusammen sehr. Dazu gehören natürlich auch **Eva, Jan und Theresa**. Es ist immer wieder schön mit euch gemütlich zu frühstücken, Zeit zu verbringen und die Patchwork-Konstellation zu feiern.

David, du bist der belesene Ruhepol der Familie. Man glaube es kaum, aber ich bin dir dankbar, dass wir uns emotional so nah stehen, dass wir uns so richtig streiten und alles sagen können und 1 Std später alles wieder vergessen haben. Du bist mein Vorbild, wenn es um Besonnenheit und Strategie geht. Man, was wünschte ich mir manchmal, dass ich so abgezockt wäre wie du. Ich bin so unglaublich froh, dich zu haben. **Sabrina**, ich freue mich, dass du inzwischen offiziell zum Froböse Clan gehörst und uns mit deiner lieben Art begeisterst.

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ABOUT THE AUTHOR

Monja Isabel Froböse was born on 6 December 1988 in Bielefeld, Germany. After graduating from Marienschule der Ursulinen in Bielefeld, Germany, in 2007 Monja moved to the Netherlands where she started her Bachelor in Psychology at the University of Twente in Enschede. Having received her Bachelor's degree (*bene meritum*) in 2010, she was admitted to the Cognitive Neuroscience Research Master at the Radboud University in Nijmegen. After graduating from the Master's program (*cum laude*), Monja received a stipend for a 6-months research stay granted by the Radboud Honours academy. During her stay at Icahn School of Medicine at Mount Sinai, New York City, she worked in the Neuropsychoimaging of addiction and related conditions (NARC) lab headed by Dr. Rita Goldstein, before returning to Nijmegen for her PhD research.

In 2013, Monja started her PhD trajectory at the Donders Institute for Brain, Cognition, and Behaviour in the Motivational and Cognitive control lab under the supervision of Prof. Roshan Cools. Over the following years, Monja investigated the role of catecholamines in cognitive control and cognitive demand avoidance by combining neuropharmacology with experimental psychology, neuroeconomics and neuroimaging. During her PhD, Monja has supervised several students and engaged in multi-disciplinary interactions. For her projects, she collaborated on a national and international level with various parties, including neuroscientists, neurologists and patients.

Next to her research, Monja is passionate about meta-science and discussing the question how scientific practice and support for the (local) science community can be improved. As such, Monja was an elected member of the Radboud University Works Council and member of the Donders Employee Council from 2015-2017. Here, she was part of a committee advising policy making of the University board on behalf of the PhD organization Nijmegen (PON). In addition, she fulfilled the role of PhD representative at the Donders Institute, organizing several educational meetings and events together with the PhD council.

In June 2019, Monja moved back to Germany, where she currently works at the Heinrich Heine University Düsseldorf as a postdoctoral researcher in the Biological Psychology of decision-making lab headed by Prof. Gerhard Jocham. Here, she will continue to work on neuropharmacological studies while advancing her analytical repertoire in MEG analysis and computational modeling. Monja lives in Düsseldorf together with her partner Stef and their son Felix (2018).

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