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Motivation-control dynamics, their neural underpinnings and the role of the IFJ

Dissertation

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Abstract

This thesis aims to enhance our understanding of neural processes that underlie the interaction between motivation and cognitive control. Specifically, it investigates how monetary incentives with distinct valance affect cognitive performance (speed and accuracy) in a classical task switching paradigm where numbers are judged by magnitude or parity. To achieve this goal, three studies were conducted, each exploring different aspects of the same paradigm using different neuroscientific methodologies.

In the first study, we used transcranial magnetic stimulation (TMS) to investigate the causal contributions of the left inferior frontal junction (IFJ) in motivated task switching. More specifically, we parsed disruptive effects of continuous theta-burst stimulation (cTBS) and repetitive TMS (rTMS) over the IFJ on the motivational impact of monetary reward (high vs low) incentives on response speed and accuracy in the paradigm. We found that IFJ disruption improved participants' behavioral performance in the high reward condition. This suggests that the IFJ is causally involved in interaction effects of reward and cognitive control.

In the second study, the paradigm was embedded into three distinct motivational conditions (prospective reward, prospective punishment and a control condition). Since evidence has linked the IFJ to the dopaminergic mesocortical network, dynamic causal modeling (DCM) was applied on fMRI data to investigate how effects of prospective reward and punishment on executive control relate to changes in effective connectivity between IFJ, ACC and VTA. The results demonstrate that behaviorally prospective punishment impacts task switching more strongly than prospective reward. On a neural level, interactions between the regions were characterized by modulations through prospective reward but not punishment. These findings suggest that punishment and reward differentially affect cognitive control networks.

In the third study, electroencephalography (EEG) was used to examine the temporal interplay between prospective reward and prospective punishment with regard to motivationally induced enhancements in cognitive control. Stimulus-locked N2 and P3 amplitudes were measured in different motivational conditions during task switching. Results exhibit stronger behavioral improvements for punishment compared to reward. This was also reflected in reduced P3 amplitudes which were observed exclusively in the punishment condition. This further corroborates the assumption that reward and punishment rely on different neural mechanisms.

Overall, the studies contribute to our understanding of motivationally enhanced cognitive control by shedding light on behavioral and neural differences between prospective reward and punishment, neural processes of switching and repeating tasks, as well as the role of the IFJ.

Zusammenfassung

Diese Arbeit hat zum Ziel, unser Verständnis der neuronalen Prozesse zu verbessern, die der Interaktion zwischen Motivation und kognitiver Kontrolle zugrunde liegen. Es wurde untersucht, wie monetäre Anreize mit unterschiedlichem Valenz die kognitive Leistung (gemessen durch Antwortgeschwindigkeit und Fehlerrate) in einem Task-Switching-Paradigma beeinflussen. Die Aufgabe der Probanden war es, Zahlen entweder anhand von Höhe oder Parität zu beurteilen. Dafür wurden drei Studien durchgeführt, die jeweils verschiedene Aspekte des Paradigmas mit unterschiedlichen neurowissenschaftlichen Methoden untersuchten.

In der ersten Studie wurde transkranielle Magnetstimulation (TMS) eingesetzt, um einen potenziellen kausalen Zusammenhang zwischen Aktivität in der linken unteren Kreuzungsregion (engl. Inferior frontal junction, IFJ) im Frontalhirn und durch Motivation geleitetem Task-Switching zu untersuchen. Konkret wurde erforscht, ob Störungen am IFJ durch kontinuierliche Theta-Burst-Stimulation (cTBS) und repetitive TMS (rTMS) den Einfluss von monetären Belohnungsanreizen (hoch vs. niedrig) auf Reaktionsgeschwindigkeit und Fehlerrate im Paradigma ändern. Die Ergebnisse offenbarten, dass sich die Leistung von Probanden nach IFJ-Stimulation in der Bedingung mit hohen Belohnungsreizen stärker verbesserte als ohne IFJ-Stimulation. Dies legt nahe, dass der IFJ kausal an Interaktionseffekten von Belohnung und kognitiver Kontrolle beteiligt ist.

In der zweiten Studie wurde das Paradigma in drei unterschiedliche Motivationsbedingungen (potenzielle Belohnung, potenzielle Bestrafung und eine Kontrollbedingung) eingebettet. Da der IFJ in früheren Studien mit den dopaminergen Netzwerken in Verbindung gebracht werden konnte, wurde mithilfe von Dynamic Causal Modeling (DCM) auf fMRI-Daten untersucht, wie sich die durch Belohnung und Bestrafung induzierte Steigerung der kognitiven Kontrolle in Veränderungen der effektiven Konnektivität

zwischen IFJ, ACC und VTA auswirkt. Die Ergebnisse zeigen, dass potenzielle Bestrafung das Task-Switching-Verhalten der Probanden stärker beeinflusst als potenzielle Belohnung. Auf der neuronalen Ebene waren die Interaktionen zwischen den Regionen durch Modulationen von Belohnung, nicht aber durch Bestrafung gekennzeichnet. Diese Ergebnisse legen nahe, dass Belohnung und Bestrafung Netzwerke der kognitiven Kontrolle unterschiedlich beeinflussen.

In der dritten Studie wurde Elektroenzephalographie (EEG) eingesetzt, um das zeitliche Zusammenspiel von verschiedenen Motivatoren (potenzielle Belohnung und Bestrafung) und der Verbesserungen der kognitiven Kontrolle auszuwerten. In unterschiedlichen Motivationsbedingungen wurden N2- und P3-Amplituden zum Zeitpunkt der Präsentation des Task-Switching-Stimulus gemessen. Die Ergebnisse zeigen stärkere Verhaltensleistungen für Bestrafung im Vergleich zur Belohnung. Dies spiegelte sich auch in reduzierten P3-Amplituden wider, die ausschließlich in der Bestrafungsbedingung beobachtet wurden. Die Erkenntnisse bekräftigen die Annahme, dass Belohnung und Bestrafung auf unterschiedlichen neuralen Mechanismen beruhen.

Zusammenfassend geben die Studien Einblick in neuronale und Verhaltensunterschiede zwischen potenzieller Belohnung und Bestrafung im Task-Switching sowie die Rolle des IFJ in der Interaktion zwischen Motivation und kognitiver Kontrolle und verbessern so unser Verständnis der zugrundeliegenden neuronales Prozesse.

Chapter 1: Introduction

Making decisions starts as early in the day as the ringing of our alarm clock. Should we get up and begin our day or sleep in and get some well needed rest? What we decide depends on our internal goals as well as external factors. Are we craving our morning coffee yet? Do we have appointments? Is it the weekend? Despite feeling tired, we might remember it's a Tuesday, we have a deadline to meet on a project and focus best in the mornings. We decide to get up and start work. Later that day we have some errands to run. On our way to the supermarket, a friend calls to tell us about a hilarious encounter she had at a coffee shop earlier. Wrapped up in her story, we have completely forgotten about the grocery shopping until passing the supermarket's neon sign. We know the shop is about to close, so even though we are curious about the continuation of our friend's story, we end the conversation and promise to call her back later.

In our dynamic environment and constant influx of stimuli, we need the ability to manage ourselves. We need to be able to direct our attention and to prioritize long-term over sometimes more appealing short-term goals. And we need to be capable of focusing on a task at hand or switch to a more urgent one. For that purpose, evolution has gifted us with a set of mental processes called "cognitive control" which are essential to what we call intelligent behavior. They serve as a filter which helps distinguish relevant from irrelevant context information to make decisions and initiate behaviors aligned with our goals. These ongoing processes flexibly adapt to ever-changing requirements in the environment. Therefore, we need cognitive control to navigate us through our complex everyday lives.

Executing cognitive control, however, is exhausting. It requires us to inhibit our impulses and urges, pay attention and desert our habits. Thus, it is not enough to have the *ability* to do something, we also need to *want* to do it. Motivational influences on cognitive control play an important role in shaping human decision-making and behavior. We only become active, if the expected benefits of reaching a goal outweigh the cost of getting there. Such a

benefit may be a reward we expect to receive or it could be negative consequence or punishment we try to avoid. Often several intrinsic and extrinsic motivational factors are present at the same time which may support the same goal but also counteract each other. In our example above, we were intrinsically motivated to listen to our friend's story. Yet, we prioritized the externally motivating time-pressure brought on by the supermarket's business hours, so we would not have to go to bed hungry (i.e. avoidance of punishment).

While motivation and cognitive control were often studied separately in the past, they are in fact inseparably connected. Given the practical relevance to our everyday lives, in recent years, research has focused on examining the interface between both concepts. Particularly neuroscientific approaches have proven valuable in understanding the mechanisms by which cognitive control and motivation interact. In the present thesis, this topic is explored further. The following chapters introduce key concepts in behavioral and neuroscientific research on motivation-based executive control. We give an overview over current literature and follow with empirical chapters in order to expand on existing findings.

1.1 Defining cognitive control

The term "cognitive control" refers to a construct from psychology and neuroscience that incorporates a set of mental processes, which counteract automatic responses and thereby enable goal-directed behavior. Basic executive functions include cognitive flexibility (Braem & Egner, 2018; Moore & Malinowski, 2009), attentional control (Baldauf & Desimone, 2014; Fan et al., 2005; Folk et al., 1994), working memory (Baddeley, 2003; Oberauer, 2019) and inhibitory control (Munakata et al., 2011; Schall et al., 2017). These core skills provide the foundation for higher-order cognitive operations such as problem solving, reasoning, planning and goal tracking (e.g. Diamond, 2013). Impairments have been linked to a wide range of neurological disorders such as schizophrenia (Abraham et al., 2007; Alfimova et al., 2007;

Oram et al., 2005), ADHD (Barkley, 1997; Marchetta et al., 2008), Parkinson's disease (e.g. Schneider, 2007) and bipolar disorder (Dixon et al., 2004; Robinson et al., 2006). Moreover, cognitive control is not only dependent on immediate external and internal factors but also varies interpersonally and changes across the life span. Accordingly, executive functioning is acquired throughout childhood along with the developing brain and declines with aging (Davidson et al., 2006; Friedman et al., 2009; Sharp et al., 2006).

Key to all cognitive operations is the ability to maintain goals and ignore distractors, while simultaneously identifying relevant environmental changes to update and select appropriate behavior if necessary. These seemingly conflicting mechanisms sketch out a dynamic process that provides challenges when in search for an overarching definition of cognitive control. As a result, cognitive control has been described along several dichotomies.

One prevailing framework views cognitive control as a mechanism that balances cognitive flexibility and cognitive stability (Dreisbach & Fröber, 2019; Goschke, 2013; Goschke & Bolte, 2014). Flexibility thereby refers to the ability to adapt goals and behavior in light of significant changes, whereas stability is characterized by the ability to maintain and shield current goals. Establishing a context-sensitive balance between these antagonistic modes of control is critical to avoid rigid behavior as well as high distractibility which both result in maladaptation to environmental demands (Dreisbach & Fröber, 2019). Empirical findings confirm that increased cognitive stability comes at the cost of reduced flexibility and vice versa (Kelly et al., 2008; Romei et al., 2012). This inevitably raises the question how an optimal and dynamic balance between both modes is obtained. One of the most relevant factors is the influence of motivation on the balance between cognitive stability and flexibility (for review see Goschke & Bolte, 2014). Müller et al., (2007), for instance, observed that the prospect of monetary gain increased cognitive stability in a set-shifting task, however, exclusively in participants who perceived increased effort was necessary to receive the potential reward.

Participants who were less motivated by reward cues, on the other hand, showed enhanced cognitive flexibility.

Another dichotomy aiming at conceptualizing cognitive control is embedded in the *Dual Mechanism of Control* (DCM) model (Braver, 2012), which distinguishes between the implementation of control as either proactive or reactive. Proactive control is goal-driven and relies on context and task goal maintenance. As an anticipatory strategy, it biases attention and behavior towards improved tasked performance and goal achievement. Due to its inherent metabolic cost, proactive control is applied in situations with a high motivational context. In contrast, reactive control is conceptualized as a stimulus-driven "late correction mechanism" (Braver, 2012) that is only deployed when necessary. It is activated by salient bottom-up stimuli that trigger control conflict (such as the supermarket's neon sign in our opening story). The strategy does not rely on advance preparation, attention maintenance or high motivation and therefore comes at a lower cost. Both control strategies have benefits and are necessary for executive functioning. Proactive control is more demanding and susceptible to inference, but also generates better performance. Reactive control on the other hand is less effective, yet less exhausting (Braver, 2012). Evidence suggests that performance-contingent rewards assist proactive control (Fröber & Dreisbach, 2014; Yamaguchi & Nishimura, 2019), while non-contingent reward promotes reactive control (Dreisbach & Fischer, 2012). Besides contextual influences, preferences in control styles can be linked to individual differences. To that effect studies have shown that proactive control is more pronounced in individuals that were raised bilingual compared to unilingual individuals (e.g. Morales et al., 2015) as well as individuals with a higher working memory capacity (e.g. Wiemers & Redick, 2018).

While both dichotomies are associated with complementary costs and benefits, unlike stability and flexibility, proactive and reactive control are considered as independent

mechanisms that can be implemented simultaneously (Gonthier et al., 2016; Mäki-Marttunen et al., 2019).

A variety of cognitive tasks are available to investigate different aspects of cognitive control and simulate real-life cognitive demands, with the choice of task depending on the cognitive processes of interest and the research questions being asked. For example, Stroop tasks primarily assess response inhibition. When presented with conflicting information, such as the word "blue" displayed in yellow, the task requires to inhibit the reflexive response to read the word and instead name its color (Egner & Hirsch, 2005; Logan et al., 1984). Likewise, in Go-NoGo tasks participants are required to only respond to certain stimuli (Go stimulus) and not to others (NoGo stimuli) thereby tapping into the ability to select or inhibit responses based on relevant and irrelevant cues (e.g. Gomez et al., 2007). N-back tasks assess working memory and attentional control. Participants are asked to remember and compare current stimuli with stimuli presented n trials earlier. This requires constant updating and maintaining information in working memory to initiate appropriate responses (Jaeggi et al., 2010; Owen et al., 2005). In the present thesis, a multimethodological approach to exploring control-motivation interactions was applied which required for a cognitive task to be reliable and versatile in combination with the demands of different neuroscientific methodologies and motivational settings. We opted for a task switching paradigm to examine cognitive flexibility closely resembling everyday situations that involve active maintenance and updating of goals in working memory. In classic task switching designs participants rapidly shift attention between different stimulus features to update and initiate appropriate task responses depending on changing task sets (Monsell, 2003). Task switching involves high levels of self-monitoring, which has been found to be susceptible to motivational influences in previous studies (e.g. Dreisbach & Goschke, 2004). Therefore, it is a particularly suitable paradigm for investigating the interplay between motivation and cognitive control.

Before delving deeper into the topic of task switching and providing a description of the experimental design of the present work, I will review recent studies on how motivation affects cognitive control.

1.2 Motivational influences on cognitive control

When we mobilize cognitive control, it is for a reason. The intrinsic costs of engaging in cognitive effort are often perceived as aversive (Kool & Botvinick, 2014; Massar et al., 2016). Thus, for us to allocate control, the expected reward upon reaching a goal needs to outweigh the effort necessary to achieve it. Yee & Braver (2018) define motivation as an "altered state" by internal or external incentives that is observable in behavior. Such motivational states have been induced by internal factors such as affect (Chiew & Braver, 2011) or need for cognition (Cacioppo et al., 1996; Satterthwaite et al., 2012), primary incentives such as food (Wagner et al., 2012), punishments (e.g. aversive noise, Dambacher et al., 2015) and are also associated with interpersonal traits (Jimura et al., 2010).

Probably the most salient phenomenon manifesting interactions between cognitive control and motivation is the enhancing effect of monetary incentives on performance in cognitive tasks. Kleinsorge and Rinkenauer (2012), for example, observed an improvement in task-switching performance, as expressed in reduced switch costs, when offering performance-contingent monetary rewards. The researchers argued that the effect can likely be contributed to reward expectancy. This interpretation is in line with models that put reward maximization at the center of motivation-control interactions. One of the most prevailing accounts is the concept of the expected value of control (EVC, Shenhav et al., 2013). The theory proposes that decisions commissioning cognitive effort resemble cost-benefit analyses with the goal of maximizing the EVC. This means that only if the expected benefits of exerting control outweigh the expected costs, are we motivated to provide the cognitive resources to perform better on a

task. Similar effects of monetary incentives have been observed for a wide range of control processes such as attention (Engelmann et al., 2009), response inhibition (Boehler et al., 2014), conflict adaptation (Padmala & Pessoa, 2011; Stürmer et al., 2011), working memory (Jimura et al., 2010) and context processing (Chiew & Braver, 2016). While the strong relationship between incentives and cognitive performance has been evidenced in a manifold of scientific settings, there are exceptions to the rule. Very small (Gneezy & Rustichini, 2000) or very large monetary rewards have been reported to undermine performance, the latter being attributed to "choking under pressure" (Mobbs et al., 2009; Zedelius et al., 2011).

It is still not well understood how reward and punishment incentives differ regarding their impact on cognitive control processes. Only few studies have directly compared these distinct motivational incentives in the same task. Even though humans in general show a greater sensitivity towards loss compared to gains (Tversky & Kahneman, 1979), the relationship between different valences of motivation and control processes is not as straightforward. Several studies report individual differences in sensitivity to reward and punishment that mediate motivation-control interactions (Braem et al., 2013; Bunford et al., 2017; Fuentes-Claramonte et al., 2015; Jimura et al., 2010). Some accounts find differential behavioral effects of reward and punishment (Leng et al., 2021; Wächter et al., 2009), while others demonstrate similar behavioral improvements for reward and punishment incentives (e.g. Cubillo et al., 2019).

In conclusion, the relationship between motivational incentives and cognitive control is complex and not yet fully understood. Prior evidence has identified several behavioral effects associated with different motivational states. However, additional research is necessary to gain a comprehensive understanding of interactions between motivation and control processes. This work aims to contribute to the existing knowledge by directly comparing the impact of

monetary reward and punishment incentives on cognitive flexibility in the same task switching paradigm. The next chapter will provide a detailed description of the experimental design.

1.3 Task switching

A hallmark of cognitive control is the ability to shift attention from one goal to another as environmental requirements change. To make this ability measurable in an experimental context, task switching paradigms are used that require participants to switch or repeat task sets that follow different response rules as indicated by task cues. Typical tasks include word reading, color naming, letter or digit categorization (Monsell, 2003). *Switches* are characterized by consecutive trials with diverging task rules, *repeats* are trials that follow the same task rule as the preceding trial. An example would be an experiment, in which participants are instructed to either perform a math task or a language task as indicated by a red or a blue square presented before the task. In this context, a sequence of red squares or of blue squares would be considered a repeat, while a sequence with alternating cue colors would be defined as a switch. The underlying assumption is that participants need to allocate enhanced top-down (i.e. proactive) control to update task rules when switching compared to repeating task sets which is thought to be expressed in slower and more erroneous responses, the so-called *switch cost* (Monsell, 2003; Wylie & Allport, 2000).

While in theory this is a relatively simple principal, practical execution has its challenges. The choice of parameters for designing a task switching paradigm depends on the objective of a study and is crucial for eliciting the mechanisms underlying attentional shifts (see Kiesel et al., 2010 for a comprehensive review). Correspondingly, it is under debate whether the same process underlies task switching and repeating or whether switching requires an additional cognitive operation for task rule updating. This seems to be particularly relevant when deciding for or against introducing preparation time between cue and task stimuli (Gilbert & Shallice,

2002; Koch & Allport, 2006). It has been found that long preparation intervals do not reduce switch costs compared to shorter preparation intervals. Presumably, an additional cognitive process would increase cognitive demand and therefore more preparation time should impact switch costs positively. However, a lack of such a pattern is considered evidence against the existence of a switch-specific and more in line with a generic process (Altmann, 2004).

The present thesis aims at exploring interactions between motivation and cognitive control by means of different neuroscientific methodologies. Consequently, the paradigm had to be easily adjustable to different demands. In all studies detailed in the following chapters, participants judged numbers either by parity or magnitude. Since we were particularly interested in exploring motivational influences on cognitive control rather than dissecting control processes themselves, we decided to make task cues a stimulus feature. Accordingly, task rules in each trial were determined by the color of the presented number. If the number was yellow, participants had to respond to its parity. If it was blue, participants had to judge it by magnitude. To ensure the paradigm was applicable in slow-paced or variable-rich designs, we only included incongruent stimuli (i.e. affording different responses for different task sets) in order to not lose trials with ambiguous responses. Each response was followed by feedback. To directly compare dynamic adjustments in cognitive control induced by different valences of motivation the task was embedded in different motivational conditions. We introduced performance-contingent incentives (monetary rewards for fast and correct responses, monetary punishments/losses for slow or erroneous responses). In order to establish stable motivational states, we arranged task switching trials of the same motivation condition in task blocks and compared cognitive performance to a baseline condition (no rewards or punishments). Participants gained small amounts of money for correctly repeating or switching between task sets only in reward blocks. Likewise, the same amount was lost for incorrect responses only in punishment blocks. Gains and losses had the same monetary value (7 cents) in order to ensure

comparability. Figure 1 depicts the general structure of the paradigm. Variations in trial sequence, motivational variables, block structure and pace are described in the methodological chapters of each study.

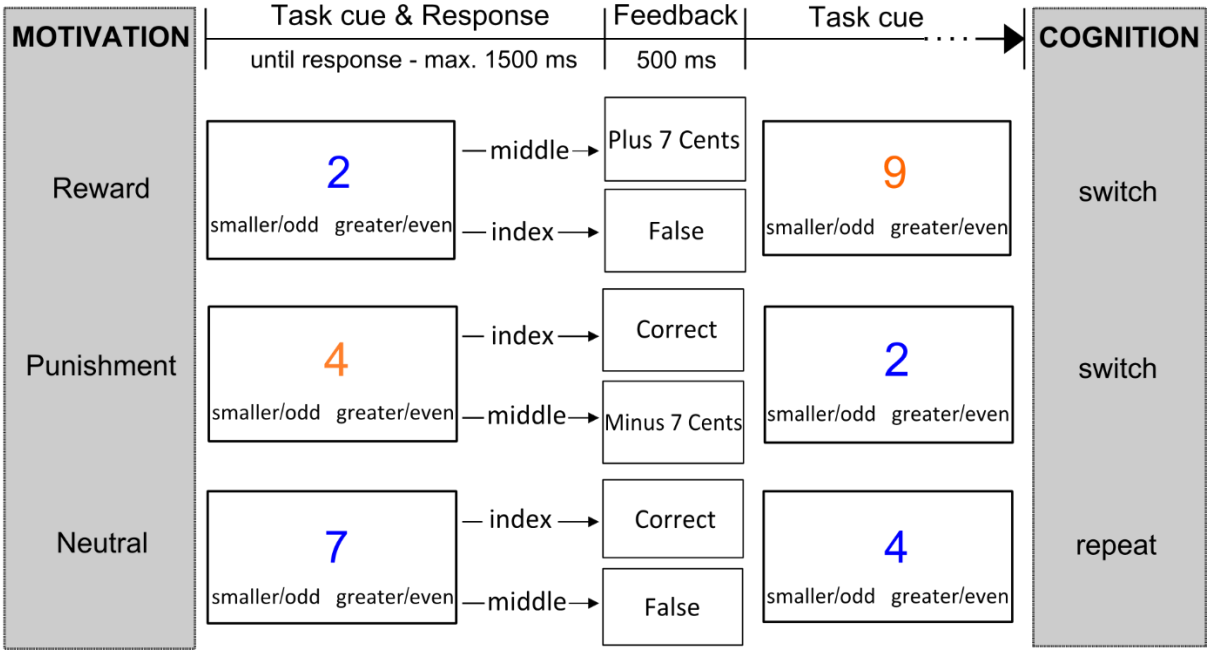

Figure 1 Experimental design. Participants judge numbers based on either their magnitude (blue) or their parity (yellow). The task involves switching between or repeating these criteria. Switch and repeat trials, defining the factor Control, are pseudo-randomized (not more than three in a row). Different levels of motivation are associated with monetary incentives. In the reward condition, participants earn monetary value for correct responses. In the punishment condition, participants lose monetary value for incorrect responses. The neutral condition does not involve any monetary gains or losses. The specific details in terms of motivational conditions, monetary value, number of trials and timing were adapted to the research question and neuroscientific method used in the respective studies.

In recognition of many outstanding issues regarding the relationship between motivation and cognitive control, it has to be acknowledged that behavioral research alone does not suffice when looking for explanations regarding underlying mechanisms. As a consequence, the focus of investigation has increasingly shifted to neuroscience which has since contributed valuable insights into the processes underlying motivation-control interactions. The following section will therefore examine current neuroscientific findings as well as unresolved questions.

1.4 Neural interactions between cognitive control and motivation

Both cognitive control and motivation are multifaceted psychological and neurological phenomena that emerge from interactions between various brain regions and widespread networks. Despite the intricately intertwined nature of these processes, they have often been examined separately in the past.

Scientific studies on cognitive control have identified a set of neural structures that contribute to the execution of cognitive control. These primarily include subregions of the prefrontal cortex (PFC), such as the inferior frontal junction and dorsolateral partitions, the anterior cingulate cortex (ACC), the anterior insula and the intraparietal cortex (Cole & Schneider, 2007; Niendam et al., 2012; Zanto & Gazzaley, 2013). In parallel, motivation has been associated with increased neural activity in the striatum, nucleus accumbens, the orbitofrontal and ventromedial cortices and, most prominently, the ventral tegmental area (VTA) in the midbrain as source of mesocortical dopamine (DA) projections (Bartra et al., 2013; Floresco & Magyar, 2006).

Although an abundance of evidence substantiates these networks, it is still unclear how they interact to generate a shared neural process. To unveil some of the interactions that characterize the interplay between motivation and cognitive control, it is necessary to explore specific brain regions, their associations with both networks and current hypotheses regarding their interaction.

The PFC is thought to serve as a control node which receives input from other cortical, subcortical and brain stem structures and in turn exerts top-down control over these areas via neural projections (Johnston et al., 2007; Lee & D'Esposito, 2012; Miller & D'Esposito, 2005; Miller & Cohen, 2001). Cognitive control is realized as a main function of the PFC which provides the infrastructure to aggregate and map inputs and outputs, constituting the basis for advanced behavioral operations (Miller & Cohen, 2001). Essential to all neural cognitive

operations is the availability of DA which has been associated with working memory, cognitive flexibility and attention (Arnsten & Rubia, 2012; Klanker et al., 2013; Thiele & Bellgrove, 2018). Cools et al., (2007), for instance, could show that performance in a delayed response task was mediated by administration of dopamine receptor antagonists. Midbrain dopaminergic neurons in the VTA appear to project to PFC via the mesocortical pathway (Gao et al., 2007). Behaviorally significant cues trigger the activation of these neurons, eliciting dopamine release in the PFC. This holds especially true for stimuli linked to reward or punishment, as they act as primary reinforcers and therefore are particularly salient (Bromberg-Martin et al., 2010; Matsumoto & Hikosaka, 2009). While most studies primarily consider projections from VTA to PFC, it has also been suggested that VTA activity may be initiated by PFC signaling when reward cues are present (Ballard et al., 2011). While there remains some uncertainty regarding the exact interplay and directionality through which these regions communicate, it has been well established that DA plays a pivotal role in connecting motivation and cognitive control (Cools, 2008; van Holstein et al., 2011; van Schouwenburg et al., 2010). Aarts et al., (2010) demonstrated dopamine-mediated motivation-cognition interaction effects by comparing performances of individuals with different dopamine transporter gene polymorphism in a task-switching paradigm including high and low reward cues. Participants with genetically high striatal DA levels showed significant reward benefits in cognitive control compared to participants with genetically low striatal DA levels.

Besides the role of DA, the ACC has been discussed a potential mediator in control-motivation interactions. The structure is involved in a wide range of functions, including cognitive control, performance monitoring and reward processing (Chudasama et al., 2013; Shackman et al., 2011; Shenhav et al., 2016). For this purpose, the ACC receives inputs from various brain regions, including PFC and VTA, before monitoring action selection (e.g. Shenhav et al., 2013). Communication between PFC and the anterior cingulate cortex (ACC)

has particular importance for the neural integration of cognitive control. The Conflict Monitoring theory (CMT, E. K. Miller & Cohen, 2001) postulates that the ACC monitors conflicts in information processing and signals the need for increased control to the PFC, which then prompts top-down adjustments of involved neural processes (for review see M. M. Botvinick et al., 2004). This account is well supported by neuroscientific evidence. Kerns et al. (2004) demonstrated that increased ACC activity was associated with reduced conflict interference in a Stroop task. Importantly, the effect was accompanied by heightened dorsolateral PFC activations and behavioral top-down adjustments on the following trial. Similarly, studies have demonstrated the significance of VTA projections to ACC in the context of reward-based cognitive processing (Haber & Knutson, 2010; Hauser et al., 2017; Köhler et al., 2016). This indicates that dopamine released from VTA can modulate the activity of the ACC, influencing its functions related to motivation and cognitive control. Some evidence suggests that the ACC in turn influences VTA activity via reciprocal connections. Aberg et al. (2020) tested the impact of reward magnitude on behavioral performance in an associative memory task by means of fMRI. They concluded that ACC evaluates the overall behavioral impact of rewards before transmitting the information to memory circuits through the VTA. This is in line with the EVC theory (Shenhav et al., 2013) which emphasizes the role of the ACC in reward-based decision making. It proposes that the ACC assesses potential outcomes of various actions and computes the expected value of these actions considering the possible rewards and efforts associated with each option. The ACC thereby considers the trade-off between the expected reward gained from exerting control and the cognitive effort required, before allocating control accordingly. This strategy is applied to adjust behavior and decision making to maximize rewards effectively.

Although the significance of ACC, PFC and VTA in shaping motivational influences on cognitive control has been acknowledged, the relationship between these structures is not characterized by simple connections. Instead, they operate as part of larger networks, collectively contribute to their overall functioning and combined impact. Recent attention has turned toward a new candidate region that could potentially play a role in the interplay. The inferior frontal junction (IFJ) is located in the lateral PFC, at the interface of the frontal and temporal lobes in the brain (Brass et al., 2005; Derrfuss et al., 2005; Sundermann & Pfleiderer, 2012). Its strategic location may allow it to serve as a hub for coordinating complex processes that involve both cognitive and motivational aspects of behavior. This idea is supported by a body of evidence linking IFJ activation to reward-based cognitive control (see Parro et al., 2017 for review). Bahlmann and colleagues (2015), for example, observed that functional connectivity between IFJ and midbrain correlates with enhancement of cognitive performance induced by monetary incentives. Stelzel et al. (2010, 2013) were further able to associate the IFJ with the dopaminergic system. The administration of dopamine receptor antagonists increased IFJ activity during task-switching. This was interpreted as an expression of stronger prefrontal control demands as compensation for weak dopamine availability under the influence of receptor antagonists. The researchers highlighted the uncertainty regarding connectivity direction from the IFJ, emphasizing the need for further investigation. Notably, connectivity between the IF and ACC is better understood. Several studies have found modulatory effects in effective connectivity from IFJ to ACC in correlation with cognitive control demands (Harding et al., 2015; Hinault et al., 2019). It has further been shown that the IFJ interacts with other brain regions, including the PFC, under different motivational conditions to coordinate attentional control processes. To that end, distinct effects of reward and loss/punishment on IFJ activation were observed in a Flanker task with punishment motivation inducing a more general mechanism in the IFJ and reward motivation leading to specific transient activation during

incongruent trials (Paschke et al., 2015). While the specific contributions of the IFJ to motivation-control interactions are not yet fully understood, its involvement in cognitive control and its connectivity with motivational regions suggest that it may play a role in mediating the interactions between motivation and cognitive control.

Besides the involvement of specific brain regions, there is an ongoing debate about whether different types of motivation, like seeking rewards or avoiding punishments, rely on common neural processes or distinct networks. Despite similar behavioral effects observed in enhancing cognitive task performance, the neuroscientific evidence remains inconclusive. Multiple studies provide evidence for distinguishable neural patterns (Camara et al., 2009; Cubillo et al., 2019; Palminteri & Pessiglione, 2017). For instance, Murty et al. (2012) highlighted differences in amygdala and ventral striatum activity in response to prospective punishment and reward, respectively. It has further been demonstrated that reward influences learning through the dorsal striatum, whereas punishment modulates insula activity to enhance motor performance (Wächter et al., 2009). However, it's important to note that there is also evidence supporting the notion of a shared neural process suggesting that certain brain regions may be involved in both reward and punishment processing (Xue et al., 2013). This unresolved question adds another dimension when attempting to unravel the intricate interplay between motivation and cognitive control.

In this thesis, I aimed at investigating the role of the IFJ in integrating motivation and cognitive control. To that end, we conducted three task-switching studies using different neuroscientific methodologies with particular emphasis on the involvement of the IFJ and variances among distinct motivational influences. The following chapter will discuss the rationale behind adopting a multimethodolgical approach and highlight the advantages it offers when investigating the complex neural interplay between motivation and cognitive control.

1.5 A multimethodological approach

In the present thesis, alterations of the same task switching paradigm were probed in combination with different neuroscientific methodologies, specifically transcranial magnetic stimulation (TMS), functional magnetic resonance imaging (fMRI) and dynamic causal modeling (DCM) as well as electroencephalography (EEG). The unique strengths and limitations of these techniques complement each other and enable them to elicit different aspects of the same neural process. A multimethodological approach therefore can provide a more comprehensive understanding of the neural mechanisms underlying the integration of motivation and cognitive control. In the following, I will briefly introduce each neuroscientific methodology used and demonstrate how they can be applied to examine the cortical dynamics underlying the exhibited task behavior.

TMS is a non-invasive technique for brain stimulation that has become increasingly popular in the field of cognitive neuroscience. By generating magnetic fields through a coil placed over the scalp, TMS can selectively enhance or disrupt neural activity in a cortical area. Given its ability to actively interfere with neural processes, TMS is used for testing specific hypotheses about the causal role of a brain region by observing resulting effects on behavior and neural activity in other regions (e.g. Klomjai et al., 2015). TMS is further employed as a therapeutic tool for the treatment of psychiatric and neurological disorders, such as depression and obsessive-compulsive disorder (Carpenter et al., 2012; Lusicic et al., 2018; Paus & Barrett, 2004). The efficacy of TMS in modulating brain activity is dependent on the stimulation protocol used - frequency, duration and intensity of the stimulation determine whether an excitatory or inhibitory effect is achieved. In the current work, we sought to investigate the role of the IFJ in motivated task switching by applying two inhibitory TMS protocols, theta burst stimulation (cTBS) and low-frequency repetitive TMS (rTMS) at 1 Hz to the IFJ. Through this

approach, we want to evaluate its causal contribution to the enhancing effect of reward on cognitive control.

Functional magnetic resonance imaging (fMRI) measures changes in the blood oxygenation level-dependent (BOLD) signal, which reflects the level of blood flow and therefore oxygenation in a specific region and serves as an indicator for neural activity in the brain. One advantage of fMRI is its high spatial resolution, which allows for identification of brain regions involved in specific tasks (e.g. Smith, 2004). This makes it particularly useful for specifying neural networks underlying complex cognitive processes. Dynamic Causal Modeling (DCM) is a statistical method used in neuroimaging to infer the causal relationship between different brain regions. The technique is based on a set of mathematical equations that help estimate the strength of connections between different brain regions, as well as the influence of external inputs on these regions. DCM therefore can be used to test hypotheses about the directionality of causal relationships between regions, such as whether one region is causing another region to become active or whether they are both influenced by common input (Friston et al., 2003; Stephan et al., 2008). In the current work, we used DCM in conjunction with fMRI to identify brain regions of the mesocortical dopaminergic system, specifically IFC, ACC and VTA, involved in motivation-control interactions and gain insights into the neural mechanisms underlying the enhancing effect of monetary incentives on task-switching performance.

Electroencephalography (EEG) measures the electrical activity of the brain through electrodes placed on the scalp. Neural data can be interpreted by analyzing neural oscillations or event-related potentials (ERPs). Due to its high temporal resolution it can capture rapid changes in brain activity associated with cognitive processes such as attention and decision making (Boksem et al., 2005; Nidal & Malik, 2014; Sawaki et al., 2015). In the current work,

we applied EEG to untangle the temporal interplay between motivational and cognitive aspects of task switching.

Due to their focus on specific domains in revealing neural activity, using these methods in combination can provide insights into the temporal and spatial dynamics of brain activity, as well as identify causal relationships between different brain regions. Hence, a multimethodological approach on the same task can provide converging evidence for hypotheses about the role of specific brain regions and their interactions in complex cognitive processes.

1.6 Summary and outline of the thesis

As outlined above, motivation and cognitive control are interdependent processes that affect our behavior and decision-making. Research has shown that motivation can enhance cognitive control by increasing our attentional focus and cognitive flexibility. This is evidenced by our ability to select task-relevant information and ignore distractions when we are motivated to achieve an important goal. The behavioral phenomenon is closely linked to distinct neural pathways in the brain with particular emphasis on the dopaminergic system, including the ventral tegmental area (VTA), the prefrontal cortex (PFC) with the inferior frontal junction (IFJ), and the anterior cingulate cortex (ACC). Despite an ever-growing body of evidence, there are still many outstanding questions that require further investigation to understand the complex mechanisms in which motivation and cognitive control interact. The present thesis aims to advance our understanding by conducting three motivation-based task switching studies, each utilizing a different neuroscientific method to explore specific aspects of the interplay.

In the first study, we employ two TMS techniques over the left IFJ to parse its causal involvement in the motivational influence of monetary rewards (high and low) on participants' task switching performance.

In the second study, we apply DCM to fMRI data to analyze changes in effective connectivity between IFJ, ACC and VTA in relation to the effects of prospective reward and prospective punishment on cognitive control.

In the third study, we compare N2 and P3 amplitudes between prospective reward and punishment in terms of motivationally-induced improvements on cognitive control by means of EEG.

Finally, the findings of all three studies are summarized and discussed within the context of the state-of-the-art literature reviewed in the Introduction.

Chapter 2: Boosting the effect of reward on cognitive control using TMS over the left IFJ[1]

2.1 Introduction

Our everyday behavior is a constant stream of actions and decisions which are intended to help us reach immediate as well as more far-reaching goals. One key component of generating these decisions is cognitive control, which has been defined as a set of mental processes that maintain a representation of current task demands and enable the flexible adaption of behavior (Botvinick & Braver, 2015). This cognitive process is subjected to environmental influences. In particular, the prospect of reward forms our behavior decisively and serves as a cue to adapt and change our strategies to reach set goals. Hence, cognitive control can also be conceptualized as a domain of reward-based decision-making. Indeed, reward has been shown to improve performance in various cognitive domains such as response inhibition or task switching (Aarts et al., 2010; Boehler et al., 2014; Padmala & Pessoa, 2010).

However, the neural mechanisms that shape such an interplay between cognitive control and reward-based decision-making are poorly understood. One potential scenario would be a dedicated cortical region which serves as an interface between the distinct networks of cognitive control and motivation (Botvinick & Braver, 2015). Recent evidence renders the inferior frontal junction (IFJ), a subregion of the lateral PFC, a promising candidate. It has long been recognized that the IFJ plays an important role in the processing of cognitive control tasks (Brass et al., 2005). Current research further associates the IFJ with mid-brain and striatal activity, which in turn is crucial for reward-seeking behavior. For instance, Stelzel and colleagues (2010) demonstrated that the involvement of the IFJ in flexible task updating is

[1] This chapter largely corresponds to: Hippmann, B., Kuhlemann, I., Bäumer, T., Bahlmann, J., Münte, T. F., & Jessen, S. (2019). Boosting the effect of reward on cognitive control using TMS over the left IFJ. *Neuropsychologia, 125*, 109-115. doi: 10.1016/j.neuropsychologia.2019.01.016.

dependent on the density of D2 dopamine (DA) receptors in the striatum. Since DA is a noted component in both cognitive control and motivation, it is likely to have a part in their interaction (Cools, 2008; Westbrook & Braver, 2016). Neuroimaging studies report incentive-related activity in DA nuclei predicting performance in control tasks (Aarts et al., 2010; Krebs et al., 2012) suggesting a fronto-striatal pathway with a mediating role of dopamine. Finally, in a recent study we showed that functional connectivity between DA-rich midbrain regions and the left IFJ correlated with the individual beneficial effect of incentives on behavioral performance in a switch task (Bahlmann et al., 2015). Given evidence that the IFJ exerts top-down control within the fronto-striatal circuit (Jahfari et al., 2011) our findings indicate that it might be involved in integrating motivational and control processes by modulating striatal activity.

While prior work therefore associates the IFJ with both, cognitive control and reward processing, we do not know whether it fulfills a causal role in an interplay between these two processes. The present study aimed to explore this possibility by means of transcranial magnetic stimulation (TMS) to temporarily alter activity of the left IFJ. This non-invasive technique uses magnetic pulses to temporarily modulate brain activity and has become a standard in the investigation of causalities in cognitive functions (Pascual-Leone et al., 2000). Muhle-Karbe and colleagues (2014), using a task-switching paradigm, have already demonstrated that repeated stimulation (rTMS) over the left IFJ reduces the ability to update task goals. However, the study did not include motivational manipulations. In the present investigation, we sought to specifically test effects of IFJ disruption on incentive-driven control processes.

Various stimulation protocols have been used in TMS research to achieve different effects on designated target regions. For instance, low frequency rTMS has been widely used to inhibit target regions (Chen et al., 1997), as well as connected areas (Fox et al., 2012). Huang et al. (2005), however, introduced a different protocol, the continuous theta burst stimulation (cTBS), that produces longer lasting inhibitory effects up to one hour and requires lower

stimulation intensities and duration (Di Lazzaro et al., 2011). Initially, we therefore chose cTBS to induce strong durable changes in the excitability of the IFJ.

To assert different levels of cognitive control, we used a task-switching paradigm with the task sets parity and magnitude similar to our prior study (Jörg Bahlmann et al., 2015). Switch costs served as a measure of task performance. They represent the difference in response times (RT) or error rates (ER) between switch and repeat trials and are assumed to reflect control processes (Wylie & Allport, 2000). Monetary incentives of different amount were included to manipulate participants' motivational states. Based on our previous results, we predicted that the prospect of gaining high rewards for correct responses would reduce switch costs of RT compared to low rewards. We further hypothesized that stimulation of the left IFJ through cTBS would diminish this effect by interrupting the interplay between cognitive control and reward. This would support the assumption that the left IFJ is causally related to the impact of reward on cognitive control, possibly by regulating striatal function.

Experiment 1

2.2 Methods

2.2.1 Participants

Twenty-three participants (12 females, mean age = 23.9, ranging between 20 and 30 years) were included in the present study. Data from two additional participants were collected but had to be discarded because they were not blind to the TMS manipulation. All reported normal or corrected-to-normal vision and were screened for common TMS exclusion criteria (Rossi et al., 2009), including their personal and family history of neurological abnormalities. They received compensation (7€ / h) for participation as well as monetary rewards in accordance with the individual performance on the task.

The study had been approved by the local ethics committee and was conducted in conformance with the principles of the Declaration of Helsinki. Participants gave their written consent after a full explanation of the procedure.

2.2.2 Stimuli and task

Participants were tested in two separate sessions that took part at least two days apart. They underwent stimulation of the left IFJ and a sham site (vertex) through navigated and robotized cTBS. In order to avoid sequence effects, the condition order was counterbalanced: Half of the participants started with IFJ stimulation, the other half with sham stimulation. After stimulation, they performed a switch task with two motivational conditions. Numbers between 1 and 50 served as stimuli. They were presented centrally on a black screen in random sequence. The color of the numbers indicated which of two tasks to perform. Yellow signaled that participants should judge a digit regarding its magnitude (smaller or greater than 25). A blue digit established the parity task (even or odd). If two subsequent trials obeyed the same task rule (parity following parity or magnitude following magnitude) this sequence was defined as a repeat. A switch was defined as a sequence of two trials with different task rules (parity following magnitude or vice versa). Participants made obligatory button responses (K / L) on a QWERTZ keyboard with the index (smaller / odd) or middle (greater / even) finger of their right hand within a limited time window. A response map was displayed below the stimuli. In order to achieve contrasting response patterns and thus avoid indistinct responses, numbers smaller than 25 were only even (e.g. 4, 8, 20) and numbers greater than 25 were odd (e.g. 27, 33, 45). For correct judgements, participants received either 1 Cent (low reward trial) or 7 Cents (high reward trial). A reward cue (“1 Cent” or “7 Cents”), indicating which amount could be gained in the following trial, was presented before the stimulus. Each response was followed by feedback (“Plus 1/7 Cent”, “wrong” or “too late”).

In order to familiarize participants with the task, they completed a brief training session before applying TMS. The training consisted of 25 trials and was repeated if participants had more than ten misses or errors. Individual mean RT from the training served as initial stimulus duration times (ranging between 800 and 1200 ms) in the task. Over the time course of the experiment the stimulus duration time changed in accordance with the individual performance. For each correct response, 15 ms were substracted from the duration. For each error, 85 ms were added. Missed responses had no influence on stimulus duration. Hence, task difficulty was continuously tailored to each participant's ability.

A trial started with a reward cue, which was displayed for 1000 ms. Then, after an inter-stimulus interval of 500 ms, a number was presented with each participant's individual stimulus duration time. Each response was followed by feedback (1000 ms) with a delay of 500 ms. The duration of the inter-trial interval was set to 1000 ms (see Figure 2A). The experiment was divided into 4 blocks with 80 trials. Each block was composed of an equal number of high and low reward trials, as well as an equal number of switches and repeats, presented in pseudo-randomized order (not more than three in a row).

In a post questionnaire we assessed participants' strategies to make judgements during the task. All participants reported using parity and magnitude as criteria and neither participant described strategies that were in conflict with our intended task requirements.

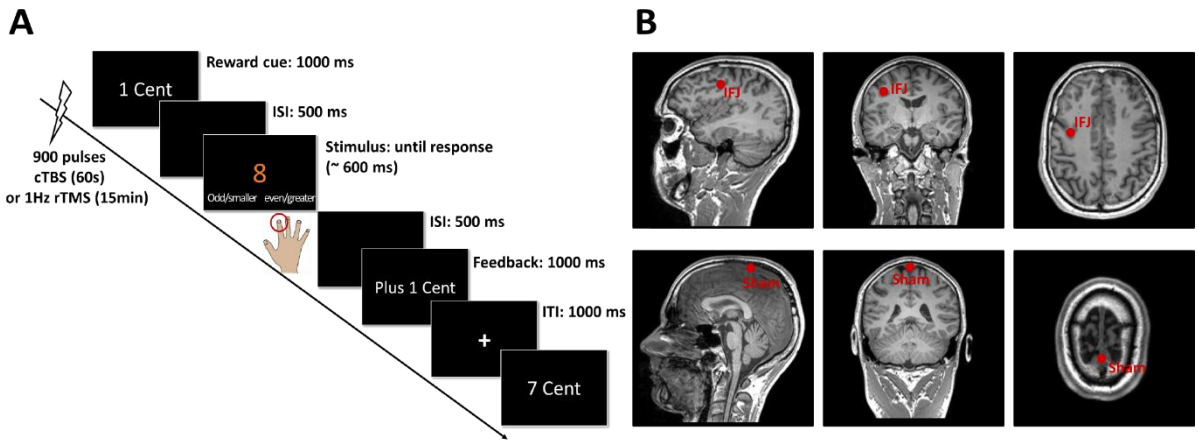

Figure 2 Experimental design. (**A**) Single trial structure of the paradigm. After stimulation by cTBS or 1Hz rTMS, participants performed a switch task with two different motivational conditions. Numbers were judged wither by parity (even or odd) or by magnitude (greater/smaller than 25). Responses were given with the index or middle finger of the right hand. Motivational cues of low reward (1 Cent) or high reward (7 Cent) trials were presented before each stimulus. Participants earned these rewards for correct responses. (**B**) Illustration of target sites. We stimulated the left IFJ (MNI coordinates: x = -40, y = 4, z = 32) and vertex (MNI: x = 0, y = -35, z = 80), which served as sham region.

2.2.3 TMS protocol and navigation

A T1-weighted anatomical image (MPRAGE, 256 × 256 matrix, 192 sagittal slices with 1 mm thickness, TR = 1900 ms, TE = 2.44 ms) was acquired for each participant with a 3T Siemens Magnetom Skyra scanner (Siemens, Erlangen, Germany) and used for individual MRI-guided neuronavigation (Sack et al., 2008). The left IFJ (MNI: x = -40, y = 4, z = 32) was determined as the junction of the inferior frontal sulcus and the inferior precentral sulcus. The sham site was located over the vertex (MNI: x = 0, y = -35, z = 80). Spherical 6 mm regions of interest were centered at both locations (see Figure 2B). The TMS neuronavigation system was employed to navigate to these anatomically defined regions in each individual. All TMS occurred offline.

Participants were seated on a chair with head and neck support to minimize head motion. A robotized system was employed for precise coil placement. The system is based on a serial seven-jointed lightweight, force-sensitive robotic arm (LBR iiwa 7 R800, KUKA AG, Augsburg, Germany) and a Polaris infrared stereo-optical tracking system (Northern Digital

Inc., Waterloo, Ontario, Canada). The system provides active motion compensation to maintain the coil position throughout the stimulation. This enables a more accurate and comparable stimulation setting in contrast to common hand-held approaches (L. Richter et al., 2013). To perform a robust system calibration for real-time motion compensation, individual 3D head reconstructions were rendered before stimulation (L. Richter et al., 2011). Passive marker spheres attached to the head and measured by the tracking system were used for precise head tracking and real-time motion compensation. The stimulation was realized with a MCF-B65 figure-of-eight coil (70mm) mounted to the robot's end effector, and driven by a MagProX100 stimulator with MagOption (MagVenture A/S, Farum, Denmark) for biphasic stimulation.

Prior to stimulation, each participant's active motor threshold (aMT) was determined through electromyographical recordings from the contracted first dorsal interosseous muscle (FDI) of the right hand. Single TMS-pulses were applied along the M1 until the designated target area with the lowest threshold for the activation of the contralateral FDI was found. There, pulses were delivered with decreasing intensity starting at 70% of the maximum stimulator output (MSO) until the minimum intensity was found that induced motor-evoked potentials with a peak-to-peak amplitude > 200µV in 3 of 5 trials. The coil was positioned at an angle of 45 degrees in relation to the surface of the skull. This procedure was executed in the first TMS session only and took approximately 20 minutes.

We applied cTBS (900 pulses) for a total duration of 60 s in bursts of three pulses (50 Hz) at intervals of 200 ms with 80 % of the individual aMT (mean stimulator output = 41.9 % MSO, ranging between 31 and 47 % MSO). We chose 80% aMT as it is predominantly used in cTBS studies (Galea et al., 2009; Gratton et al., 2013).

2.2.4 Analyses

RT and ER were subjected to separate repeated-measures analyses of variance (ANOVAs) with the factors Site (IFJ, sham), Reward (high, low) and Control (repeat, switch). RT were analyzed on correct trials only. Post-hoc t-tests were carried out on significant main effects and effect sizes for ANOVAs are reported as partial eta-squared. Data were analyzed using R v3.3.2 (R Core Team, 2016) and Matlab (TheMathWorks, Inc., Natick, MA).

2.3 Results

2.3.1 Response times

Participants responded slower on switch trials than on repeat trials, as established by the significant main effect of Control ($F_{(1,22)} = 17.41$, $p < .001$, $\eta_p^2 = .44$, repeat = 579 ms, switch = 603 ms). An interaction between Control × Reward ($F_{(1,22)} = 4.71$, $p = .041$, $\eta_p^2 = .17$) revealed that switch costs were significantly lower for high reward trials than low reward trials (p = .03, see Figure 2A). Although participants were nominally faster in high reward trials, the main effect of Reward did not reach significance ($F_{(1,22)} = 3.76$, $p = .065$, $\eta_p^2 = .15$, low = 594 ms, high = 587 ms). The interactions Control × Site ($F_{(1,22)} = 1.13$, $p = .30$, $\eta_p^2 = .05$), Reward × Site ($F_{(1,22)} = 1.45$, $p = .24$, $\eta_p^2 = .06$) and Control × Reward × Site ($F_{(1,22)} = 1.62$, $p = .22$, $\eta_p^2 = .07$) were not significant. Even though we observed a trend for the main effect of Site ($F_{(1,22)} = 3.16$, $p = .089$, $\eta_p^2 = .13$) with slower RT for IFJ stimulation (609 ms) compared to sham stimulation (578 ms), there was no significant difference induced by cTBS between IFJ and sham site in terms of RT.

2.3.2 Error rates

The significant main effect of Control ($F_{(1,22)} = 46.94$, $p < .001$, $\eta_p^2 = .68$, repeat = 9.6 %, switch = 15.0 %) revealed that participants made more errors on switch trials than on repeat trials. Error rates were significantly lower on high reward trials compared to low reward trials ($F_{(1,22)}$

= 5.20, p = .033, η_p^2 = .19, high = 11.6 %, low = 13 %). Importantly, we found a significant interaction between Control × Reward × Site ($F_{(1,22)}$ = 7.79, p = .011, η_p^2 = .26). Following stimulation of the IFJ only, ER on switches were significantly reduced in high reward trials compared to low reward trials (p < .01, see Figure 2B) leading to a significant decrease in switch costs (repeat minus switch) in high reward trials compared to low reward trials (p < .01). The main effect of Site ($F_{(1,22)}$ = 1.53, p = .23, η_p^2 = .07) and the interactions Control × Reward ($F_{(1,22)}$ = 2.61, p = .12, η_p^2 = .11), Control × Site ($F_{(1,22)}$ = 3.24, p = .086, η_p^2 = .13) and Reward × Site ($F_{(1,22)}$ = 0.64, p = .43, η_p^2 = .03) were not significant.

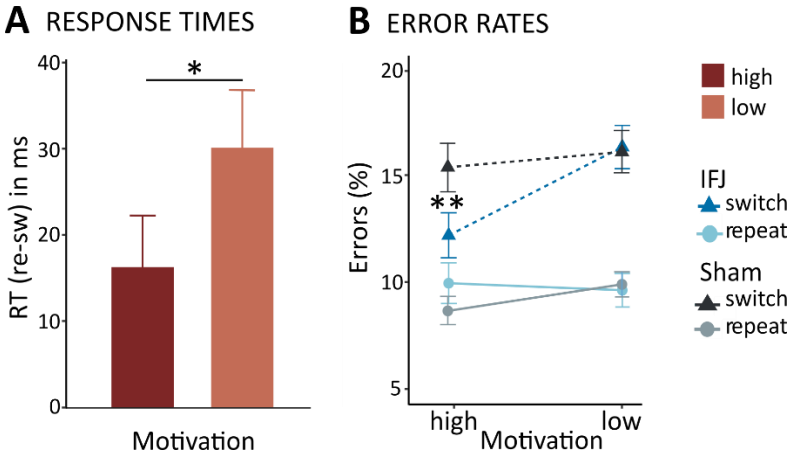

Figure 2 Behavioral results following cTBS. (**A**) Switch costs (repeat-switch) of response times (mean ± SE). We found a reduction of switch costs for high reward trials regardless of which region was stimulated. (**B**) Error rates (mean ± SE). We found a reduction of errors on high reward switch trials after inhibition of the IFJ. * p < .05, ** p < .01.

Table 1
Summary of behavioral measures of experiment 1.

	IFJ				Sham			
	High		Low		High		low	
	Switch	Repeat	Switch	Repeat	Switch	Repeat	Switch	Repeat
RT in ms (SE)	610 (22)	593 (18)	629 (24)	593 (19)	582 (15)	565 (13)	589 (15)	566 (13)
ER in % (SE)	12.3 (1.0)	10.0 (1.0)	16.4 (1.0)	9.7 (0.8)	15.4 (1.1)	8.7 (0.6)	16.1 (1.0)	9.9 (0.6)

Note: Means of response times (in milliseconds) and error rates (in percent) separately for each task condition following cTBS. SE=standard error.

2.4 Interim discussion

Our results demonstrated an enhancing effect of reward on cognitive control. Consistent with our previous findings (Bahlmann et al., 2015), the prospect of earning higher rewards facilitated switching between task sets which manifested in lower RT switch costs. Unlike predicted, cTBS over the left IFJ did not influence this RT effect. Instead, IFJ stimulation induced an interaction on ER that was not evident in the control condition. This finding is in contrast to prior studies reporting that TMS over the right (Coutlee et al., 2016; van Campen et al., 2018; Verbruggen et al., 2010; Zanto et al., 2011) as well as left IFJ (Lee & D'Esposito, 2012; Muhle-Karbe et al., 2014, 2018; Wittkuhn et al., 2018) decreases cognitive performance. A potential explanation for this discrepancy might be methodological differences with respect to the TMS stimulation protocol. While in the present study, we used cTBS in order to maximize the duration of the stimulation effect, most investigations targeting the IFJ or proximal regions in the lateral PFC used the more conventional 1 Hz rTMS protocol (Coutlee et al., 2016; van Campen et al., 2018; Wittkuhn et al., 2018; Zanto et al., 2011), which we have also successfully applied in a previous study (Bahlmann et al., 2015). Recent work shows that rTMS and cTBS do not always produce similar results and the equation of either protocol with inhibition might be too simple (Bonnì et al., 2015; Luber & Lisanby, 2014). To examine the specificity of the obtained cTBS effect and to increase comparability to prior studies, we decided to replicate the experiment with a different group of participants using 1-Hz rTMS.

Experiment 2

2.5 Methods

2.5.1 Participants

We included twenty participants (12 females, mean age = 23.3, ranging between 20 and 28 years) in the second experiment. Inclusion criteria, compensation, and ethics approval were identical to Experiment 1.

2.5.2 Stimuli and task

Participants underwent stimulation of the left IFJ and sham site (vertex) through navigated 1 Hz rTMS with exactly one week between sessions (IFJ / sham, counterbalanced sequence). Stimuli and task were identical to experiment 1.

2.5.3 TMS protocols and navigation

Target sites and coil position were the same for experiment 1 and 2 (see Figure 2.1B). The MNI coordinates for the left IFJ (x = -40, y = 4, z = 32) were reverse-normalized into each participant's individual brain space using SPM8 (available at http://www.fil.ion.232 ucl.ac.uk/spm).

Since the robotized TMS system was not available during data acquisition of the rTMS experiment, we then mounted the figure-of-eight coil (70 mm) on a mechanical arm, which allowed for immediate readjustment in case the coil had moved from its target position. Online head tracking was accomplished via Brainsight TMS Frameless Navigation system (Rogue Research Inc., Montreal, Quebec, Canada). Passive marker spheres attached to the head and coil were continuously registered by the tracking system and allowed for head tracking through visual inspection on a screen.

In the second experiment, we altered several stimulation parameters in order to increase comparability to our own previous work and other TMS studies, which successfully inhibited the lateral PFC (Bahlmann et al., 2015; van Campen et al., 2018). We determined the resting motor threshold (rMT) through electromyographical recordings from the first dorsal interosseous muscle of the right hand. It was defined as the minimum intensity necessary to induce motor-evoked potentials with a peak-to-peak amplitude > 50µV in 3 of 5 trials over the M1. 1Hz rTMS (900 pulses, 15 min) was delivered with 90 % of the individual rMT (mean = 55.6 % MSO, ranging between 49 and 60 % MSO) at the stimulation sites. This protocol has been reported to reduce cortical excitability for up to 45 min (Hallett, 2007).

2.5.4 Analyses

Data analysis was analogous to experiment 1.

2.6 Results

2.6.1 Response times

We found significant effects for Control ($F_{(1,19)}$ = 12.16, p = .002, η_p^2 = .39, repeat = 633 ms, switch = 652 ms) and the interaction between Control × Reward ($F_{(1,19)}$ = 15.68, p < .001, η_p^2 = .45) with lower switch costs for high reward trials compared to low reward trials (p < .01, see Figure 3A). In addition, the main effect of Reward ($F_{(1,19)}$ = 6.55, p = .019, η_p^2 = .26, high = 638 ms, low = 648 ms) showed that participants reacted significantly faster in high reward trials compared to low reward trials. The main effect for Site ($F_{(1,19)}$ = 0.26, p = .62, η_p^2 = .01) and the interactions Control × Site ($F_{(1,19)}$ = 3.28, p = .086, η_p^2 = .15), Reward × Site ($F_{(1,19)}$ = 0.41, p= .53, η_p^2 = .02) and Control × Reward × Site ($F_{(1,19)}$ = 2.77, p = .11, η_p^2 = .13) were not significant. Hence, we did not find any evidence for an influence of rTMS over the IFJ on RT compared to stimulation over the sham site, similar to the results in experiment 1. See Table 2 for response time values of each task condition.

2.6.2 Error rates

Significant main effects of Control ($F_{(1,19)}$ = 67.92, p < .001, η_p^2 = .78, repeat = 9.8 %, switch = 16.6 %) and Reward ($F_{(1,19)}$ = 6.16, p = .023, η_p^2 = .25, high = 12.2 %, low = 14.2 %) were obtained, indicating that participants responded more accurately on repeat trials compared to switch trials as well as high reward trials compared to low reward trials. Crucially, the interaction Control × Reward × Site ($F_{(1,19)}$ = 6.23, p = .022, η_p^2 = .25) was also found in experiment 2. While high reward trials had significantly reduced ER compared to low reward trials following IFJ stimulation only (p < .01, see Figure 3B), the reduction in switch costs in high reward trials compared to low reward trials was not significant (p = .09). The main effect of Site ($F_{(1,19)}$ = 0.92, p = .35, η_p^2 = .05) and the interactions Control × Reward ($F_{(1,19)}$ = 0.28, p = .60, η_p^2 = .02), Control × Site ($F_{(1,19)}$ = 0.73, p = .40, η_p^2 = .04) and Reward × Site ($F_{(1,19)}$ = 1.07, p = 0.31, η_p^2 = .05) were non-significant.

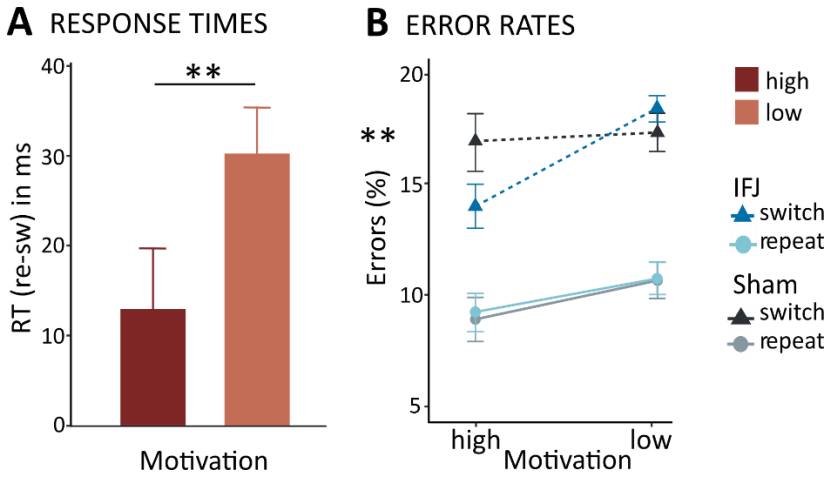

Figure 3 Behavioral results following 1 Hz rTMS. (**A**) Switch costs (repeat-switch) of response times (mean ± SE). We found a reduction of switch costs for high reward trials regardless of which region was stimulated thereby replicating the results of experiment 1. (**B**) Error rates (mean ± SE). As in experiment 1, we found a reduction of errors on high reward switch trials after inhibition of the IFJ. * p < .05, ** p < .01.

Table 2
Summary of behavioral measures of experiment 2.

	IFJ				Sham			
	High		Low		High		low	
	Switch	Repeat	Switch	Repeat	Switch	Repeat	Switch	Repeat
RT in ms (SE)	628 (17)	628 (18)	655 (22)	625 (20)	654 (35)	637 (33)	671 (34)	640 (29)
ER in % (SE)	14.0 (1.0)	9.1 (0.9)	18.4 (0.6)	10.7 (0.7)	17.0 (1.4)	8.9 (1.0)	17.3 (0.9)	10.6 (0.8)

Note: Means of response times (in milliseconds) and error rates (in percent) separately for each task condition following 1Hz rTMS. SE=standard error.

2.7 Discussion

Experiment 2 replicated the behavioral results obtained in experiment 1. Importantly, similar to the effect induced by cTBS, we found an increase in switch accuracy in high reward trials following 1 Hz rTMS. This provides strong evidence that the observed effect indeed results from neural changes to IFJ function by TMS and that the region is causally involved in the interaction between reward and cognitive control.

2.8 General discussion

The aim of the present study was to investigate the role of the IFJ in cognitive control and its modulation by motivation. To this end, we examined the effects of cTBS and 1Hz rTMS, both believed to be inhibitory, over the left IFJ using a task-switching paradigm with different motivational conditions. Contrary to our hypothesis, our results indicate that inhibition of the left IFJ increases the effect of motivation on cognitive control.

In the study, participants either had to repeat or switch between the task sets parity and magnitude. A large body of evidence on task switching shows that switches demand more cognitive effort than repeats and are therefore accompanied by slower, more frequently erroneous reactions (Monsell, 2003), a pattern also evident in the present study. Participants earned varying amounts of incentives for correct responses, which successfully induced different motivational states. This was expressed through faster and more accurate responses

when reward expectancy was high. Further, our paradigm was effective in generating behavioral interactions between cognitive control and motivation. In accordance with prior studies probing motivated task-switching (Aarts et al., 2010; Kleinsorge & Rinkenauer, 2012), we observed that high reward expectancy facilitated switching between tasks. Switch costs on response times were reduced when participants anticipated to be awarded with a high reward compared to a low reward regardless of which site was stimulated and what protocol was used.

Based on our prior fMRI work, in which we observed that functional connectivity between the left IFJ and midbrain correlated with the individual effect of reward on response times switch costs (Bahlmann et al., 2015), we had hypothesized that stimulation to the IFJ should affect this interaction between switch costs and expected reward. However, this was not the case in the present experiments. Note, though, that from the current results, we cannot deduct if the IFJ is not a causal contributor in this correlation or if stimulation simply failed to alter the neural mechanisms in a way that led to significant changes in participants' response speed.

Interestingly, while we did not find an effect of IFJ stimulation on *response times*, IFJ stimulation enhanced the effect of motivation on cognitive control for *error rates*. Across protocols, participants responded more accurately on switches in high reward trials when the left IFJ was stimulated. Hence, disrupting the left IFJ seemed to increase the impact of reward on behavioral performance, as evidenced by a facilitated switching between tasks. While this observation is in line with an assumed causal role of IFJ in the interaction between cognitive control and motivation, it stands in contrast to our prediction that inhibition of the region would *reduce* the effect of reward on cognitive control.

A possible explanation for this discrepancy might be found in the interplay of IFJ and striatum. It has been reported that the IFJ is involved in top-down control in posterior direction (Cole & Schneider, 2007; Miller & Cohen, 2001) and may modulate striatal activation (Jahfari

et al., 2011), which is essential to reward-related behavior (Delgado, 2007). If this connection is of inhibitory nature, disrupting the IFJ may have enhanced motivational processes by causing disinhibition of DA synthesis. Recent findings on D2 receptor density in the striatum support this interpretation. The involvement of the IFJ in task-switching has been linked to high D2 receptor density (Stelzel et al., 2010). Reward-related activity in the ventral striatum, however, seems to be enhanced when D2 receptor density is low (Forbes et al., 2007). Consequently, inhibition of the IFJ may have led to reduced D2 receptor occupancy, resembling low density and thus causing more DA release. If motivation shapes cognitive control, as discussed by Botvinick and Braver (2015), and this shaping process is mediated by the left IFJ through inhibition, then a temporary disruption of the region would have strengthened the effect of motivation on cognitive performance. This mechanism would explain the exclusive enhancement of performance for high reward switch trials. Yet, the interpretation remains speculative and to a degree stands in contrast to other studies associating the IFJ with the striatum and posterior cortexes. In a combined PET-fMRI study, Landau et al. (2009), for instance, could show that working-memory-related activity in the left IFJ positively correlated with caudate dopamine function and task accuracy. Ko and colleagues (2008) applied TMS to the dlPFC and thereby impaired set-shifting performance as well as DA release in the ipsilateral caudate–anterior putamen and contralateral caudate nucleus. In a similar vein, several studies report decreased visual working-memory accuracy after rTMS to the left or right IFJ and account the effect to diminished top-down modulation of activity in the posterior cortex (Lorenc et al., 2015; Zanto et al., 2011). However, since neither of these studies included motivational manipulations in their designs, they only tell part of the story when it comes to the interaction between motivation and cognitive control. Several studies suggest a link between IFJ activation and reward processing. For instance, Wagner et al. (2013) showed that depleted dieters exhibited enhanced neural responses to reward as top-down control from the inferior frontal

gyrus decreased. Reward sensitivity further has been known to modulate brain activity in the frontostriatal circuit and the anterior cingulate cortex (ACC) in response to task switching (Ávila et al., 2012; Fuentes-Claramonte et al., 2015).

It is also conceivable that the stimulation effect we observed may not stem from direct control of the IFJ to striatal regions but might be mediated by another brain region. A recent meta-analysis (Parro et al., 2017) on the neural basis of motivational influence on cognitive control identified several implicated regions, including the IFJ, striatum and the cingulate cortex. Since the ACC has been consistently associated with the enhancing effect of reward on cognitive control (Kouneiher et al., 2009; Rowe et al., 2008; Vassena et al., 2014), the area is likely a vital component in its neural genesis. This conclusion is supported by Tik et al. (2017), who could show that high-frequency rTMS over the left DLPFC resulted in higher resting state network connectivity of the ACC with structures of the meso-cortico-limbic DA system. The specific interplay between those brain regions, however, is not resolvable with our study. Even though, to our knowledge, we are the first to demonstrate causal cortical contributions at the interface of cognitive control and reward, our results do not point in the predicted direction and need to be considered preliminary. Future research could probe in what way the IFJ assists to integrate motivational and cognitive processes by combining TMS over the IFJ with imaging techniques, or by investigating effective connectivity between IFJ and striatum during motivated task-switching.

Furthermore, it should be noted that paradoxical results following TMS are not uncommon. Prior studies applying inhibitory protocols have shown improvements in behavior (Luber & Lisanby, 2014) as well as paradoxical changes in network connectivity (Eldaief et al., 2011; Watanabe et al., 2014). Gratton and colleagues (2013) observed increases in connectivity of the frontoparietal cognitive control network following cTBS over the left dlPFC and considered their results could reflect a compensatory mechanism, similar to that seen in patients

with brain damage (Voytek et al., 2010). Others have credited unexpected TMS-induced changes to release from cross-hemispheric inhibition (Hilgetag et al., 2001; Kobayashi, 2010) or suggested inhibition only affected irrelevant stimulus information, which in turn speeded task processing (Oliveri et al., 2010).

Most explanations provided for paradoxical results follow the construct of the 'virtual lesion' (Pascual-Leone, 1999), which theorizes that inhibitory TMS is able to simulate the effects of actual lesions. In fact, though, the exact neurological mechanisms underlying effects of TMS are still far from understood and even though inhibitory TMS protocols have produced changes in participants' performance, they have never generated clear behavioral deficits comparable to those observed in lesion patients. In recent years, new concepts that go beyond the virtual lesion account have been proposed. Rather than terminating or simply reducing neuronal activity in the stimulated area, it is assumed that TMS generates neural noise that is unrelated to task-relevant information and thus interferes with performance through increased unsynchronized firing of neurons (Miniussi et al., 2013). Accordingly, depending on the particular protocols used, TMS-induced noise may not only disrupt but also add to task-relevant activity (Silvanto et al., 2008; Silvanto & Pascual-Leone, 2008).

Interestingly, both cTBS and 1Hz rTMS over the left IFJ produce comparable behavioral results and therefore likely evoke the same underlying neuronal process. Participants showed the same response pattern across stimulation protocols that was not evident in the control condition. Nevertheless, the facilitating effect of reward on switch trials was more pronounced following cTBS than rTMS. This led to a significant reduction in switch costs of error rates in the cTBS experiment that can merely be described as a trend in the rTMS experiment. Since it has been shown that cTBS produces stronger, longer-lasting effects compared to 1Hz rTMS (Huang et al., 2005) it is possible that the effect induced by 1Hz stimulation was less intense. Nonetheless, it is remarkable that stimulation with either protocol

generated an enhancing effect of reward on cognitive control. Especially in light of rTMS effects' dependency on frequency, intensity and duration of stimulation (Sack & Linden, 2003), the robust effect additionally stresses the causal role of the IFJ in this context. By combining different protocols, we were able to demonstrate reliable results, which may prove a promising approach to allow for deducing accurate casual statements regarding the functions of stimulated regions.

One limitation of our study might be that stimuli were imbalanced in the sense that numbers smaller than 25 were only even and numbers greater than 25 were odd. We chose this distribution to avoid indistinct responses since otherwise we could not distinguish between a correct switch and incorrect repeat. This however renders stimulus features (parity versus magnitude) predictive of responses in both task sets. Consequently, we cannot rule out the possibility that participants used divergent strategies to make judgements during the task.

In summary, our results provide evidence that the left IFJ is involved in integrating reward and cognitive control and suggest that it mediates the motivational impact on cognitive performance via top-down modulation of striatal structures.

Chapter 3: Effective connectivity underlying reward-based executive control[2]

3.1 Introduction

Every action we take in our daily lives has potential consequences, which we perceive as either positive or negative. These consequences shape our future behavior substantially and fuel our motivation to make decisions that lead towards desirable outcomes, such as the receipt of rewards, but also the avoidance of punishments. Importantly, heightened motivation facilitates executive functioning (for review, see Botvinick & Braver, 2015). An illustrative example is the enhancing effect of monetary incentives (i.e. potential gain or loss) on the performance in cognitive tasks (Boehler et al., 2014; Engelmann & Pessoa, 2014; Etzel et al., 2015; Guitart-Masip et al., 2012; Padmala & Pessoa, 2011; Tricomi et al., 2004; Wächter et al., 2009). Krebs and colleagues (2010), for instance, could show that performance-contingent monetary reward improved cognitive control such that participants named the color of a Stroop stimulus faster and more accurately in prospective-reward compared to no-reward trials.

On a neural level, the beneficial effect of motivation on executive control seems to depend on communication between structures within the dopaminergic system (Cools, 2008). Particularly, the anterior cingulate cortex (ACC), inferior frontal junction (IFJ) and ventral tegmental area (VTA) located in the midbrain have been suggested as instrumental in the integration of cognitive control and motivation (Aarts et al., 2010, 2011; Bahlmann et al., 2015; Parro et al., 2017; Westbrook & Braver, 2016).

The ACC takes the center stage in this setting (Shenhav et al., 2016) and has consistently been associated with interactions between motivation and control. In particular, it is thought to serve as an integrative node, where input from other areas signaling the prospect of reward or

[2] Largely corresponds to Hippmann, B., Tzvi, E., Göttlich, M., Weiblen, R., Münte, T. F., & Jessen, S. (2021). Effective connectivity *Brain* underlying reward-based executive control. *Human Mapping*. doi: 10.1002/hbm.25564

punishment on the one hand and the need for enhanced control on the other hand is combined (Fujiwara et al., 2009; Kahnt et al., 2011; Mansouri et al., 2017; Vassena et al., 2014; Wallis and Kennerley, 2011). According to the "expected value of control" theory (Shenhav et al., 2013), the ACC assesses the estimated benefit and cost to expend cognitive effort and appropriates control correspondingly. This account is substantiated by studies linking ACC activity with both anticipated effort and anticipated reward (Croxson et al., 2009; Prévost et al., 2010)

Besides the ACC, the VTA as a source of dopaminergic neuromodulation in goal-directed behaviors is assumed to play a pivotal role in the interaction between cognitive control and motivation (Arias-Carrión et al., 2010; Beier et al., 2015; Zellner and Ranaldi, 2010). For instance, dopamine (DA) is key in implementing the influence of incentives on executive control (Aarts et al., 2010; Adcock et al., 2006). Activations of the VTA have been associated with cognitive flexibility as well as both reward and punishment motivation (Carter et al., 2009; D'Ardenne et al., 2008; Guitart-Masip et al., 2012). Of particular interest in this context are DA projections from VTA to the lateral prefrontal cortex (lPFC) via the mesocortical pathway, which are thought to be essential in constituting cognitive function (Durstewitz & Seamans, 2008; Goldman-Rakic, 1992). Likewise, VTA projects to the ACC and is assumed to thereby contribute to reward-based cognitive processing (Haber & Knutson, 2010; Hauser et al., 2017; Köhler et al., 2016).

Alongside ACC and VTA, the IFJ, a subregion of the lPFC, recently has come into focus as a critical neural substrate in the integration of control demands and potential outcomes. Numerous studies have demonstrated IFJ activation during reward-based executive control (see Parro et al., 2017 for a meta-analysis). Modulations in effective connectivity from IFJ to ACC have been associated with changes in cognitive demand (Harding et al., 2015; Hinault et al., 2019). Evidence further suggests that the IFJ is closely linked to the dopaminergic system

(Stelzel et al., 2010, 2013) and serves task demands by selectively engaging brain regions related to control (Asplund et al., 2010; Baldauf & Desimone, 2014; Kim, 2014) and motivation (Paschke et al., 2015). In addition, functional connectivity between IFJ and midbrain has been found to correlate with the individual enhancing effect of reward on cognitive performance (Bahlmann et al., 2015).

All three regions – IFJ, VTA, and ACC – therefore appear to be interconnected and involved in the interplay between motivation and cognitive control. While the body of evidence suggests that both IFJ and VTA direct ACC activity in motivation-based executive functioning, the exact pathways and in particular the direction of connectivity between IFJ and VTA remains unclear. In an initial study using transcranial magnetic stimulation, we could show that the left IFJ is causally involved in reward-related cognitive facilitation and suggest that this effect may be realized via modulation of the dopaminergic network (Hippmann et al., 2019). Likewise, previous evidence suggests that the lPFC initiates motivated behavior by influencing VTA activity in anticipation of reward (Ballard et al., 2011). These findings therefore support the notion that the lPFC, and particularly the IFJ, exerts control over VTA and ACC to shape motivated cognitive control. However, an alternative possibility is that interactions between motivation and control are rooted in DA projections from VTA to the lPFC, essential positing an influence in the opposite direction. For instance, DA levels in the lPFC have been associated with cognitive control and attention (Durstewitz & Seamans, 2008; Vijayraghavan et al., 2007).

Another unsolved issue concerns potential differences in neural processing between two main motivational goals: pursuing reward and avoiding punishment. Even though activations in the aforementioned regions have been associated with both processes, it is unclear whether they act via the same neural mechanism to produce cognitive performance increments. Some researchers argue in favor of a common mechanism (Xue et al., 2013), while others support the

idea of opponent systems for reward and punishment (Palminteri & Pessiglione, 2017; Wächter et al., 2009).

The goal of the present study therefore was to discern these possibilities by means of dynamic causal modeling (DCM) within a proposed network of ACC, IFJ and VTA considering both, reward- and punishment-driven influences on cognitive control. Even though DCM has been criticized in terms of biophysical realism (Daunizeau et al., 2011), it serves as a valuable tool to observe information flow between critical structures as it allows to make inferences about the strength and directionality of connections between regions of interest (Friston et al., 2003).

We designed a functional magnetic resonance imaging (fMRI) study using a task switching paradigm that included motivational manipulations through monetary incentives. Participants either switched between or repeated two competing tasks (i.e. numbers were judged either by parity or magnitude). These tasks were embedded in two motivational conditions, in which participants received performance-contingent monetary reward or punishment, and a neutral condition without monetary incentives. We expected that switching (compared to repeating) tasks would be facilitated through both prospective reward and prospective punishment. Based on the evidence outlined above, we hypothesized that both IFJ and VTA would exert control over ACC activity and that these modulations would relate to interactions between motivation and cognitive control. We also suspected that neural interactions between IFJ and VTA would be modulated by cognitive control and motivation and considered modulations in either direction to be possible scenarios. Furthermore, we were interested in whether prospective reward and punishment recruited these structures in the same manner.

3.2 Methods

3.2.1 Participants and procedure

Twenty-nine right-handed participants took part in the present study after giving informed consent. All reported normal or corrected-to-normal vision and were screened for common fMRI exclusion criteria as well as their personal and family history of neurological abnormalities. They received compensation (7€ / h) for participation as well as monetary rewards in accordance with their individual performance on the task. Data from two participants had to be discarded due to structural abnormalities on the basis of a T1-weighted structural scan evaluated by a neuroradiologist. Four additional data sets were excluded because of technical issues during measurement (i.e. scanner failure, no recording of responses, incorrect display of stimuli). The remaining 23 participants (13 females, mean age = 23.0, ranging between 19 and 29 years) were included in the behavioral and fMRI analysis. The study was approved by the local ethics committee and conducted in conformance with the principles of the Declaration of Helsinki.

3.2.2 Experimental paradigm

Participants performed a task switching paradigm including different motivational conditions while being comfortably placed in an MRI scanner. Stimuli were numbers between 1 and 50 presented on a black screen in random sequence (see Figure 1A) and viewed over a mirror mounted on the MR head coil. The color of these numbers established which of two tasks to perform. Blue required participants to judge a number regarding its magnitude (smaller or greater than 25), while a yellow number constituted the parity task (even or odd). If two subsequent trials obeyed the same task rule (parity following parity or magnitude following magnitude) this sequence was defined as a repeat. A switch was defined as a sequence of two trials with diverging task rules (parity following magnitude or vice versa). Participants gave

responses on a fiber optic response pad with the index (smaller/odd) or middle (greater/even) finger of their right hand. A response map was displayed below the stimuli. Numbers were chosen to create contrasting response patterns and thus avoid indistinct responses. To that end, only even numbers smaller than 25 and odd numbers greater than 25 were included (Hippmann et al., 2019). The task was divided into blocks with different motivational conditions: In the punishment condition, participants lost 7 Cents when they gave an incorrect response but did not gain any money for correct responses. In the reward condition, participants earned 7 Cents for correct responses but did not lose any money for incorrect responses. In the neutral condition no money was gained or lost. Participants were instructed to respond as fast as possible. Each response was followed by feedback displayed on the screen ("Plus 7 Cent", "Minus 7 Cent", "Correct" or "False").

The total of six blocks was divided by a short break into two scan runs. Each run was composed of a reward, a punishment and a neutral block (order counterbalanced across participants, see Figure 4B). An instruction screen (10s) before each block indicated which motivational condition would follow. After completing a block, participants received feedback about the amount of money they gained or lost (10s). A block contained 50 trials and 10 null-trials (white fixation cross, randomized) and was composed of an equal number of switches and repeats, presented in pseudo-randomized order (not more than three in a row). Null trials were introduced for jittering purposes in order to increase detectability of task-related responses (Burock et al., 1998). A fixation cross presented for 3, 3.5, or 4s initiated each trial followed by the presentation of a stimulus (3s) and feedback (500ms). Each stimulus was displayed for 3s regardless of response time. A depiction of the trial structure can be found in Figure 4A.

Prior to the MR session, participants familiarized themselves with the task in a brief preparatory training outside the scanner, which consisted of 25 trials without motivational cues. If participants had more than ten misses or errors, the training was repeated. The individual

mean response time from the training served as initial response window duration (ranging between 900 and 1400 ms) in the task. Over the time course of the experiment the width of this window changed depending on the individual performance in order to continuously tailor task difficulty to each participant's ability. For each correct response, 15 ms were subtracted from the duration. For each false response, 85 ms were added. Missed responses had no influence on the duration.

In the debriefing, we asked participants which strategies they used to make judgements during the task. All participants reported using parity and magnitude as criteria and neither participant described strategies that were in conflict with our intended task requirements. The whole experiment lasted approximately 60 minutes.

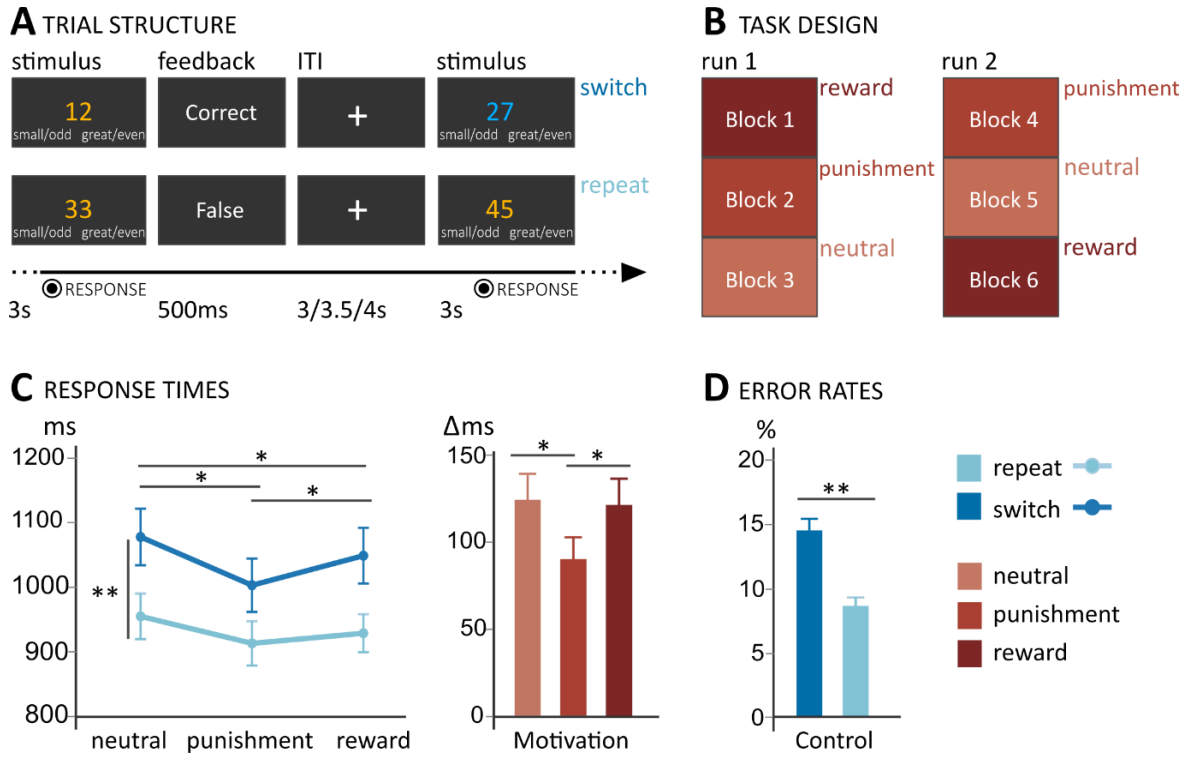

Figure 4 Design and behavioral results. (**A**) Participants judged numbers according to either magnitude (blue) or parity (yellow). Switch and repeat trials, defining the factor Control, were pseudo-randomized (not more than three in a row). (**B**) Three levels of motivation were linked to monetary incentives. Reward: Participants earned 7 Cent for correct responses. Punishment: Participants lost 7 Cent for incorrect responses. Neutral: No money could be gained or lost. The factor Motivation was blocked and randomized within two fMRI runs. Each block was composed of 50 trials and 10 null-trials (white fixation cross). (**C**) Response times (mean ± SE) per task condition and switch costs (switch minus repeat) per motivational condition in milliseconds. Switch trials were followed by slower responses compared to repeat trials. This effect was reduced in the punishment condition. (**D**) Error rates (mean ± SE) in percent. Across motivational conditions, participants made more errors on switch compared to repeat trials. ITI = inter-trial interval. * $p < .05$, ** $p < .001$, FDR-corrected. n=23.

3.2.3 Behavioral analyses

Response time (RT) and error rate (ER) were subjected to separate repeated-measures analyses of variance (ANOVAs) with the factors Motivation (neutral, punishment, reward) and Control (repeat, switch). First trials of each block and those following null-trials were excluded from the analysis, since they could not be categorized as switch or repeat trials. RT was analyzed on correct trials only. Post-hoc t-tests were carried out on significant main effects and interactions and corrected for multiple comparison using the false discovery rate (FDR) method. Effect sizes

for ANOVAs are reported as partial eta-squared. Data were analyzed using R v3.3.2 (R Core Team, 2016).

3.2.4 fMRI data acquisition

Structural and functional MR imaging was performed at the Center of Brain, Behavior and Metabolism (CBBM, University of Lübeck) using a 3-T Siemens Magnetom Skyra scanner equipped with a 64-channel head-coil. Functional MRI data were acquired in two runs, each containing 3 experimental blocks (reward, punishment, neutral in randomized order). A gradient echo-planar imaging (EPI) sequence sensitive to blood oxygen level-dependent (BOLD) contrast was used with the following specifications: TR = 1690 ms, TE = 25 ms, flip angle = 80°, parallel imaging acceleration factor 2 (GRAPPA), 3 × 3 mm^2 in-plane resolution, 192 × 192 mm^2 field of view, 34 transversal ascending slices of 2.5 mm thickness and 25 % gap co-planar to AC-PC. Structural images were collected using a 3D T1-weighted MPRAGE sequence (TR = 1900 ms, TE = 2.44 ms, TI = 900 ms, flip angle = 9°, 1 × 1 × 1 mm^3 resolution, 192 × 256 × 256 mm^3 field of view).

3.2.5 fMRI data analysis

Functional data were analyzed using the Statistical Parametric Mapping software package SPM12 (available at http://www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB 2015a (Mathworks, Sherborn, MA). Preprocessing included slice-timing correction to the first slice, realignment to the first functional volume, co-registration to T1 structural image, segmentation, normalization to Montreal Neurological Institute (MNI) space in native voxel space, smoothing with an 8 mm full width half maximum (FWHM) Gaussian kernel and high-pass temporal filtering (T = 128 ms). Autocorrelation in fMRI time series have been accounted for by applying an autoregressive AR(1) model during parameter estimation.

For each participant, event-related responses were estimated using a general linear model (GLM) approach. The model included separate regressors for correct trials for the six conditions (punishment switch, punishment repeat, neutral switch, neutral repeat, reward switch, reward repeat) convolved with the hemodynamic response function. Events were time-locked to the onset of each trial (appearance of colored number) and were modeled as having a duration of 0 seconds. Additionally, for each run the model comprised six regressors for movement and three regressors of no interest for error trials, null-trials, and feedback onsets.

Statistical analyses on the group level were specified as flexible factorial design and implemented in SPM12 with each subject treated as a random effects variable. The main effects of cognitive control (switch > repeat) and motivation (punishment > neutral and reward > neutral) were tested using t-contrasts, the interaction between both factors was assessed via F-contrasts. Contrast weights were assigned according to Gläscher and Gitelman (2008). An uncorrected voxel-level threshold of $p < .001$ was selected for all analyses, with a family-wise error (FWE) correction threshold of $p < .05$ at cluster level.

3.2.6 Dynamic causal modelling

We used dynamic causal modelling (DCM, Friston et al., 2003) as implemented in SPM12 version DCM12, to disentangle the directional interactions between brain regions underlying the enhancing effect of motivation on cognitive control.

DCM models describe changes in regional activity as:

$$\frac{d\vec{x}}{dt} = \left(A + \sum_{j=1}^{m} u_j B^{(j)} \right) \vec{x} + C\vec{u}$$

with $\vec{x}$ representing a neuronal state vector and $\vec{u}$ representing an input vector. $\boldsymbol{A}$ describes latent connectivity between brain regions irrespective of experimental conditions, $\boldsymbol{B}$ describes the modulatory influence of experimental conditions on the intrinsic connections, and $\boldsymbol{C}$ describes

the extrinsic effects of input $\vec{u}$ on activity. Since DCM is considered a hypothesis-driven rather than data-driven approach (Daunizeau et al., 2011), prior knowledge of, or hypotheses on network connections and modulations are essential for inferring an optimal, thus most plausible, model of effective connectivity out of an a priori defined model space. For each model, the state equation is transformed into a predicted BOLD signal by a biophysical forward model of hemodynamic responses (Friston et al., 2000; Stephan et al., 2007), which is then fitted to the actual BOLD signal through a gradient ascent on the free-energy bound. Note, that while interactions between nodes in the network may occur on a millisecond level, the predicted BOLD signal as the actual measured signal represents changes on a second-level. A "winning model" is subsequently selected based on the posterior probability associated with each model's evidence using the Bayesian model selection procedure (BMS, Penny et al., 2004). We extracted connectivity parameters from the winning model and used random-effects parametric analysis across participants to estimate changes in modulatory effects on connectivity.

3.2.7 Time series extraction

We specified left IFJ, left ACC and left VTA as volumes of interest (VOIs). We limited the DCM analysis to the left hemisphere since previous studies report hemispheric specialization in cognitive control (e.g. Badre and Wagner, 2007; Serrien and Sovijärvi-Spapé, 2013; Stephan et al., 2003). Regarding the research questions addressed in the present study, previous work finds control and motivation effects related to the IFJ in the left hemisphere (Bahlmann et al., 2015; Harding et al., 2015; Hippmann et al., 2019). As there is limited knowledge about interhemispheric interactions between the selected VOIs, we wanted to avoid making unsupported assumptions about network connections in order to narrow down the model space**.**

Coordinates of the VOIs for IFJ (x = -45 mm, y = 5 mm, z = 29 mm) and VTA (x = -5 mm, y = -25 mm, z = -10 mm) were selected based on the group level maxima in the task >

baseline contrast (p < .05, FWE-corrected, see Table 4B) in order to account for changes in BOLD signal related to all six task conditions. VOI coordinates for the ACC (x = -10 mm, y = 8 mm, z = 41 mm) were isolated from the task > baseline contrast with an anatomical mask (see Figure 5 for visualization of VOIs). Time series for each VOI were extracted from significant voxels (p < .01, uncorrected) in the individual task > baseline contrasts. For each participant, the sphere center of each VOI was moved to the closest suprathreshold voxel, which was kept within a 10 mm radius from the group peak coordinates. Xjview toolbox (http://www.alivelearn.net/xjview) and AAL brain atlas were applied to verify that the individual sphere centers were located within the regions of interest. This individualized peak approach allows targeting those regions on the single-subject level that are most likely to drive ongoing neural processes in the group level while ensuring that individual regions remain comparable. The approach is in line with prior comparable studies examining task-related DCM effects (Heim et al., 2009; Kleineberg et al., 2018; Roswandowitz et al., 2021).

Using a singular value decomposition procedure implemented in SPM12, we computed the first eigenvariate across all suprathreshold voxels within 6 mm radius from the sphere center for each participant. We chose a larger radius for the spheres to avoid including signals in the DCM analysis, which are derived from VOIs with very few voxels and thus are more susceptible to noise. Time series were then adjusted for effects of interest and sharp improbably temporal artifacts were smoothed by an iterative procedure implementing a 6-pint cubic-spline interpolation. We could not extract time series in three participants for all VOIs (one IFJ, two ACC) based on these criteria. Since DCM requires time series from the full network, we repeated the procedure for the respective participants and VOIs with a more tolerant threshold of p < .05 (uncorrected), which allowed the inclusion of all 23 participants in the analysis.

We conducted a power analysis using G*Power v3.1.9.2 to estimate the power that could be achieved on a one sample t test (as applied to test the strength of intrinsic and

modulatory connections in DCM models). Analysis revealed that 23 participants suffice for 96% power on strong effects (d = .8), 63% power on medium effects (d = .5) and 15% power on small effects (d = .2) with an alpha of .05.

3.2.8 DCM specification

Input vector $\vec{u}$ was constructed as a stick function of the single events of stimulus presentation. Given that distinct motivational states (i.e., neural processes related to reward and punishment) may differentially interact with task processing in the selected regions of interest, we built separate model families for the three motivational conditions (neutral, punishment, reward). These model families were based on the same task, comprised the same number of trials and consisted of models with identical architecture between the same set of regions. They only differed in terms of the modulatory effect (B-matrix) meaning, for instance, the modulatory input for the reward family derived from "reward switch" and "reward repeat" trails. The DCM framework allows to compare plausible models that are constructed based on a set of pre-defined regions of interest and a priori knowledge on network connections between those regions. We therefore made a few assumptions regarding the model space in order to restrict the amount of comparisons. First, we allowed bidirectional intrinsic connections between the VOIs in all models. Second, we considered both IFJ and midbrain to be plausible input regions, based on the evidence outlined in the introduction. In order to avoid inflating the model space and thereby decreasing the stability of results, we opted against establishing the input region computationally by building separate models for different input nodes. We decided to admit task input on both IFJ and midbrain in all models. This allowed us to identify each region's contribution to the neural processes on the parametric level. Note that it is plausible that an unmodeled region such as the visual cortex could serve as better input node to the model. Still, the summed influence of the input on the chosen input regions should be evident. Third, the

model space comprised all possible permutations of modulatory connections between the VOIs, except for the connection from IFJ to ACC. Since previous work on effective connectivity during cognitive tasks showed that the IFJ directs activity in the ACC (Harding et al., 2015; Hinault et al., 2019), the connection was operative in all models. This amounted to 32 models per family and 96 models in total. Assuming variability across participants, we compared models and model families using RFX BMS (Penny et al., 2010). After selecting a winning model based on the highest exceedance probability, we extracted the estimated model parameters in each participant and calculated an average parameter estimate for each connection, which was then tested for strength using one-sample *t* tests. Multiple comparisons were corrected using FDR.

3.3 Results

3.3.1 Behavioral results

Response time

We found significant effects on response time for Control ($F_{(1,22)}$ = 67.34, p < .001, η_p^2 = .75, repeat = 933 ms, switch = 1044 ms) and Motivation ($F_{(2,44)}$ = 5.71, p < .01, η_p^2 = .21). Participants were significantly faster in the punishment condition (957 ms) compared to the reward (988 ms, p = .02) and neutral conditions (1017 ms, p < .01). Response time in the neutral and reward blocks differed significantly (p = .04). Moreover, we found a significant interaction between Control × Motivation ($F_{(2,44)}$ = 3.74, p = .03, η_p^2 = .15). Post-hoc analyses revealed significant differences between switch and repeat trials for all three motivational conditions with p < .001. Switch costs were significantly lower in punishment (90 ms) compared to neutral (123 ms, p = .04) as well as reward blocks (121 ms, p = .04, see Figure 4C). Neutral and reward blocks did not differ significantly in regard to switch costs (p = .83). See Table 3 for response time values of each task condition.

Error rates

The significant main effect of Control ($F_{(1,22)}$ = 29.16, p < .001, η_p^2 = .57) revealed that participants showed lower error rates on repeat trials (8.7 %) than on switch trials (14.5 %, see Figure 4D). The main effect of Motivation ($F_{(2,44)}$ = 1.17, p = .32, η_p^2 = .05) and the interaction between Control × Motivation ($F_{(2,44)}$ =.04, p = .96, η_p^2 = .002) were not statistically significant. Error rates for each task condition can be found in Table 3.

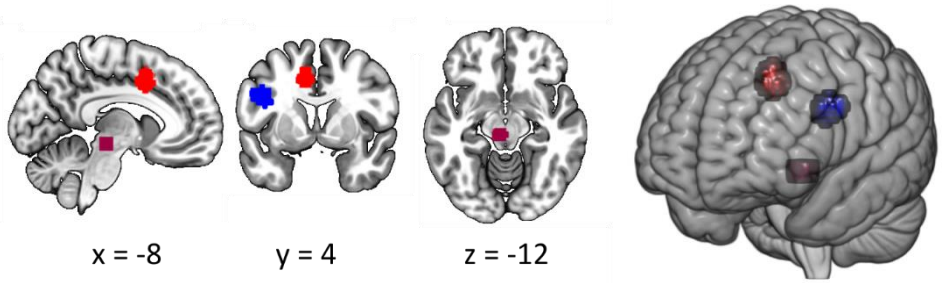

Figure 5 Clusters entering DCM analysis. Pooled participants' individual VOIs for anterior cingulate cortex (ACC, red), interior frontal junction (IFJ, blue) and ventral tegmental area (VTA, violet). n = 23.

Table 3 Summary of behavioral measures.

	Neutral		Punishment		Reward	
	Switch	Repeat	Switch	Repeat	Switch	Repeat
RT in ms (SD)	1079 (210)	956 (169)	1004 (198)	914 (165)	1050 (207)	929 (141)
ER in % (SD)	15.3 (6.8)	9.1 (5.2)	14.8 (5.9)	9.2 (5.3)	13.6 (5.6)	7.8 (4.6)

Means of error rates in percent and response times in milliseconds separately for each condition. SD=standard deviation. n = 23.

3.3.2 fMRI results

Higher cognitive demand (switch > repeat, see Table 4A) was associated with significantly increased neural activity in the right insula, left midbrain, supplementary motor area (SMA), precuneus and inferior parietal sulcus (IPS). For the reverse contrast (repeat > switch) a significant cluster was found in the right superior frontal gyrus (SFG). We found no significant clusters associated with the main effect of Motivation or the interaction between Control and Motivation.

Table 4 Whole brain imaging results.

Contrast/Brain region	MNI coordinates x	y [mm]	z	Cluster size (voxel)	T-value (peak)	p_{FWE} (cluster)
A switch > repeat						
R insula	31	23	5	187	6.94	.000
L midbrain	-2	-25	-13	157	6.55	.000
L SMA	-5	2	56	144	4.68	.000
L IPS	-30	-52	53	72	4.37	.022
L precuneus	-7	-70	50	64	4.15	.036
repeat > switch						
R SFG	6	50	38	72	4.87	.022
B task > baseline						
L precentral gyrus	-30	-22	56	1598	14.70	.000
L midbrain	-5	-25	-10	443	11.83	.000
R insula	31	23	5	118	10.08	.000
R cerebellum	11	-52	-16	89	9.24	.000
R precentral gyrus	36	-7	50	77	8.73	.001
L insula	-30	20	5	63	9.14	.000
R IPS	33	-46	47	27	8.22	.002
R middle occipital gyrus	31	-91	17	24	8.44	.001
L IFJ	-45	5	29	24	7.66	.005

Results are reported with a cluster defining threshold of p = .001 and FWE-correction at p < .05. L = left, R = right, SMA = supplementary motor area, IPS = inferior parietal sulcus, SFG = superior frontal gyrus, IFJ = inferior frontal junction. n = 23.

3.3.3 DCM results

Figure 6A depicts exceedance probabilities derived from the Bayesian model comparison. Family level inference results showed that the reward family had a higher exceedance probability (*p_ex* = .73) compared to the punishment (*p_ex* = .10) or neutral family (*p_ex* = .17) suggesting that interactions between IFJ, ACC and VTA are more prominent during reward blocks. The Bayesian omnibus risk (BOR) indicator measuring the probability that all model frequencies are distinguishable was 0.9 indicating that the models were not well distinguishable (Rigoux et al., 2014). Note however that this is to be expected with a large number of models of similar structure. BOR calculation further cannot consider family grouping of the models. We thus continue to report the results from the winning model and compare its modulatory parameters to those of the models from the other families with the same architecture.

Accordingly, the winning model (Model 82) belonged to the reward family with *p_ex* = .039 followed by the next best reward model with *p_ex* = 0.031 (see Figure 6A, right panel). No neutral or punishment model exceeded a posterior probability of .010. We found significant positive intrinsic connections, independent of cognitive control or motivation, from IFJ and VTA to ACC and significant negative intrinsic connections from ACC to IFJ and VTA as well as from IFJ to VTA and vice versa (Figure 6B, left panel). Moreover, we observed four modulatory connections in the winning reward model: both switch and repeat significantly enhanced connectivity from IFJ and VTA to ACC. Switch trials also significantly increased connectivity from VTA to IFJ, while repeat trials did not. Modulations from IFJ to VTA were not significant (see Figure 6B). Parameter estimates, T- and p-values of intrinsic and modulatory connections of the winning reward model are listed in Table 5. We compared connectivity strength of switch and repeat input on these modulatory connections. We found significant modulation differences on the connection from IFJ to ACC with stronger positive modulation by switch trials ($t = 2.32$, $p = .030$). All other modulatory connections showed no significant differences between switch and repeat trials (all $t < 1.8$ and $p > .09$). We neither found significant differences in the strength of driving input between IFJ and VTA (all $t < .73$, $p > .47$) nor between switch and repeat trials (all $t < 1.5$, $p > .20$). We further explored modulatory parameters of the model from the punishment and neutral families with the same architecture as our winning reward model (see Figure 6C). We observed that all three models display significant modulation with same valence on the same connections, except for positive modulation from VTA to IFJ for switch trials, which was exclusively found in the reward condition. Another unique characteristic of the reward condition are differences between switch and repeat trials in modulation from IFJ to ACC.

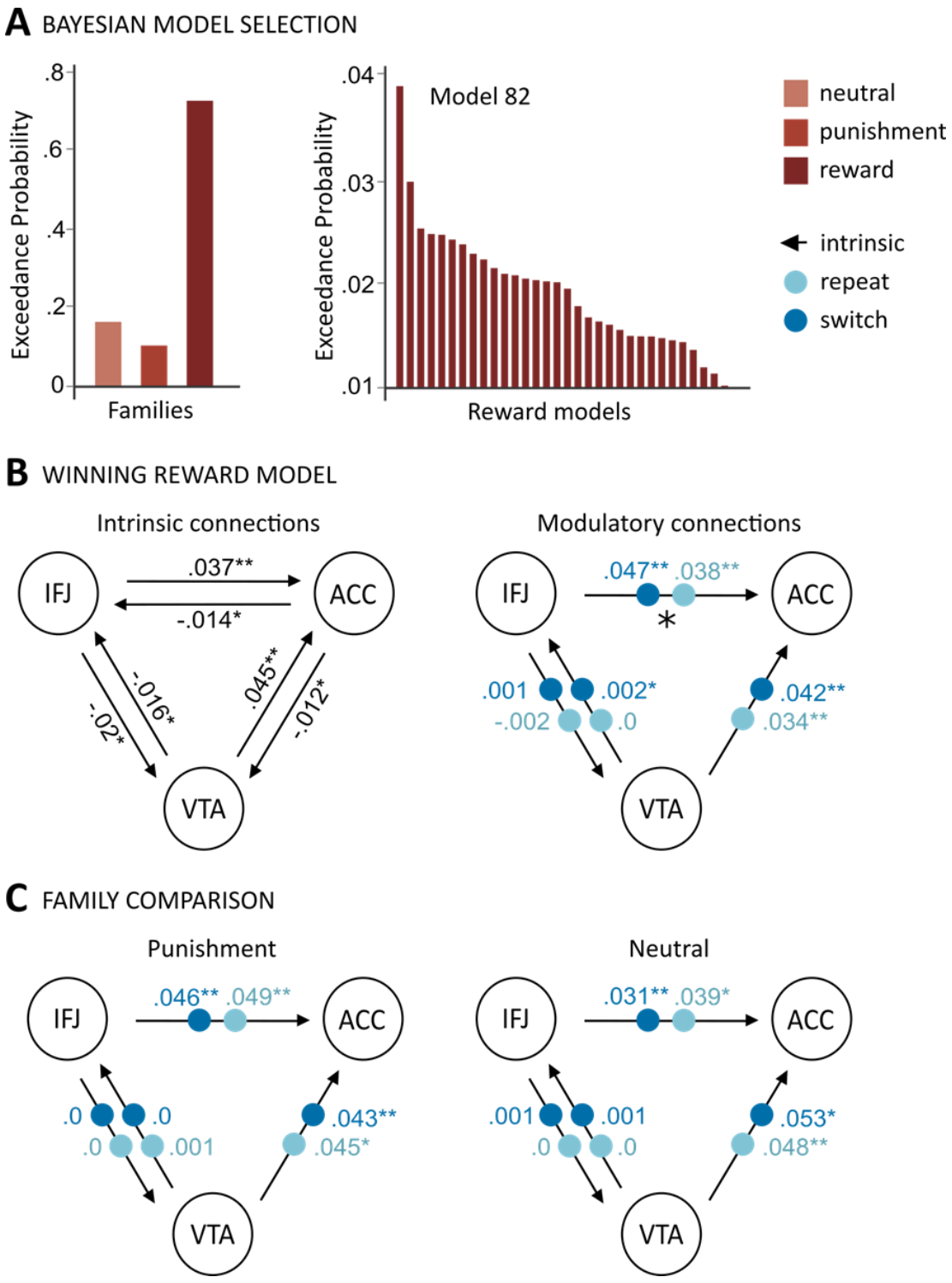

Figure 6 DCM results. (**A**) RFX family-wise inference. Models were grouped into families by motivational input (neutral, punishment, reward, 32 models each). The reward family attained the highest posterior probability with .73. Exceedance probability for the winning reward model was .039 among all 96 models. No neutral or punishment model exceeded a posterior probability of .010. (**B**) Architecture of winning model. Under the prospect of reward, cognitive control modulates the connections from IFJ to ACC and VTA as well as the connection from VTA to IFJ and ACC. (**C**) Modulatory parameters of models from the punishment and neutral families with same architecture as winning model. IFJ = inferior frontal junction, ACC = anterior cingulate cortex, VTA = ventral tegmental area. * p < .05, ** p < .001, FDR-corrected. n = 23.

Table 5 Average parameter estimates of intrinsic connections and input modulations for the winning reward model.

	Strength (Hz)	SD	T-value	p
Intrinsic connections				
IFJ to ACC	.037	.040	4.39	.001
IFJ to VTA	-.020	.027	-3.41	.007
ACC to IFJ	-.014	.023	-3.01	.005
ACC to VTA	-.012	.018	-3.18	.008
VTA to IFJ	-.016	.033	-2.31	.030
VTA to ACC	.045	.046	4.69	.001
Modulation by switch				
IFJ to ACC	.047	.051	4.38	.001
IFJ to VTA	.001	.002	.75	.610
VTA to IFJ	.002	.003	2.93	.012
VTA to ACC	.042	.034	5.92	.000
Modulation by repeat				
IFJ to ACC	.038	.046	3.95	.001
IFJ to VTA	-.002	.002	-.51	.610
VTA to IFJ	.000	.004	.55	.610
VTA to ACC	.034	.036	4.49	.001
Switch input				
IFJ	.327	.257	6.10	.000
VTA	.358	.193	8.88	.000
Repeat input				
IFJ	.326	.232	6.74	.000
VTA	.336	.197	8.20	.000

SD = standard deviation. IFJ = inferior frontal junction, ACC = anterior cingulate cortex, VTA = ventral tegmental area. p-Values were corrected using FDR. n = 23.

3.4 Discussion

We aimed to disentangle the interplay between IFJ, ACC and VTA in motivated cognitive control. Using DCM, we characterized dynamic interactions between these brain regions during task switching under different motivational states. Our results reveal fundamental differences in the behavioral and neural effects of prospective reward and punishment on decision-making.

Participants performed a switch/repeat task embedded in three distinct motivational conditions, namely, prospective monetary reward or punishment, and a neutral condition with no external motivators. For all motivational conditions, switching between tasks led to slower, more error-prone responses compared to repeating tasks, indicating a successful manipulation of cognitive control through our paradigm. Such a disruption of performance is thought to

represent the higher cognitive demand inherent to shifts in attention from one competing task to another (Monsell, 2003). This was also reflected on a neural level. Switch trials elicited heightened activity in a number of cortical and subcortical areas that are notably related to cognitive control, such as the supplementary motor area, inferior parietal sulcus, insula and midbrain (Bahlmann et al., 2015; Dosenbach et al., 2007; Köhler et al., 2016). Unlike evidenced in prior studies (Derrfuss et al., 2005), the IFJ was not differentially activated by switch and repeat trials in our paradigm. Since it did, however, show robust activation across all trials, the area was likely strategically involved in both conditions. Several explanations are possible: First, due to the slow pace of our fMRI design, participants may have treated each trial as a distinct event instead of establishing continual task sets. Thus, the IFJ may have activated task rules anew for every trial. This, however, seems arguable in light of the robust behavioral switch costs observed in the experiment. Second, as prior studies failing to demonstrate switch related activity (Brass & von Cramon, 2004; Crone et al., 2006), our paradigm may have diminished neural differences between switch and repeat trials by including approximately 50% trials of each type. This composition has been suggested to induce different preparatory processes for task switches than classical task switching designs due to their high frequency (for relevant discussion see Richter & Yeung, 2014).

Task performance differences between switch and repeat trials were modulated differentially by prospective punishment and reward. While a main effect of Motivation revealed that across Control tasks (switch and repeat trials) response speed was enhanced when participants were motivated to avoid punishments as well as when pursuing rewards (compared to the neutral condition), switch costs were reduced exclusively in the punishment condition. This observation concurs with studies showing that potential losses attract more focus of attention and thereby affect decision-making more strongly than equivalent gains (for review, see Yechiam & Hochman, 2013). Given the large body of literature stressing the importance of

reward in executive functioning (Botvinick and Braver, 2015; Chiew and Braver, 2014; Jimura et al., 2010), it nevertheless is remarkable that we found no effect of reward on switch costs. One explanation for this finding might be the notion that the subjective value of money changes depending on its perception as a loss or gain (Tversky & Kahneman, 1979). Thus, in our study, unlike punishment magnitude, reward magnitude (both 7 Cents) might have been too small to effectively reduce switch costs.

Our dynamic causal modeling (DCM) further suggest that reward and punishment rely on different neural mechanisms to influence executive functioning. We tested whether and how cognitive enhancements through prospective punishment and reward relate to interactions between IFJ, ACC and VTA, and found that reward is more likely to modulate connectivity between these structures during cognitive processing. Using RFX family level inference (Penny et al., 2010), we show that changes in causal connections within this network are best explained by models that included modulations through reward-based decision-making.

While it is surprising that the obtained hemodynamic responses were not reflected in behavioral results and vice versa, they support accounts postulating separate motivational systems for reward and punishment with distinguishable behavioral and neural signatures (Camara et al., 2009; Cubillo et al., 2019; Galea et al., 2015; Palminteri & Pessiglione, 2017; Stefano Palminteri et al., 2015). Wächter et al. (2009) for instance, showed that reward improved implicit learning and retention mediated through the dorsal striatum, while punishment facilitated online motor performance by modulating insula activity. Others have reported increased amygdala activity in response to prospective punishment, while prospective reward was associated with activity in the ventral striatum (Murty et al., 2012; Yacubian et al., 2006). Relatedly, it has been suggested that unlike reward, punishment does not operate through the dopaminergic but serotonergic neurotransmitter system to enhance executive control and that these systems act as mutual opponents (Daw et al., 2002; den Ouden et al., 2013; Guitart-

Masip et al., 2014). However, since we found no neural activations associated with punishment, it is unclear whether this rationale can be applied to our findings. Future studies could shed light on this issue by probing the influence of serotonin and dopamine antagonists on the effects of punishment and reward on task switching and its neural substrates.

In our winning reward model, intrinsic connections were significantly positive from IFJ and VTA to ACC and significantly negative from ACC to VTA and IFJ as well as between VTA and IFJ. While both switch and repeat trials modulated the connection from IFJ to ACC positively, the modulation was significantly stronger for switch trials. This supports previous studies associating signaling from IFJ to ACC with increased cognitive effort (Harding et al., 2015; Hinault et al., 2019). Importantly, this difference in cognitive modulation was exclusively found in the reward condition suggesting that distinct motivational settings differentially affect neural interactions between IFJ and ACC. The connection from VTA to ACC was positively modulated by switch and repeat trials alike, potentially due to dopaminergic projections between the two areas playing a fundamental role irrespective of task demands (Haber & Knutson, 2010; Hauser et al., 2017; Köhler et al., 2016). Our findings thereby concur with the notion that the ACC receives and integrates signals carrying information about prospective reward and the need to expend control from other brain regions (Shenhav et al., 2013, 2016). Complementing prior research (Bahlmann et al., 2015; Hippmann et al., 2019), we found a positive modulatory connection from VTA to IFJ exclusively for switch trials, suggesting that the VTA exerts causal influence on the IFJ when cognitive demand is high. This was observed exclusively in the reward condition emphasizing the importance of projections from the VTA as a source of dopaminergic neuromodulation to the prefrontal cortex in the integration of prospective reward and control demands. However, note that the modulation is comparably weak, and we did not find differential IFJ activation with respect to switch vs. repeat trials. As discussed above, our design encompassed a high frequency of switch trials, which may also

have decreased a potential interaction between IFJ and VTA. Future studies using revised study designs (i.e. less frequent switches, cued task-switching) are clearly warranted to further corroborate our results.

Taken together, our DCM results show that the IFJ and VTA modulate ACC activity independently to serve task demands in reward-based cognitive control. They further emphasize differences in neural processing of reward and punishment related to executive functions.

Limitations

A few limitations of the current findings should be noted. First, the paradigm used in our study consisted of incongruent stimuli only (i.e. numbers smaller than 25 were even, numbers greater than 25 were odd). Given the time constraints of fMRI experiments, we wanted to ensure a reasonable number of trials to include in the analysis. Therefore, we chose this task to obtain responses that could unmistakably be classified as correct or incorrect and thus avoid interpretational problems of congruent stimuli. This however allows participants to use stimulus features to predict responses in both task sets. Even though none were reported in the debriefing, we cannot rule out that participants applied such strategies, and commend future studies to implicate both congruent and incongruent stimuli to rule out a potential use of alternative strategies.

Second, motivated by specific assumptions about neural interactions between motivation and cognitive control and limited by technical constraints of DCM, we only included a small number of brain regions in the DCM analysis thereby neglecting other areas presumably involved in motivated control, for instance the ventral striatum (Aarts et al., 2011; Asci et al., 2019; Cools, 2008). Note, however, that effective connectivity does not reflect anatomical connectivity. Rather, DCM allows to reveal a net effect between relay regions and is intended to answer hypothesis-driven questions. We further recognize that neither of our candidate regions were associated with the main effect of cognitive control. Nevertheless, DCM can

detect changes in effective connectivity between VOIs even when void of significant clusters regarding specific contrasts and thus does not depend on activation analysis. In the present study we were particularly interested in disentangling neural interactions with respect to the interface between cognitive control. We therefore aimed at including areas in the DCM analysis that would relate to all aspects of the task. The results of this study could allow future studies to explore a more extended network.

Conclusion

The current study explored the neural interactions between executive functions and distinct qualities of motivation by means of dynamic causal modeling. We found that structures from the dopaminergic system - specifically the IFJ, VTA and ACC - contribute to the integration of cognitive control and reward but not punishment. Our findings therefore point to different neural mechanisms underlying the influence of reward and punishment on cognitive control.

Chapter 4: Electrophysiological exploration of the enhancing effect of motivation on task switching

4.1 Introduction

In our complex everyday lives, a set of mental abilities termed executive function enables us to flexibly act in and react to our surroundings. These high-level cognitive processes, including cognitive flexibility, working memory and inhibitory control, serve as a filter for relevant information in order to enable decision-making and implement behavioral responses.

In experimental settings, task switching has become a standard tool to investigate executive control. Switching between tasks compared to repeating tasks has been shown to impair behavioral performance as indicated by reduced response speed and accuracy. This so-called switch cost serves as an indicator for the increased cognitive effort necessary to establish new task rules (e.g. Kiesel et al., 2010; Wylie & Allport, 2000). Interestingly, switch costs can be reduced if motivation is high. The prospect of reward or punishment in particular has been shown to procure an enhancing effect on cognitive control (Boehler et al., 2014; Braem et al., 2013; Dreisbach & Fischer, 2012; Guitart-Masip et al., 2012; Krebs et al., 2010; Padmala & Pessoa, 2011; Umemoto & Holroyd, 2015; Wächter et al., 2009). Kleinsorge and Rinkenauer (2012) for instance, demonstrated that offering monetary incentives as a bonus for successful task-switching significantly reduced switch costs and concluded that this effect was mediated through reward expectancy.

While motivation though punishment and reward elicit similar effects on control at the behavioral level, on a neural level they seem to rely on different mechanisms (Camara et al., 2009; Galea et al., 2015; Murty et al., 2012; S Palminteri & Pessiglione, 2017; Stefano Palminteri et al., 2015; Wächter et al., 2009; Yacubian et al., 2006). Cubillo, Mawkana & Hare (2019) showed that while monetary reward and punishment had a similar effect on participants'

task-switching behavior, the effect was mediated by distinct neurobiological substrates. This was most pronounced in heightened ACC activity during engagement of control for reward relative to punishment incentives. In Chapter 3, we have expanded on these findings by showing that neural interactions between structures from the dopaminergic system, namely left IFJ, VTA and ACC, were characterized by motivated cognitive control through prospective reward but not prospective punishment. It has further been argued that reward and punishment may engage cognitive control via opposing neurotransmitter systems, as evidence suggests punishment is associated with serotonergic rather than dopaminergic pathways (Daw et al., 2002; den Ouden et al., 2013; Guitart-Masip et al., 2014).

Even though we are beginning to understand their neural underpinnings, there is a lack of knowledge regarding the temporal interplay between the mechanisms that generate motivationally induced enhancements in task-switching. With its high temporal resolution, EEG might be more suitable to address these issues. Existing ERP studies on motivational influences in cognitive control have emphasized the importance of heightened error related negativity (ERN) as a reflection of enhanced performance monitoring on cognitive tasks induced by rewarding incentives (Boksem et al., 2006; Hajcak et al., 2005; Stürmer et al., 2011). Likewise, the ERN is amplified when task performance errors are punished (Hajcak et al., 2005; Riesel et al., 2012).

While these studies have parsed interaction effects primarily *after* a response to a stimulus was given, it remains elusive how prospective reward and punishment affect ERP components *in preparation* of successfully switching between tasks. To address this, we modified the paradigm from Chapter 3 for electrophysiological exploration. Participants were present with digits and switched between the task sets parity and magnitude as indicated by a digit's color. We limited the number of stimuli to four single digits in order to reduce complexity in a faster-paced EEG design. This task was embedded in different motivational

blocks (punishment, reward, neutral) with performance-contingent monetary incentives (7 Cents). Since we were particularly interested in neural activity related to the preparation of decision making rather than performance evaluation, we narrowed the EEG analysis to components following stimulus presentation instead of components following responses or feedback. We expected to observe stimulus-locked ERPs that have been reliably evoked by task-switching in terms of task preparation. The fronto-central N2, which is generated in the ACC, has consistently been found to be increased in latency and amplitude for switches compared to repeats and is thought to reflect response selection and monitoring (Gajewski et al., 2008; Mansfield et al., 2013; Nieuwenhuis et al., 2003; Yeung et al., 2004). To the contrary, the parietal P3 exhibits larger amplitudes for repeat compared to switch and is associated with context updating and allocation of cognitive resources (Barceló et al., 2000; Gajewski et al., 2010; Kieffaber & Hetrick, 2005; Rushworth et al., 2002). At first glance it may seem counterintuitive that switching should require less context updating and cognitive resources. However, it has been argued that the P3 represents a fully established cognitive set, thus accounting for its decrease when switching task sets is required (Barcelo et al., 2000). We hypothesized we would observe same patterns for these components and anticipated that these differences in activation between switching and repeating task sets would be reduced in a motivated state (reward or punishment blocks) compared to a neutral setting.

4.2 Methods

4.2.1 Participants

Thirty-two right-handed participants aged between 21 and 29 (17 females, mean = 24.00, SD = 2.62) years volunteered to take part in the experiment. All reported normal or corrected-to-normal vision. They received incentives for their participation as well as monetary awards in accordance with individual performance on the task. The study had been previously approved

by the local ethics committee and was conducted in conformance with the principles of the Declaration of Helsinki. Participants gave their written consent after full explanation of the procedure. Due to excessive artifacts (< 25 remaining trials in at least one condition) in the EEG data one participant was excluded from data analysis. Three additional participants had to be discarded due to poor behavioral performance (accuracy or response time mean > 2SDs from the group mean).

4.2.2 Experimental paradigm

Participants performed a similar switch task as described in Chapter 3 while continuous EEG activity was recorded. The paradigm only differed regarding stimuli and timing as will be described in the following: Stimuli were digits (2, 4, 7 and 9) presented on a black screen in random sequence using Presentation® software (Version 18.1, www.neurobs.com). The color of the digits indicated which of two tasks to use. Blue signaled that participants should judge a digit regarding its parity (even or odd), while a yellow digit established the magnitude task (smaller or greater than 5). If two subsequent trials obeyed the same task rule (parity following parity or magnitude following magnitude) this sequence was defined as a switch. A repeat was a sequence of two trials with diverging task rules (parity following magnitude or vice versa). The digits were chosen to create contrasting response patterns and thus avoid indistinct responses. Participants made obligatory button responses on a computer mouse with the index (smaller/odd) or middle (greater/even) finger of their right hand. A response map was displayed below the stimuli. An instruction screen (10s) before each of the six blocks indicated which condition would follow. In the punishment condition, participants lost 7 Cents when they gave an incorrect response but did not gain any money for correct responses. In the reward condition participants gained 7 Cents when they gave a correct response but did not lose any money for incorrect responses. In the neutral condition no money could be gained or lost regardless of the

given responses. After completing a block, participants received feedback about the amount of money they gained or lost (10s). Each block contained 80 trials and was composed of an equal number of switches and repeats, presented in pseudo-randomized order (not more than three in a row). A fixation cross presented for 2000 or 2500 ms (randomized) initiated each trial followed by the presentation of a stimulus. Feedback (500 ms) was presented on the screen with a randomized delay (1000 or 1200 ms). For visualization see Figure 7A.

Participants were seated in a large chair within an experimental behavior chamber and asked to find a comfortable position that allowed them to sit as still as possible. In order to get familiarized with the task, they took part in a brief training session prior to EEG preparation. The training consisted of 25 trials and was repeated if participants had more than ten misses or errors. Individual mean response times from the training served as initial stimulus duration times (ranging between 800 and 1200 ms) in the task. Over the time course of the experiment the stimulus duration time changed in accordance with the individual performance.

In a post questionnaire we assessed whether participants used any particular strategies for solving the task. All participants used parity and magnitude as criteria. The experiment lasted around 60 minutes.

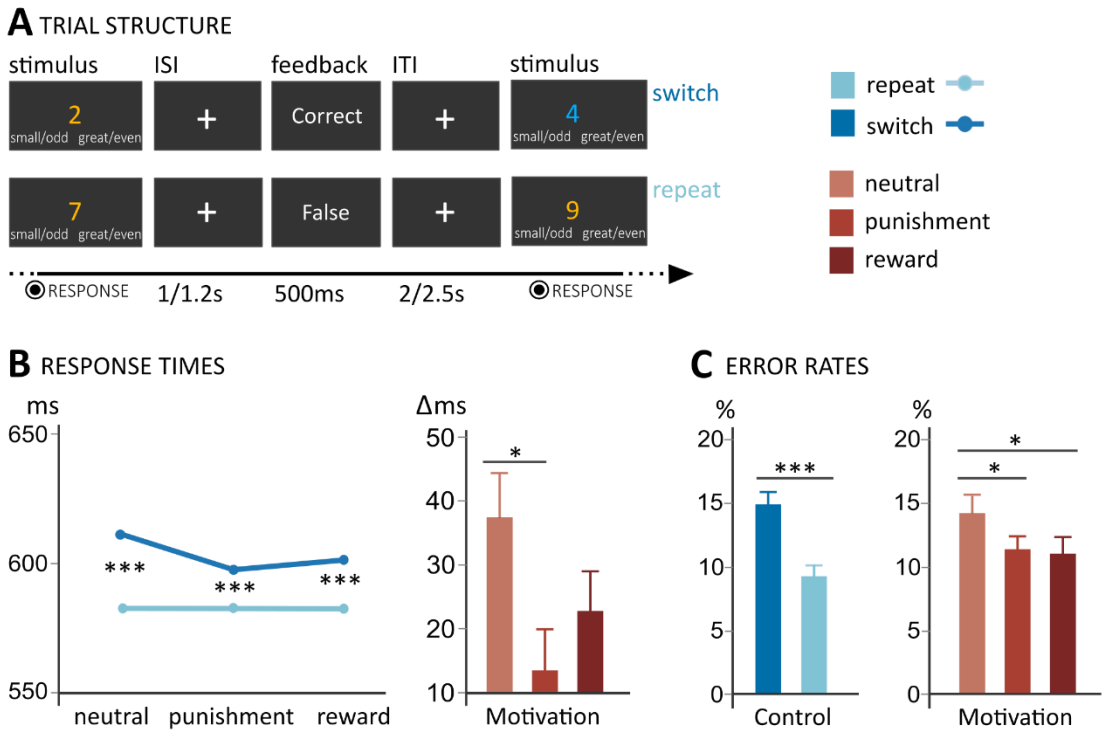

Figure 7 Design and behavioral results. (**A**) Participants judged digits according to either magnitude (blue) or parity (yellow). Switch and repeat trials, defining the factor Control, were pseudo-randomized (not more than three in a row). The task was embedded in six blocks with different motivational context (monetary reward or punishment and a neutral condition without monetary manipulation; two blocks each) (**B**) Response times (mean ± SE) per task condition and switch costs (switch minus repeat) per motivational condition in milliseconds. Switch trials were followed by slower responses compared to repeat trials. This effect was reduced in the punishment condition. (**D**) Error rates (mean ± SE) in percent. Across motivational conditions, participants made more errors on switch compared to repeat trials. Switch costs were reduced in both the punishment and in the reward condition. ITI = inter-trial interval. * $p < .05$, ** $p < .001$, FDR-corrected. n=23.

4.2.3 EEG recording

Electroencephalographic (EEG) signals were registered from 29 standard channels (10/20 system, positions: Fz, Cz, Pz, Fp1/2, F3/4, F7/8, FC1/2, Fc5/6, C3/4, T3/4, CP1/2, CP5/6, P3/4, P7/8, O1/2, PO3/4) using Ag/AgCl electrodes mounted on an elastic cap (EasyCap, BrainProducts GmbH, Munich, Germany). They were recorded online with a right mastoid reference at a sampling rate of 500 Hz and filtered with a bandpass of 0.1-70 Hz. Eye movements were monitored by electrodes above and below the left eye and on the outer canthi of both eyes. Impedances were kept below 10 kΩ.

4.2.4 Behavioural analysis

Response times (RT) and error rates (ER) were subjected to separate repeated-measurement analyses of variance (ANOVAs) with the factors Control (repeat, switch) and Motivation (punishment, neutral, reward). Switch costs (repeat minus switch) were calculated for interactions including the factor Control. Post-hoc t-tests were carried out on significant main effects and interactions and corrected for multiple comparison using the false discovery rate (FDR) method. Effect sizes for ANOVAs are reported as partial eta-squared. All data were analyzed using R v3.3.2 (R Core Team, 2016).

4.2.5 EEG analysis

EEG data were analysed on correct trials only. Analyses were performed using Matlab R2015a and the Matlab-toolbox EEGLAB 13.4.4b (Delorme & Makeig, 2004). EEG data were re-referenced to the average signal of both mastoid electrodes. For noise reduction, data were bandpass filtered between 1 and 49 Hz before being segmented around the onset of the stimuli (−1000 to 2000 ms). Following, data were downsampled to 250 Hz. Independent component analysis (ICA; Bell & Sejnowski, 1995) was performed to correct for ocular and cardiac artifacts. After applying an automatic artifact removal criterion of ±70µV, each trial was visually controlled for residual artifacts. ERP effects were time-locked to the onset of stimuli as well as feedback and a time window of −100 and 0 ms before stimulus respectively feedback onset was used as baseline. Averaged ERPs were calculated separately for stimuli and feedback for each of the following conditions: switch punishment, switch reward, switch neutral, repeat punishment, repeat reward and repeat neutral.

To assess statistical differences between these conditions, average amplitudes within 200 to 300 ms (N2) and 300 to 600 ms (P3) at 9 electrodes (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4) were subjected to repeated measures ANOVAs. The time windows were based on previous studies

(Diez & Marco-Pallarés, 2021; Gajewski & Falkenstein, 2011) and visual inspection of the peak latency of the components classically studied in task-switching paradigms. To probe changes related to task requirements ERPs were analyzed as repeated-measurement 2×3×3×3 ANOVA with the factors Control (switch, repeat), Motivation (reward, neutral, punishment), Anteriority (anterior, central, posterior) and Laterality (left, middle, right). For all statistical effects involving more than two degrees of freedom, the Greenhouse–Geisser correction was applied to correct for possible violations of the sphericity assumption (Greenhouse & Geisser, 1959). We report the uncorrected degrees of freedom and the corrected probabilities. Post-hoc t-tests were carried out on significant main effects and interactions and corrected for multiple comparison using the false discovery rate (FDR) method. Effect sizes for ANOVAs are reported as partial eta-squared. For illustrative purposes only, the grand average ERPs were filtered using a 12-Hz low-pass filter.

4.3 Results

4.3.1 Behavioral data

Response times

We observed a significant Control × Motivation interaction ($F_{(2,54)} = 4.50$, $p = .02$, $\eta_p^2 = .14$), as well as a significant main effect of Control ($F_{(1,27)} = 21.44$, $p < .001$, $\eta_p^2 = .44$) with faster RTs on repeat trials (mean = 584 ms) than on switch trials (mean = 608 ms). The main effect of Motivation ($F_{(2,54)} = .30$, $p = .74$, $\eta_p^2 = .01$) did not reach significance. Post-hoc analyses revealed significant differences between switch and repeat trials for all three motivational conditions with $p < .001$. Moreover, switch costs were significantly lower for punishment trials (15 ms) compared to neutral (35 ms, $p = .03$) but not reward trials (24 ms, p = .15, see Figure 7B). Neutral and reward trials did not differ significantly in regard to switch costs ($p = .08$).

Error rates

The significant main effect of Control ($F_{(1,27)}$ = 37.40, p < .001, η_p^2 = .58) showed that participants responded more accurately on repeat trials (9.4 %) than on switch trials (14.9 %). Further, we found a significant main effect for the factor Motivation ($F_{(2,54)}$ = 4.16, p = .02, η_p^2 = .13). Compared to neutral trials (14.5 %) participants made significantly less errors on punishment (11.9 %, p = .01) and reward trials (11.6 %, p = .047, see Figure 7C). The difference in ERs between punishment and reward trials was not statistically significant (p = .74). Neither was the interaction between control and motivation ($F_{(2,54)}$ = 1.96, p = .15, η_p^2 = .07).

Table 6 Summary of behavioral measures.

	Neutral		Punishment		Reward	
	Switch	Repeat	Switch	Repeat	Switch	Repeat
ER in % (SD)	17.1 (7.4)	10.1 (4.1)	13.6 (4.8)	9.1 (3.9)	13.4 (4.7)	8.7 (4.1)
RT in ms (SD)	616 (193)	581(176)	597 (171)	582 (170)	604 (197)	580 (172)

Means of error rates (in percent) and response times (in milliseconds) separately for each condition. SD=standard deviation.

4.3.2 EEG data

N2

We found no significant main effects or interactions related to control or motivation (all F < 2.8 and p > 0.07).

P3

ANOVA revealed a significant Motivation × Anteriority × Laterality interaction ($F_{(8,216)}$ = 2.22, p = .04, η_p^2 = .08) with significant differences in P3 amplitude between punishment and neutral blocks on the electrodes P3 (p < .03; punishment: 7.6 μV, reward: 7.5 μV, neutral: 7.1 μV), C3 (p < .02; punishment: 4.4 μV, reward: 4.2 μV, neutral: 3.7 μV) and F4 (p < .01; punishment: 3.6 μV, reward: 2.9 μV, neutral: 2.7 μV). We found no further significant main effects or interactions related to control or motivation (all F < 2.6 and p > 0.1).

4.4 Discussion

In the present study we explored spaciotemporal dynamics of task-preparation in motivated cognitive control. More specifically, we used EEG to parse effects of different motivational states on stimulus-locked N2 and P3 amplitudes during task switching.

Participants performed a switch/repeat task, in which they judged a digit by either parity (even/odd) or magnitude (greater/smaller than 5). These alternating task sets were embedded in distinct task blocks with different motivational settings, namely, prospective monetary reward or punishment, and a neutral condition with no external motivators. Across motivational conditions, participants responded slower and were more prone to making errors when switching to a different task set compared to repeating task sets. This is in line with prior studies parsing effects of task-switching and reflects the increased effort to update processing to follow an altered task rule (Kiesel et al., 2010; Monsell, 2003; Wylie & Allport, 2000).

We observed that performance was improved by both prospect of punishment and reward, suggesting a successful induction of motivation through our paradigm. Over all trials, participants produced less errors when they faced prospective punishment as well as when they were rewarded for avoiding errors. In terms of reaction times as in our previous chapter, we found that reaction time switch costs were exclusively reduced in the punishment condition. This confirms our interpretation that punishment engages as a stronger motivator in executive functioning compared to reward on a behavioral level. We have argued this may be explained by findings showing that potential losses influence decision-making more strongly by drawing more attention than equivalent gains (Yechiam & Hochman, 2013). The concept of "loss aversion" postulates that outcomes which are perceived as losses have more subjective weight than outcomes which are perceived as gains (Tversky & Kahneman, 1979). In the context of our study this means that a loss compared to a win of 7 Cents may have carried more external incentive.

On the neural level, we found no effects related to cognitive control or the interaction between motivation and cognitive control. This is surprising given extensive evidence of N2 and P3 modulation in task switch preparation (Barceló et al., 2000; Gajewski et al., 2008, 2010; Kieffaber & Hetrick, 2005; Mansfield et al., 2013; Nieuwenhuis et al., 2003; Rushworth et al., 2002; Yeung et al., 2004). Several explanations are possible. Many of the studies separate cue and target stimulus to examine the question of preparation processes in task switching. In order to maintain task comparability with our studies from Chapter 2 and 3 we decided against this option, and thereby may have neglected to bring into full play the strengths of the EEG methodology. In our paradigm cue and target were presented at the same time in the same stimulus. It has, however, been established that cue-switching and task switching rely on different neural mechanisms (De Baene & Brass, 2011). Consequentially, our approach may have led to confounded neural signatures of cue and target processing (for relevant discussion see Hsieh & Yu, 2003 and Schneider & Logan, 2007). Hsieh & Cheng (2006) made similar observations, which were accounted to carry-over effects from the previous trial. While our data do not allow inference in that regard, they reveal a mismatch between behavioral and neural response and might point towards a functional dissociation between processing of task set updating and response mode (Gajewski & Falkenstein, 2011).

Another explanation can be found in the unresolved question whether task switching and repeating do represent different neural mechanisms. Kiesel and colleagues (2010), for example, have argued that increased ERP amplitudes in switch compared to repeat trails rather reflect a more pronounced control process rather than a qualitatively distinct one. In our paradigm, we tailored response speed to match each participant's capability. Regardless of task type, giving responses within the speeded task was perceived as increasingly challenging. If switching and repeating task sets does, in fact, rely on the same neural process, a task setting that is cognitively demanding in both task types may diminish neural differences. Future studies

are warranted to be mindful of these obstacles and explicitly test for functional differences between switch and repeat trials.

We observed significantly reduced P3 amplitude in trials motivated by the prospect of punishment. Since a reduction in positivity in the component has been associated with increased cognitive effort (Kapanci et al., 2019; Ries et al., 2016; Segalowitz et al., 2001), it is likely more cognitive resources were allocated in order to avoid punishment suggesting that facing potential loss presents a greater challenge to the neural system than potentially receiving an equivalent gain. Similar P3 effects of prospective monetary punishment have been reported for behavior monitoring in flanker (Potts, 2011) and go/no-go tasks (De Pascalis et al., 2010). Accordingly, the P3 may be a marker for motivation-control interactions that could be further explored in future studies.

In summary, the present study confirms our previous behavioral results ascribing prospective punishment a stronger motivational influence on cognitive performance than prospective reward. This was also reflected in a distinct neural response during the punishment condition. While our EEG results are otherwise inconclusively, they point towards a shared neural process of switching and repeating between tasks.

Chapter 5: General discussion

In combination, the three studies of this thesis offer a comprehensive investigation of the interaction between cognitive control and different qualities of motivation and specifically aimed at revealing underlying neural mechanisms. After summarizing the main findings, I will highlight specific strengths and potential weaknesses of the present empirical studies before discussing their implications with regard to differences between reward and punishment in task-switching. Lastly, I will take a look at the dynamics underlying motivation-control interactions with particular focus on the role of the IFJ and conclude by reviewing the efficacy of the applied neuroscientific methodologies in unveiling complex cognitive processes.

5.1 Summary of findings

In the first study (chapter 2), we probed causal contributions of the left IFJ in motivated task switching by temporarily disrupting its activity using continuous theta burst stimulation (cTBS) or 1 Hz repetitive transcranial magnetic stimulation (rTMS). After TMS application over the left IFJ or a control site (vertex), participants performed a switch task in which numbers had to be judged by magnitude or parity. Different amounts of monetary rewards (high vs low) were used to manipulate the participants' motivational states. We measured reaction times and error rates. Irrespective of TMS stimulation, participants exhibited slower responses following task switches compared to task repeats. This effect was reduced in high reward trials. Importantly, we found that disrupting the IFJ improved participants' behavioral performance in the high reward condition. For high reward trials exclusively, error rates decreased when the IFJ was modulated with cTBS or 1 Hz rTMS but not after vertex stimulation. Our results suggest that the left IFJ is causally related to the increase in cognitive performance through reward.

In the second study (chapter 3), we tested how cognitive facilitation through prospective reward or punishment relates to interactions between regions from the dopaminergic

mesocortical network, particularly the VTA, IFJ and ACC. In the fMRI study, we used DCM to investigate effective connectivity between these regions in a similar task-switching paradigm as in chapter 2, however, comprising three distinct motivational conditions (prospective monetary reward or punishment and a control condition). We found that while prospective punishment significantly facilitated switching between tasks on a behavioral level, interactions between IFJ, ACC, and VTA were characterized by modulations through prospective reward but not punishment. Our DCM results show that IFJ and VTA modulate ACC activity in parallel rather than by interaction to serve task demands in reward-based cognitive control. Our findings further demonstrate that prospective reward and punishment differentially affect neural control mechanisms to initiate decision-making.

In the third study (chapter 4), we adapted the paradigm from the previous chapter for EEG analysis. We were interested in modulations of the N2 and P3 components, which are classically associated with task switching, through our task. Specifically, we probed interactions between different qualities of motivation and cognitive control during the task-preparation period. Following previous evidence, we expected the differences in N2 and P3 amplitude between switching and repeating task sets to be reduced in a motivated state (reward and punishment blocks compared to neutral blocks). We found that both punishment and reward reduced switch costs behaviorally. On a neural level, we did not find significant effects for cognitive control or its interaction with motivation. We did, however, observe a reduction in positivity in response preparation in the punishment condition which points toward heightened cognitive effort.

All three studies have demonstrated the influence of monetary incentives on cognitive control. High rewards yielded greater behavioral benefits compared to low rewards, showing improved task switching performance and reduced switch costs. When comparing the effects of prospective rewards to those of prospective punishments, the latter exhibited more pronounced behavioral benefits. On a neural level, motivational effects of prospective reward

on cognitive control were associated with modulations in regions of the mesocortical network. The results suggest that the left IFJ plays a role in mediating the impact of rewards by signaling cognitive demand to the ACC.

5.2 Strengths and limitations

While designing a study, the accuracy of observed results relies on aligning the study objectives with the selected methodology. Particularly the interplay of motivation and control, with its subtle nuances, is sensitive even to slight variations in the task. Although the design of the present studies was carefully considered, every decision in this regard comes with advantages and limitations, which are subject to the following discussion.

In the present thesis, we combined different neuroscientific methodologies on the same task, which is a significant strength of the current work. The approach allows for a broad investigation of the neural mechanisms of motivation-control interactions by making use of each methodology's unique strengths. The combination of cTBS and rTMS in the first study provided insights into the causal contributions of the left inferior frontal junction (IFJ) in motivated task switching. The second study explored this further by investigating effective connectivity between the VTA, IFJ, and ACC by means of DCM on fMRI data. The findings uncover some aspects of the interplay between the regions and provide insights into how this interaction shapes the modulatory role of prospective reward on neural control mechanisms. Lastly, the third study used electroencephalography (EEG) analysis to investigate the N2 and P3 components associated with motivated task switching to probe temporal dynamics of neural processing under different motivational conditions. Overall, the combination of these methodologies provides complementary perspectives, strengthening the understanding of the complex interplay between motivation, cognitive control, and neural processes in task switching. This will be laid out in more detail in the following chapter.

An issue with experimental settings in general, but also particularly relevant for the current work, is the artificiality that comes with study designs. Motivation is highly subjective and therefore hard to induce and measure. We aimed at establishing a motivated state in our participants by offering or withdrawing monetary value based on their performance in a task switching paradigm. To this end, we introduced incentives of 7 Cents per response. While this does not closely resemble "real life motivation", it offers an objectively measurable value. However, the subjective value to the participants and therefore the underlying motivational processes may have differed greatly. External motivators are also likely to be confounded with internal motivational factors that we cannot always identify or differentiate, particularly on the neural level. Several studies report a decrease in intrinsic motivation through external motivators or paradoxical effects of incentives on cognitive performance, highlighting the challenges in finding the "sweet spot" when inducing motivation externally (Gneezy & Rustichini, 2000; Mobbs et al., 2009; Zedelius et al., 2011). The issues associated with studying motivation and potential confounding effects of external incentives therefore need to be acknowledged. Nevertheless, we observed consistent patterns of enhanced cognitive control when participants were faced with prospective monetary reward or punishment based on their task switching performance. The obtained behavioral results consequently suggest the presence of motivation induced by our design.

Many studies on task switching are based on designs which consist of both congruent (stimulus requires same response in each task set) and incongruent trials (stimulus requires different response in each task set) (Kiesel et al., 2007; Meiran et al., 2010; Schneider, 2015). As a consequence, *correct switches* cannot be distinguished from *false repeats* on congruent trials in the following data analysis. In order to obtain as many trials per condition as possible – particularly for the slower-paced fMRI design - we opted at only including incongruent trials in our task. This, however, holds the danger of stimulus features becoming predictive of task

responses because of opposing response patterns (e.g. all uneven numbers smaller than 25 correspond to left finger response). Although we cannot rule out that participants developed alternative behavioral strategies to give responses, none were reported in the debriefing. We further found robust switch costs throughout all studies, which implies that the predefined task sets were in fact utilized for task decisions. Nevertheless, future studies are warranted to resolve limitations of different task-switching methodologies in order to facilitate the inference process from collected data to modelled control mechanism.

Another limitation of the current work is the restricted investigation of a small set of cortical regions, primarily focusing on the left hemisphere. Although this selection was based on existing evidence, it should be noted that cognitive control and motivation engage large networks and encompass areas throughout the entire brain and both hemispheres (Camara et al., 2009; Cole & Schneider, 2007; Menon & D'Esposito, 2022). The interactions between these networks involve complex processes that are not yet fully understood, particularly in regard to the specific involvement of the IFJ in the enhancing effect of motivation on cognitive control or lateralization effects. Therefore, while our studies provide new insights, they likely only capture a fraction of the neural dynamics that shape control-motivation interactions and future studies will be able to expand the scope of investigation by building upon the present results. A first step in that direction could be the introduction of the striatum into the DCM model. IFJ activation during flexible task updating as well as reward-related activation patterns have been shown to be dependent on the density of dopamine receptors in the striatum (Forbes et al., 2007; Stelzel et al., 2010), rendering the region a likely contributor in the interaction.

The following chapter will delve deeper into the main findings presented in the current work, examine their implications and propose potentials for future research.

5.3 Implications and future directions

5.3.1 Differences in the effects of prospective reward and punishment

Across all studies, the behavioral results suggest that a motivated state was induced in participants through monetary incentives. This was expressed by reduced switch costs, lower error rates and faster reaction times when faced with both prospective reward and prospective punishment. These effects were more pronounced for punishment, which is in line with theories suggesting that the impact of loss is stronger than that of an equivalent gain (Tversky & Kahneman, 1979). Interestingly, we observed a discrepancy between these behavioral results and effects on the neural level. Despite the consistent behavioral patterns, neural interactions were characterized by modulations through reward and not punishment. Within the context of our EEG findings, it is noteworthy that although we did observe a reduction in positivity in the P3 component during response preparation in the punishment condition, suggesting increased cognitive effort, this neural pattern did not directly align with measures of cognitive control or correlate with the observed behavioral effects. Our DCM analysis on fMRI data, on the other hand, showed that interactions between IFJ, VTA and ACC shape cognitive control when motivation is induced via rewarding monetary incentives. One possible explanation lies in potentially differential involvement of neurotransmitter systems. Previous studies have suggested that reward primarily operates through dopaminergic pathways, whereas punishment may rely on the serotonergic system (Daw et al., 2002; den Ouden et al., 2013; Guitart-Masip et al., 2014). Therefore, it is conceivable that our neural measures, biased toward the dopaminergic system, failed to capture the neural mechanisms underlying the effects of prospective punishment on task switching performance. Taking this idea further, one question arises: Since cognitive control is highly dependent on dopamine, it is unclear how this hypothesized serotonergic response would affect control processes and whether it would

directly interface with the control network or be translated into a dopaminergic response beforehand. To gain deeper insight into the interplay between these neurotransmitter systems, future studies could compare the effects of serotonin and dopamine antagonists in motivation-control interactions. This approach would provide valuable evidence regarding the specific contributions of these neurotransmitters.

5.3.2 Insights on IFJ activation in motivation-control dynamics

While inhibiting the IFJ via TMS enhanced the impact of reward on cognitive processing, the weak modulation observed from the midbrain to the IFJ in the DCM results suggests that the role of the region in reward-based control may not rely on direct connectivity. Our combined evidence suggests that the region may act in support of the ACC by signaling cognitive demand. This finding is in line with the expected value of control theory which places the ACC at the center of motivation-control interactions (Shenhav et al., 2013). Since we did not find significant communication between IFJ and midbrain, it remains unclear what the exact neural interactions involving the IFJ are in the interplay between reward and control. It is possible that an additional region, such as the striatum (Stelzel et al., 2013), serves as a mediator in the communication. We found that IFJ inhibition appeared to magnify the influence of reward signals on cognitive control. A study by Armbruster-Genç and colleagues (2016) explored the role of IFJ activation variability in task switching. They demonstrated that variability in the region exerts opposing effects on cognitive stability and flexibility. It is therefore possible that our observed effect may stem from a disruption in the balance between cognitive stability and flexibility. Shifting the neural network towards heightened flexibility via IFJ inhibition could have enhanced participants' responsiveness to reward signals.

Another aspect that needs to be mentioned is the absence of activation differences in the IFJ between switch and repeat trials, despite the large evidence on this effect. There are

several plausible explanations for this finding. It is possible that these results may indicate a shared process, rather than distinct cognitive processes underlying switching between and repeating task rules, aligning with arguments proposed in previous research (Xue et al., 2013). Alternatively, our experimental design, including large inter-trial intervals and no preparation time between cue and stimulus, may have biased the neural network towards reactive rather than proactive control mechanisms (Kiesel et al., 2010). Following this line of thought, it is conceivable that the IFJ predominantly contributes to proactive control. It is important to acknowledge that all these interpretations remain speculative at this stage, and further studies will be necessary to delve deeper into these questions.

5.3.3 Methodological evaluation

In the present work, interactions between motivation and control within a task-switching framework were explored using different neuroscientific techniques. Our approach included investigations by means of TMS, fMRI with DCM analysis, and EEG. Based on our obtained results, we find fMRI most suitable for examining the interplay between motivation and control. Due to the involvement of several subcortical structures, capturing the process through EEG or TMS proves challenging. Additionally, fMRI, due to its high spatial resolution, seems more effective in detecting potential differences between responses to punishment and reward, given the potential involvement of different neurotransmitter systems. Still, TMS remains a valuable tool, allowing insights into the interactions and causal contributions within the complex networks of cognitive control and motivation.

FMRI and TMS therefore offer distinct advantages in investigating motivation-control interactions. Considering the potential synergies between the techniques, a combined application of the methods could proof valuable in exposing the role of the IFJ further by targeted manipulation of brain activity and observing succeeding network effects.

5.4 General Conclusion

This thesis offers a comprehensive investigation of the intricate interplay between cognitive control and diverse motivational influences, revealing underlying neural mechanisms. The obtained results underscore the significant impact of rewards and punishments on cognitive performance and task switching. Notably, it highlights the role of the IFJ in cognitive enhancement driven by monetary incentives. The findings discern distinct neural pathways that underlie reward-driven cognitive facilitation within the mesocortical network. Collectively, this work advances our comprehension of how motivation and cognitive control interact.

The significance extends beyond the complexities of experimental designs and holds practical implications for our daily lives. The identification of the IFJ as a crucial player in the interaction between reward and cognitive control offers a pathway for support in clinical settings. For individuals who struggle with cognitive control, such as patients with depression or ADHD, the IFJ can serve as a potential focal point for cognitive training, neuromodulation, and targeted interventions to enhance executive function. The differential impact of reward and punishment on cognitive control networks may be leveraged in tailoring treatment to individual motivational profiles. Furthermore, findings hinting towards differential involvement of distinct neurotransmitter systems open up possibilities for exploring pharmacological interventions. Besides clinical application, our results shed new light on our everyday decision-making processes. While the IFJ's role in motivation-control dynamics was explored in experimental settings, we can get a grasp on its significance on a broader scale as an active participant in our daily lives, influencing our actions and responses to cues in our environment. In the constant influx of stimuli, the IFJ appears to support directing our attention, facilitating our ability to focus on a task or switch to a more urgent one. As part of a broader network the IFJ collaborates to enable us to pursue our goals and manage our everyday routines. This starts with the familiar sound of the alarm clock urging us to start our day. Should we get up or get some more sleep?

The decision we make, whether motivated by the anticipation of an exciting day ahead or the comfort of being well-rested, is partly shaped by the interplay between IFJ, ACC and midbrain. So as this work concludes, we find ourselves where we began – only now, armed with a deeper understanding of the neural mechanisms at play, we approach the morning ritual of making coffee with newfound appreciation and a richer perspective on the subtle forces shaping our daily lives.

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