# Shifting the balance:

## Understanding the causal contribution of the lateral prefrontal cortex to flexible cognition under stress and no-stress

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**Summary**

Things do not always go according to plan. What we thought to be reliable in one moment might have drastically changed in the next, forcing us to reassess and adjust our behavior. Whether we miss an important flight or whether a new job forces us to relocate to a new city, being flexible is crucial to successfully navigate our daily lives. However, constantly reconsidering alternative behavioral options is effortful, as it drains our cognitive resources. By automatizing many of our recurrent and mundane actions, for example by developing habits, we might spare these resources and become more efficient, albeit losing our ability to quickly change our behavior. Many fields of science have described this balance between flexible and rigid forms of behavior, although in different terms and concepts. Recent accounts have made significant progress in integrating knowledge gathered in psychology, economics and neuroscience. This thesis sets out to add to our understanding of how our brain enables flexible cognition. In three studies, we used non-invasive brain stimulation to investigate the causal role of the lateral prefrontal cortex in flexible cognition. In the first study, we tested whether the dorsolateral prefrontal cortex is involved in inducing social norm associated biases in economic decisions. In the second study, we investigated whether stimulation of the dorsolateral prefrontal cortex might ameliorate deficits in working memory processes following the experience of acute psychosocial stress, a condition well-known to impair top-down executive control and to lead to a shift away from flexible and towards rigid behavior. Finally, in the third study, we investigated the interplay of flexible and rigid cognition by stimulating the inferior lateral prefrontal cortex that has recently been suggested to arbitrate between both forms of behavior. We found that the lateral prefrontal cortex is indeed involved in these processes, highlighting the importance of this structure for enabling flexible cognition across paradigms and research traditions.

## Introduction

The ability to adapt behavior to ever-changing environmental demands is arguably one of the most important properties for any species, as well as one of the most complex. It requires the organism to represent the current state or situation it is placed in, to evaluate its options and their associated consequences, to choose the best of these options and finally to convert this choice into behavior while concurrently controlling competing behavioral tendencies. Possessing this kind of cognitive flexibility has been crucial to survival in the evolution of our species and even today, it remains utterly advantageous, as our modern society is highly dynamic. Constant changes in technologies, the job market, the political climate, as well as in more personal affairs such as our relationships or our health require us to adjust, to learn new things and to overcome our habits, sometimes even on a daily basis. Accordingly, we cherish individuals that show high levels of flexibility and self-control, thereby reaching difficult long-term goals by not giving in to tempting short-term gratification. We admire the student who spent her Friday nights in the library instead of a bar in order to become a successful lawyer or the alcoholic successfully resisting the urge to drink. On the other hand, we often look down on people who seemingly lost control over their behavior, such as the cousin who tries to eat healthier but habitually buys the same convenience food he has bought for years or the criminal who is repeatedly convicted for violating social norms and breaking the law. Despite this rather bad reputation, however, less cognitively controlled behavior is not inherently bad. Many forms of behavior, such as riding a bike, driving a car or preparing a cup of coffee in the morning can be performed more automatically and without much deliberate thought, freeing cognitive resources for other tasks. Successful adjustment of our behavior thus depends on a balance between more efficient automatic behavior and more controlled, cognitively demanding behavior (Dickinson, 1985; Kahneman, 2003b; Rangel et al., 2008; Balleine and O'Doherty, 2010; O'Doherty et al., 2017). Unfortunately, we do not always manage to maintain this balance. Sometimes we overthink a simple decision (e.g. which shirt to wear to work), leading to an inability to function efficiently. Oftentimes, however, it is the other way round and we fail to adjust our behavior to changes in our environment. Whether this is due to the limited capacity of our cognitive systems preventing consideration of all available information, or whether our cognitive flexibility is impaired by experiencing a

stressful situation, failing to adapt to dynamic situations may result in severe intra- and interpersonal as well as in, on a larger scale, legal or political problems. In addition, many psychiatric conditions are characterized by dysfunctional behavioral adjustment, such as addiction (Everitt et al., 2001; Hogarth and Chase, 2011) or obsessive-compulsive disorder (Gillan et al., 2011; Gillan and Robbins, 2014). It is thus of utmost importance to understand the processes involved in the balance of flexible and habitual behavior and to identify the neural structures causally contributing to both forms of behavior, how they interact, and how potential impairments might be counterbalanced.

## Perspectives on flexible cognition

The processes and mechanisms behind the brain's ability to successfully guide behavior have received great interest over the last decades and inspired a large amount of research in various fields, such as economics, psychology and neuroscience. Historically, these research strands were investigated mostly separate from each other, each providing a unique point of view concerning the relation of deliberate and more automatic behavior. For example, research on learning and memory processes examined how (and if) organisms link consequences to prior actions or discriminative signaling cues, as well as how these associations can be used to subsequently guide behavior (Tolman, 1948; Adams and Dickinson, 1981; Balleine and Dickinson, 1998a; Wikenheiser and Schoenbaum, 2016). In contrast, studies investigating economic decision-making processes have been trying to clarify how people assign values to competing (behavioral) options and why we are often less rational in our choices then we think (Tversky and Kahneman, 1974; Kahneman et al., 1991; Gottfried et al., 2003; Rangel et al., 2008). Finally, research on top-down executive control investigated the processes underlying deliberate and flexible behavior, the ability to hold, compare and manipulate information for a short amount of time, to suppress stimulus-driven thoughts or actions and to switch between changing task demands (Baddeley and Hitch, 1974; Logan and Cowan, 1984; Monsell, 2003; Diamond, 2013). Despite conceptual differences depending on the respective research tradition, theories in all of these fields often propose a dual-systems perspective, supporting the idea that behavior can be controlled by a rather undemanding and fast but rigid system or a more cognitively demanding and thus slow but flexible system (Evans, 2003; Barrett et al., 2004; Strack and Deutsch, 2004; Rangel et

al., 2008; Balleine and O'Doherty, 2010; O'Doherty et al., 2017). In the next sections, I will present a short introduction to each of these fields and their contributions to our understanding of behavioral control and its neural correlates.

**Flexible cognition in learning and memory**

The distinction between a rigid and a more flexible system of learning and memory has been made at least as early as in the 1940s when first evidence emerged that rats navigating different maze configurations for food rewards did so not only by using simple stimulus-response (S-R) strategies but also by forming spatial representations of their environment (so called cognitive maps; Tolman, 1948). These maps allowed the rats to flexibly adjust how they navigated the maze when placed in different starting positions or when their usual way was blocked. Further studies consolidated the idea that animals are able to use these map-like, allocentric representations to plan routes instead of solely relying on perceptual, egocentric views of the current surroundings (O'Keefe and Nadel, 1978; Poucet, 1993; Wills et al., 2010), although there is debate about the actual complexity of these representations (Bennett, 1996; Wang and Spelke, 2002). Experiments examining navigational learning in real-world and, more recently, in virtual environments, provided evidence for a similar distinction in spatial strategy use in humans (Maguire et al., 1998; Miller et al., 2013; Schinazi et al., 2013). Converging evidence from animal and neuroimaging studies investigating brain mechanisms related to this differentiation in navigational learning linked the more automatic S-R system to the dorsal striatum (specifically the dorsomedial striatum in rodents or the caudate nucleus in humans, respectively), whereas the formation of the more flexible cognitive maps has been associated with the hippocampus (O'Keefe and Nadel, 1978; Morris et al., 1982; Packard and McGaugh, 1992; McDonald and White, 1994; Packard and McGaugh, 1996; Burgess et al., 2002; Hartley et al., 2003; Iaria et al., 2003; Bohbot et al., 2007; Doeller et al., 2008; Pfeiffer and Foster, 2013; Wikenheiser and Schoenbaum, 2016). Notably, recent evidence suggests a functional dissociation between dorsomedial (or caudate) and dorsolateral (or putamen) striatum, indicating that while the dorsomedial striatum is important for initial space-based learning, the dorsolateral striatum is responsible for a behavioral shift towards habitual S-R strategies (Devan and White, 1999; Khamassi and Humphries, 2012; Woolley et al., 2013; Siller-Pérez et al., 2017).

A very similar distinction has been implicated in differential strategy use in tasks assessing probabilistic classification learning, such as the weather prediction task (WPT; Knowlton et al., 1994; Knowlton et al., 1996; Reber et al., 1996). The WPT represents a slightly different approach to distinguish between flexible and habitual behavior, as it was designed to test implicit memory and, in contrast to other tasks, better performance in the WPT is associated with less flexible behavior. In this task, participants are required to learn the predictive value of a series of stimuli (e.g. game cards) for different outcomes (e.g. “rain” or “sunshine”) using trial-by-trial feedback. Since these stimulus-outcome associations are probabilistic and thus difficult to remember explicitly, they were initially thought to be formed implicitly and to be mainly dependent on the striatum (Yin and Knowlton, 2006). However, using mathematical models to assess learning performance in the WPT, studies found that participants could learn the associations using various strategies including more declarative, hippocampal-based approaches. Interestingly, participants were able to switch between strategies, generally moving from declarative to more optimal implicit strategies over time (Poldrack et al., 2001; Gluck et al., 2002; Poldrack and Rodriguez, 2004; Meeter et al., 2006; Rustemeier et al., 2013). In addition, it has been shown that, while usually impaired in implicit S-R learning (Knowlton et al., 1996), patients suffering from conditions affecting striatal functioning such as Parkinson’s disease can achieve performance comparable to healthy controls in the WPT by engaging structures in the medial temporal lobe (MTL), indicating declarative involvement in probabilistic classification learning (Moody et al., 2004; Yin and Knowlton, 2006). Notably, these findings shed light on how flexible and more implicit learning processes may interact and complement each other. Moreover, showing a functional dissociation between the hippocampus and the dorsal striatum in probabilistic classification learning that is quite comparable to navigational learning expands the significance of these structures beyond the spatial domain.

In an account more similar to navigational learning, researchers investigating instrumental learning processes have made the distinction between habit behavior, guided by S-R associations and goal-directed behavior, guided by the association between discriminative stimuli and actions and, importantly, their respective outcomes (S-O-R associations; Dickinson, 1985; Balleine and O'Doherty, 2010; Dolan and Dayan, 2013). Specifically, goal-directed behavior is characterized by the ability to flexibly change

behavior in accordance to the present value of its outcome, meaning that behavior will only be shown for as long as its consequences are desirable. In contrast, occurrence of habitual behavior solely depends on the presence of a cue stimulus that has previously been repeatedly associated with reward and will be unaffected by changes in the outcome value. This consideration has been the critical feature in paradigms trying to differentiate between these two forms of learning, most of which use some variant of contingency degradation or an outcome devaluation test (Corbit and Balleine, 2003; Yin et al., 2005; Ostlund and Balleine, 2008; Tricomi et al., 2009; Bradfield et al., 2015). In both tasks, animals or humans are trained to respond to a certain stimulus to receive a reward. In contingency degradation, the predictive value of an action for an outcome is then weakened by giving rewards even in the absence of the associated action. In the outcome devaluation test, the desirability of former rewards is reduced, for instance by post conditioning (i.e. associating the outcome with negative sensations) or by selective satiation (i.e. granting unlimited access to an outcome). Several studies have shown that rats trained to press a lever for a food reward are faster to adapt their behavior in the following extinction trials when they had received taste aversion conditioning compared control animals (Adams and Dickinson, 1981; Killcross and Coutureau, 2003; however, with longer training, the difference vanished Adams, 1982). Contingency degradation and outcome devaluation paradigms have also been successfully adapted to research in human subjects (Wasserman et al., 1993; Valentin et al., 2007; Schwabe and Wolf, 2009; Tricomi et al., 2009; Liljeholm et al., 2011). On a neural level, corresponding brain structures in humans and animals have been associated with habitual and goal-directed behavior (Balleine and O'Doherty, 2010). Specifically, in rodents, habits are thought to be subserved by the dorsolateral striatum, whereas the dorsomedial striatum and the medial prefrontal cortex support goal-directed behavior (Balleine and Dickinson, 1998a; Killcross and Coutureau, 2003; Yin et al., 2004; Yin et al., 2005). Accordingly, in humans, habitual behavior has been associated with the putamen while goal-directed behavior depends on the caudate nucleus as well as the orbitofrontal cortext (OFC) as part of the ventromedial prefrontal cortex (vmPFC; Bechara et al., 1994; Tricomi et al., 2004; Valentin et al., 2007; Tanaka et al., 2008; Tricomi et al., 2009).

Finally, based on instrumental learning theory and the engineering literature, a more recent computational conceptualization of this dual systems approach builds upon

the distinction of habitual and goal-directed behavior by formalizing how outcomes guide behavior in what is called model-free and model-based learning (Sutton and Barto, 1998; Doya, 1999; Daw et al., 2005; Keramati et al., 2011; Gillan et al., 2015). While the retrospective model-free system mainly depends on S-R contingencies based on rewards received in the past, the prospective model-based system goes beyond the simple incorporation of expected outcome value to guide behavior but is instead proposed to rely on an internally generated model of the task structure or environment. By evaluating and comparing outcomes of currently possible actions, this model allows to deliberately plan behavior in order to choose the action associated with the highest value for the individual. Model-free and model-based contributions to behavior are usually assessed using Reversal Learning paradigms (Hampton et al., 2006; Beierholm et al., 2011) or multistep decision tasks in which varying reward is given after a series of individual decisions (Fermin et al., 2010; Gläscher et al., 2010; Daw et al., 2011; Simon and Daw, 2011; Doll et al., 2012; Wunderlich et al., 2012). In the latter, participants need to learn about the optimal choice at each stage (or decision state) of the task to maximize reward. However, since rewards are distributed probabilistically, participants need to represent the overall structure of the task instead of relying on the outcome of the prior trial (i.e. they need to act model-based instead of model-free). As model-based and model-free behavior are conceptualized as a broader construct incorporating not only reinforcement learning but also pavlovian conditioning as well as more sophisticated forms of cognitive control and decision-making, it is not surprising that studies investigating their neural basis report a multitude of brain structures to be relevant (O'Doherty et al., 2017). In particular, model-free learning has been associated with striatal structures, such as the putamen and the ventral striatum (Balleine, 2005; Lee et al., 2014), stressing especially the role of corticostriatal dopaminergic projections (Pessiglione et al., 2006). However, brain regions exclusively coding model-free behavior are sparse (Doll et al., 2012). In contrast, the greater complexity of strategies that are relevant for model-based behavior as well as the integration of signals arising from both systems is reflected by the large number of associated brain regions, which include the hippocampus (Bornstein and Daw, 2013; Doll et al., 2015), the amygdala (Balleine, 2005; Prévost et al., 2013) and prefrontal cortical areas including the vmPFC, OFC and the dorsolateral prefrontal cortex (dlPFC; Hampton et al., 2006; Padoa-Schioppa and Assad, 2006; Plassmann et al., 2007; Gläscher

et al., 2010; McDannald et al., 2011; Wunderlich et al., 2012; Smittenaar et al., 2013; Lee et al., 2014). By emphasizing the role of these prefrontal areas in model-based behavior, this framework draws connections to the concepts investigated in studies on value-based decision making and top-down executive control, both of which will be presented next.

**Flexible cognition and biases in value-based decision-making**

Every day we make countless decisions, ranging from mundane to potentially life-changing. In each of these decisions, we would like to choose the option that results in the best possible outcome. But how do we decide and what factors influence our decisions? Traditionally, human decision-making was thought to be strictly rational, invoking the concept of the "homo economicus" (Edwards, 1954; Simon, 1959; Elster, 2000; Frank and Bernanke, 2006; Cabantous and Gond, 2011). According to this view, being confronted with a choice between two or more options, we should base our decision (and subsequent actions) on the subjective value (or the expected utility) we ascribe to the outcome of these options. Since decisions often involve some kind of uncertainty about their consequences, an estimated probability of the expected action-outcome associations needs to be incorporated into our decision-making processes, weighting the utilities. In this way, we might choose the option that provides a small but highly likely positive outcome instead of an option promising a large positive outcome that is, however, very unlikely to occur. On a theoretical level, this relation between expected value of an outcome and its probability to occur is formulated in the "Expected-utility theory" (Rangel et al., 2008; Glimcher and Fehr, 2013). Economic and psychological studies have used a wide range of experimental designs to investigate these regularities in different settings, including tasks involving maximizing personal reward, sometimes under conditions of risk, as well as social settings where maximizing reward depends on cooperation with others (Ernst et al., 2002; Lejuez et al., 2002; Sanfey et al., 2003; Fukui et al., 2005). These experiments show that healthy humans are indeed capable of adjusting their decisions according to expected outcome values. However, it has also become clear that decision-making processes are more complex and often far less rational as one might think (Tversky and Kahneman, 1974). This has led to the development of alternative theories of decision-making, such as the "Prospect theory", that takes into account the individual's point of reference (Kahneman and Tversky, 1979;

Barberis, 2013). Instead of being driven by outcome value and probability alone, decisions can be biased by other factors such as emotions, the framing of the presented choice, or morals and social norms (Tversky and Kahneman, 1985; Sitkin and Weingart, 1995; Bechara et al., 2000; Schwarz, 2000; Greene et al., 2001; Bechara et al., 2003; Greene et al., 2004; De Martino et al., 2006; Seymour and Dolan, 2008; Haller and Schwabe, 2014). These biases often come into play when analytical decision processes are hindered due to information being incomplete or too complex or because there is not enough time to properly evaluate all options. Under these circumstances, people rather rely on faster and less demanding heuristics that, while not leading to optimal decisions in some cases, usually provide sufficient or even superior accuracy in complex situations than complex calculations (Tversky and Kahneman, 1974; Gigerenzer and Gaissmaier, 2011). However, outside of classic economic theories, heuristics and affective influences are no indication of irrationality but are instead thought to represent adaptive strategies supporting good and fast choices in real world scenarios, where decision-making processes are most likely limited by time, knowledge and capacity (Gigerenzer and Selten, 2002). Following this view, the use of heuristics is much more psychologically plausible than models assuming unlimited resources (e.g. heuristics do not require individuals to compute extraordinarily complex value calculations) and they allow fast adaptation to the physical and social structure of the environment. As adequate use of heuristics depends on the individual's cognitive abilities and the current environment, the term "bounded rationality" has been coined, contrasting classic "unbounded" decision-making models that imply no constraints in resources (Simon, 1982; Simon, 1991; Gigerenzer and Selten, 2002; Kahneman, 2003a, b). Heuristics play an important part in everyday life as the vast majority of our decisions are made without thorough consideration, which is usually reserved for important and more consequential situations that require in-depth thoughts (and even then we might rely on certain heuristics to guide choices). While these observations did not match with the classic economical point of view picturing humans to be rational decision-makers, they gave rise to the idea of a distinction between an automatic, effortless system and a flexible, more effortful system of choice behavior, sometimes termed as intuition and reasoning or plainly system 1 and system 2, respectively (Sloman, 1996; Kahneman and Frederick, 2002; Evans, 2003, 2008). This dichotomy resembles, to a certain degree, the differentiation between habitual/model-

free and goal-directed/model-based behavior found in learning and memory research (Rangel et al., 2008).

While the former findings primarily resulted from behavioral studies, neuroscientists have been eager to investigate the neurobiological basis of decision-making processes using neuroimaging techniques. Not surprisingly, many studies focused on identifying brain regions that represent the expected value of a choice. A large body of evidence points to the vmPFC and the medial part of the adjacent orbitofrontal cortex (mOFC) as the most important structures for calculating the value of different options (Padoa-Schioppa and Assad, 2006; Chib et al., 2009; Gläscher et al., 2009; Hare et al., 2009; Grabenhorst and Rolls, 2011). However, considering how the "rationality" of our choices is often affected by biases and the use of cognitive heuristics, more recent accounts on the neuroscience of value-based decision making seek to paint a broader picture of the underlying neural dynamics contributing to our decisions. By incorporating findings from economics, psychology, neuroscience and computer science, the integrative field of neuroeconomics aims to not only investigate how values are represented in the brain but also how we learn and remember these values, how their calculation can be affected by contextual information and how values are transformed into actions (Glimcher and Rustichini, 2004; Camerer et al., 2005; Sanfey et al., 2006; Rangel et al., 2008). As expected due to this broad approach, decision scientists show a growing interest in brain regions formerly studied primarily in learning and memory processes, such as the hippocampus and the amygdala (Johnson et al., 2007; Seymour and Dolan, 2008; Frank et al., 2009; Enkavi et al., 2017). Importantly, similar to the recent distinction between model-free and model-based behavior, neuroeconomics emphasize the modulating properties of prefrontal structures on behavioral control (Glimcher and Rustichini, 2004; Sanfey et al., 2006; O'Doherty et al., 2017). This is in line with the well-established role of the prefrontal cortex in executive control (Smith and Jonides, 1999; Miller and Cohen, 2001; Koechlin et al., 2003). The next section will thus cover research on executive functions and the role of the prefrontal cortex in enabling deliberate, top-down controlled behavior.

**Flexible cognition due to executive control**

Originally being a hallmark of research on visual attentional processes (Desimone and Duncan, 1995; Buschman and Miller, 2007; Theeuwes, 2010; Schneider, 2013), the idea that primarily stimulus-driven, bottom-up controlled behavior can be modulated by primarily task or goal-driven, top-down controlled behavior has also gained some interest in emotion and memory research (Pessoa et al., 2002; Ciaramelli et al., 2008; Wright et al., 2008; Ochsner et al., 2009). Quite similar to the distinction between habitual and goal-directed behavior in instrumental learning, bottom-up and top-down controlled behavior can broadly be characterized as reflexive, automatic and fast versus reflective, deliberative and slow, respectively. The cognitive mechanisms underlying top-down behavioral control have been investigated extensively and are often grouped together as executive functions. Executive functions are necessary for self-regulation (Hofmann et al., 2012) as they enable us to control cognition and behavior more voluntarily and flexibly, thus working against automatic or habitual tendencies (Robbins et al., 1996; Mansouri et al., 2009; Miyake and Friedman, 2012). Although there is a large number of higher order cognitive processes that are sometimes labeled as executive functions, general consensus suggests that there are three core processes of cognitive control, namely inhibition, set-shifting/cognitive flexibility and working memory (Miyake et al., 2000; Diamond, 2013). Inhibition includes the ability to focus our attention and thoughts, while suppressing distracting stimuli or memories (Posner and DiGirolamo, 1998; Anderson et al., 2004; Theeuwes, 2010). Importantly, it also allows us to inhibit our emotions and behavior so that we can refrain from impulsively acting upon highly desirable stimuli when they conflict with our long term goals or social norms (Ochsner and Gross, 2005; Phelps and LeDoux, 2005; Cascio et al., 2014; Buckholtz, 2015). Exemplary tasks used to investigate Inhibition, such as the Erikson-Flanker-Task, the Simon-Task or the Stop-Signal-Task, are usually based on a response conflict, requiring participants to overwrite an automatic response in favor of the goal-relevant response (Simon, 1990; Eriksen, 1995; Aron et al., 2003; Verbruggen and Logan, 2008).

Set-shifting or cognitive flexibility, on the other hand, refers to the ability to detect change in task demands and to adjust behavior accordingly (Miyake et al., 2000; Monsell, 2003). It is important to note that despite these properties and the similar denomination, this executive function is not equivalent to the general meaning of flexible, deliberate

cognition outlined in this thesis. As a far more specific process, set-shifting refers to the ability to engage and disengage different mental task-sets and their associated responses (Miyake et al., 2000; Badre and Wagner, 2006). However, this also includes the ability to change perspectives and to reframe the way we think about a given situation, enabling new, creative and flexible ways of problem solving, which is why the term cognitive flexibility is also used in the literature (Collins and Koechlin, 2012; Diamond, 2013; for a recent concept using the term to refer to executive functions in general, see: Dajani and Uddin, 2015). Set-shifting is often probed using tasks requiring the participants to continuously switch between two sub tasks (e.g. responding to either a digit or a letter depending on the concurrent position of both) or to adjust to a changing set of rules, as in the Wisconsin Card Sorting Test (WCST; Monchi et al., 2001; Monsell, 2003; Nyhus and Barceló, 2009).

The third core executive function is working memory. The (multicomponent) concept of working memory emerged as a more refined model of short-term memory, incorporating not only two separate storages for maintaining a limited amount of verbal and spatial information in the absence of stimulation (i.e. the phonological loop and the visual spatial sketch-pad, respectively) but also the ability to actively manipulate, relate and update this information via its central executive component (Baddeley and Hitch, 1974; Smith and Jonides, 1999; Baddeley, 2003; D'Esposito and Postle, 2015). Given these properties, it is no surprise that working memory is considered a central component of cognitive control, closely working in concert with both inhibition and set-shifting. After all, inhibiting the need to act on desirable stimuli requires a mental representation of potentially conflicting long-term goals and switching between different sets of rules or tasks is impossible without keeping these rules available. Working memory is usually assessed by tasks that require participants to hold and reorganize information over a short period of time. For example, participants might be asked to repeat a string of numbers in a different order than they have been presented with (e.g. backwards or in numerical order; Engle, 2002; Conway et al., 2005) or to repeat a series of spatial positions by tapping on a real or virtual board (Corsi/spatial block span; Corsi, 1972; Berch et al., 1998; Kessels et al., 2008). A more complex test of working memory is the n-back task, in which participants need to constantly update and compare stimuli with past information (Owen et al., 2005; Barbey et al., 2013). Combined, these cognitive control

processes allow us to hold our goals in mind and shield our thoughts and behavior from internal or external interferences arising from automatic bottom-up processes.

Mimicking their strong functional interaction, individual executive functions have been associated with similar and anatomically proximate prefrontal brain regions. In fact, given how all prefrontal areas are heavily interconnected, accurately distinguishing specific contributions of these areas to individual cognitive functions remains difficult (Ridderinkhof et al., 2004). Instead of relying on one specific cortical region, cognitive control is subserved by a broad cortical network (Smith and Jonides, 1997; Pessoa, 2008). Nonetheless, several areas, predominantly in the lateral prefrontal cortex (lPFC), have been reliably associated with task performance requiring different forms of executive control. Specifically, response inhibition has been consistently shown to be dependent on the inferior (or ventral) lateral prefrontal cortex (ilPFC/vlPFC; Konishi et al., 1999; Aron et al., 2003; Aron et al., 2004; Hampshire et al., 2010; Aron et al., 2014), while emotion regulation is accomplished by a more distributed network, including the medial PFC (mPFC) and the anterior cingulate cortex (ACC), both of which may inhibit amygdala activity (Quirk and Beer, 2006; Goldin et al., 2008; Wager et al., 2008; Etkin et al., 2011). In a similar vein, set-shifting seems to be supported by the ACC and the vlPFC as well, in addition to the parietal cortex and the dlPFC (Konishi et al., 1998; Sohn et al., 2000; Monsell, 2003; Kerns et al., 2004; Liston et al., 2006; Gläscher et al., 2012; Bissonette et al., 2013). In contrast, research on working memory has mostly focused on the dlPFC ever since first evidence of prolonged neural activity during a retention interval in this area emerged in non-human primates (Fuster and Alexander, 1971; Miller and Orbach, 1972; Bauer and Fuster, 1976; Goldman-Rakic, 1987; Miller et al., 1996). Since then, innumerable studies have translated these findings to humans, making the vital role of the dlPFC for working memory processes one of the most consistent findings in neuroscience (e.g. McCarthy et al., 1996; Aron et al., 2003; Curtis and D'Esposito, 2003; Wager and Smith, 2003; Barbey et al., 2013; D'Esposito and Postle, 2015). In general, the lPFC is thought of as a mostly “cognitive” brain structure, perfectly positioned to modulate and regulate processing in “emotional” brain regions, such as the mPFC that receives major inputs from limbic structures, especially from the amygdala (Barbas, 2000; Miller and Cohen, 2001; Ridderinkhof et al., 2004; Pessoa, 2008). Importantly, the lPFC also features various (often) reciprocal connections to most of the structures relevant in

learning and memory as well as decision-making processes (Fuster, 2001). Specifically, studies in humans and animals show that the lPFC possesses projections from and to the vmPFC (Longe et al., 2010), the hippocampal complex (Goldman-Rakic et al., 1984; Barbas and Blatt, 1995; Verwer et al., 1997) and the caudate nucleus (Selemon and Goldman-Rakic, 1985) as well as to the amygdala, albeit to a significantly lesser extent compared to the medial PFC (Sarter and Markowitsch, 1984; McDonald, 1991; McDonald et al., 1996). Given the extraordinary importance of the lPFC in cognitive control processes it would not be surprising if this structure was also involved in deciding which system guides behavior at any given point. Indeed, a recent study proposed the ilPFC to act as an arbitrator, allocating behavioral control based on the reliability of predictions made by each system (Lee et al., 2014).

Taken together, it becomes clear that flexible cognition depends on the interplay of various separable cognitive domains, including learning, memory, executive control and decision-making (Rangel et al., 2008; Balleine and O'Doherty, 2010; O'Doherty et al., 2017). By being able to learn and to remember what stimuli and actions lead to positive or negative outcomes, to incorporate the contextual circumstances under which these associations hold true, to reflectively compare a current situation with these representations, to inhibit reflexive tendencies when necessary and to constantly recalculate the value of competing options as they arise, our brain provides us with a large number of processes tailored to adjust our behavior flexibly. Yet, we do not always make use of these processes, be it due to a decision being too complex, due to a distraction or simply because we performed a certain action or chose a certain option so often, that it has become automatic. In fact, a lot of our everyday behavior is governed by shallower cognitive processing, freeing resources and leaving effortful control for important or unusual instances. This balance between effortless and effortful behavioral control is crucial to efficient functioning. There are however, conditions, in which this balance is distorted, including psychiatric disorders specifically characterized by such an imbalance, e.g. addiction, eating disorders, or obsessive-compulsive disorder (Everitt and Robbins, 2005; Woolley et al., 2007; Gillan et al., 2011). As an example of a more common condition most of us experience every day and that has been found to exert a profound influence on cognitive processes, stress has received growing interest in the study of

flexible cognition (Dias-Ferreira et al., 2009; Schwabe and Wolf, 2009; Plessow et al., 2012; Schwabe and Wolf, 2013; Maier et al., 2015).

**Flexible cognition under acute stress**

When we encounter a potentially threatening stimulus or situation our body reacts by engaging a complex neurochemical cascade initiated by the hypothalamus (Herman and Cullinan, 1997; Tsigos and Chrousos, 2002; Joëls and Baram, 2009). First, the fast reacting sympathetic-adrenal-medullary (SAM) system is activated, resulting in a secretion of adrenalin and noradrenalin from the adrenal medulla which in turn leads to peripheral effects such as an increase in heart rate, blood vessel dilatation and respiration (Carrasco and van de Kar, 2003; Ulrich-Lai and Herman, 2009). In addition, noradrenalin is also released in the brain by the Nucleus Coeruleus, following the adrenergic activation of the vagus nerve and the Nucleus Tractus Solitarius (McGaugh and Roozendaal, 2002; Roozendaal, 2002; Morilak et al., 2005; Lupien et al., 2007). Activation of the SAM also results in an increased release of dopamine in various brain regions, including the PFC as well as the dorsal and ventral striatum (Thierry et al., 1976; Abercrombie et al., 1989; Arnsten, 2009; Vaessen et al., 2015). These processes happen in a matter of seconds and last merely minutes (Joëls and Baram, 2009; Hermans et al., 2014). They are thought to mediate the reflexive fight or flight response enabling the individual to act upon a threat as fast as possible. A second, slower, endocrinal reaction to threatening stimuli is mediated via the hypothalamic-pituitary-adrenal (HPA) axis (Turnbull and Rivier, 1999; Joëls and Baram, 2009; Ulrich-Lai and Herman, 2009). From the Nucleus Paraventricularis of the hypothalamus, the corticotropin releasing hormone (CRH) is secreted which in turn leads to the release of the adrenocorticotropic hormone (ACTH) from the anterior pituitary gland and, consequently, to the release of glucocorticoids (Cortisol in humans, corticosterone in animals) from the adrenal cortex. Cortisol is able to pass the blood-brain barrier and thus may exert effects directly in the brain by binding to mineralocorticoid and glucocorticoid receptors (MRs and GRs, respectively; Reul and Kloet, 1985; de Kloet et al., 2005; Vogel et al., 2016). Activation of the HPA axis is controlled via feedback loops that inform the hypothalamus about the momentary level of hormone secretion at each step (Herman and Cullinan, 1997; Tsigos and Chrousos, 2002; Herman et al., 2003). Cortisol levels in the brain reach their peak at about 20 to 25 minutes after stress onset

and normalize over the course of several hours (Joëls and Baram, 2009; Quaedflieg and Schwabe, 2017). Given these different time courses, it is not surprising that the effects of stress on brain activity and function depend on the exact time point of investigation (Henckens et al., 2010; Schwabe et al., 2012b; Hermans et al., 2014; Schwabe and Wolf, 2014; Quaedflieg and Schwabe, 2017). Following the sudden increase in catecholamine secretion after a stressor, prefrontal cortical areas show reduced activity, as the rise of both noradrenaline and dopamine concentrations lead to excessive binding at α1 and D1 receptors, respectively (Arnsten, 2009; Hermans et al., 2011). At the same time, amygdala activity is elevated (Phillips et al., 2003; de Kloet et al., 2005; van Marle et al., 2009). After several minutes, glucocorticoids reach the brain and bind to MRs and GRs abundantly expressed in the PFC and the Hippocampus. These early, non-genomic glucocorticoids actions presumably interact and enhance the catecholaminergic effects (Roozendaal et al., 2009; Krugers et al., 2012). At this point in time, higher, top-down cognitive functions are thought to be suppressed while bottom-up functions are suggested to be enhanced, probably to allow optimal processing of the current stressful situation (Qin et al., 2009; van Marle et al., 2010; van Stegeren et al., 2010; Schwabe et al., 2012a; Quaedflieg et al., 2015). At later stages (i.e. about 60-90 minutes after stress onset), genomic glucocorticoid effects set in and might last for several hours (Hermans et al., 2014). This is thought to reverse the earlier effects, to restore the organism's homeostasis and to normalize top-down control in order to enable us to fully process the stressful experience. Incorporating these findings, it has been proposed that acute stress leads to large-scale brain network changes, enabling individuals to reallocate cognitive and neural resources to environmental needs (Seeley et al., 2007; Hermans et al., 2011; Hermans et al., 2014). According to this view, stress leads to time-dependent modulation of activity in the brain's salience and executive control networks, favoring the salience network early after stress but later reversing the pattern, restoring the balance between the networks. Indeed, acute stress has been found to increase selective attention (Chajut and Algom, 2003), to attenuate the attentional blink (Schwabe and Wolf, 2010b) and to amplify amygdala activity as well as sensory processing in early visual regions (van Marle et al., 2009). Concerning learning and memory processes, experiencing a stressful situation before learning has been found to impair or enhance subsequent memory performance, depending on stimulus material and task timing. In contrast, consolidation processes have

primarily been reported to be enhanced by stress, whereas memory retrieval as well as memory reconsolidations are seemingly impaired (Schwabe et al., 2012b; Schwabe and Wolf, 2014; Quaedflieg and Schwabe, 2017).

Importantly, stress also affects the quality of learning and memory, as it seems to induce a shift from more flexible to more rigid forms of behavior (Schwabe et al., 2010a; Schwabe et al., 2012b; Quaedflieg and Schwabe, 2017; Wirz et al., 2018). For example, after stress, both rodents and humans where shown to rely more strongly on striatum-based S-R strategies than hippocampus-dependent strategies in tasks requiring spatial orientation (Kim et al., 2001; Schwabe et al., 2007; Vogel et al., 2017). A similar shift away from hippocampal and towards striatal strategy use was found using probabilistic classifications tasks (Schwabe and Wolf, 2012; Schwabe et al., 2013b; Wirz et al., 2017). Moreover, stress also was also shown to affect the balance between habitual and goal-directed behavior. Specifically, rats and humans are less sensitive for changes in outcome values following stress as assessed by outcome devaluation tests (Schwabe and Wolf, 2009, 2010a; Braun and Hauber, 2013). This reduced flexibility seems to occur mainly due to impaired goal-directed control (Fournier et al., 2017). In accordance with these findings, first evidence indicates a similar stress-induced shift in the balance of model-based and model-free reinforcement learning, although modulated by working memory capacity (Otto et al., 2013b) and chronic stress level (Radenbach et al., 2015).

Acute stress has also been shown to alter (mPFC dependent) economic as well as social decision-making, for example by increasing risk-seeking behavior and decreasing feedback sensitivity (Porcelli and Delgado, 2009; Starcke and Brand, 2012; van den Bos et al., 2013; Buchanan and Preston, 2014; Gathmann et al., 2014; Lenow et al., 2017; Porcelli and Delgado, 2017). These effects interestingly do not seem to be universal, but to mainly depend on factors such as the framing of the task and the sex of the participants. They also seem to be mainly caused by cortisol (Kluen et al., 2017), which contrasts findings in learning and memory research stressing the importance of concurrent actions of catecholamines and cortisol (Barsegyan et al., 2010; Schwabe et al., 2010b, 2012a).

Concerning cognitive functions specifically associated with the lPFC, effects of acute stress are more consistent. The lPFC is thought to be one of the most stress sensitive structures in the brain (de Kloet et al., 2005; McEwen and Morrison, 2013). Consequently, stress exerts a large detrimental impact on executive functions, most likely

due to a decrease in prefrontal activity following catecholaminergic and early, non-genomic glucocorticoid actions in the brain (Arnsten and Li, 2005; Elzinga and Roelofs, 2005; Arnsten, 2009; Shansky and Lipps, 2013). Specifically, stress has been shown to impair working memory processes (Oei et al., 2006; Schoofs et al., 2008; Qin et al., 2009; Schoofs et al., 2009; Arnsten et al., 2012; Gärtner et al., 2014) as well as set-shifting (Alexander et al., 2007; Plessow et al., 2011; Plessow et al., 2012) and cognitive inhibition (Vinski and Watter, 2013; Sänger et al., 2014) but not response inhibition (Schwabe et al., 2013a; for a review see: Shields et al., 2016).

Taken together, these findings demonstrate that acute stress leads to a shift towards the reliance on more rigid behavior in expense of the ability to adaptively adjust to changing task demands by impairing various brain regions associated with flexible behavior, including the lPFC.

## Methodological approach and scope

As explicated, several lines of research have proposed dual-systems accounts of behavioral control, implicating that adaptive behavior depends on a balance of efficient and reflective cognition (Barrett et al., 2004; Evans, 2008; Rangel et al., 2008; Balleine and O'Doherty, 2010; O'Doherty et al., 2017). Accordingly, many studies have been trying to clarify how our brain enables us to overcome our habits and automatisms in order to act upon a greater goal. While science in the fields of learning and memory, value-based decision making and executive functions has been conducted rather separately from one another for a long time, recent approaches, such as the concept of model-free vs. model based learning and the new field of neuroeconomics show a much needed consolidation of ideas (Rangel et al., 2008; O'Doherty et al., 2017). Indeed, researchers in each of these fields have been successful in linking behavior to brain activation, identifying brain structures consistently activated in tasks requiring flexible cognition (O'Keefe and Nadel, 1978; Goldman-Rakic et al., 1984; Bechara et al., 1999; Miller and Cohen, 2001; Burgess et al., 2002; Iaria et al., 2003; Koechlin et al., 2003; Daw et al., 2005; Hare et al., 2009; Gläscher et al., 2012; Barbey et al., 2013). Due to its manifold connections to brain regions associated with learning, memory and decision-making and its role in executive control, the lPFC might play a central role in orchestrating flexible cognition (Sarter and Markowitsch, 1984; Barbas, 2000; Fuster, 2001; Hampton et al., 2007; Longe et al., 2010).

However, most of the available data are based on lesions or neuroimaging studies. While these kinds of studies are very valuable, especially when investigating structures lying deeper within the brain, they provide only limited insight about the causal role of specific brain regions. For this reason, an increasing number of recent studies have used non-invasive brain stimulation (NIBS) techniques to investigate brain functions in human subjects (Fregni et al., 2005; Huang et al., 2005; Boggio et al., 2006b; Andrews et al., 2011; Ott et al., 2011; Ruff et al., 2013). These methods provide a larger informative value about causality, as they allow the experimental manipulation of brain activity, at least in cortical regions in close proximity to the skull. The most common forms of NIBS are transcranial direct current stimulation (tDCS), transcranial alternate current stimulation (tACS) and transcranial magnetic stimulation (TMS). While tACS can be used to study effects of brain oscillations by inducing neural synchronization at specific frequencies, tDCS and TMS have been frequently employed to either systematically excite or inhibit activity of the cortical areas of interest (Hallett, 2007; Nitsche et al., 2008; Mills, 2017; Sellaro et al., 2017). As tDCS and TMS are the most important forms of NIBS to this work, they will be briefly introduced.

**Transcranial direct current stimulation (tDCS)**

For tDCS (Fig. 1A), participants receive a low intensity electrical stimulation via (usually) two electrodes positioned on the head (Nitsche and Paulus, 2000; Nitsche et al., 2008). The basic idea is that a current flowing between these two electrodes affects the underlying brain tissue, resulting in altered brain functioning and, consequently, to measurable behavioral effects. Importantly, tDCS effects are specific for polarity. It is usually assumed that activity in the brain tissue covered by the (positively charged) anodal electrode is elevated whereas activity in brain tissue under the (negatively charged) cathode is reduced (Bindman et al., 1964; Purpura and McMurtry, 1965; Baudewig et al., 2001; Turi et al., 2012; Filmer et al., 2014). Importantly however, tDCS does not directly elicit action potentials. Instead, tDCS changes the cells' resting potential, facilitating or hampering the occurrence of naturally evolving action potentials (Nitsche and Paulus, 2000; Filmer et al., 2014; Sellaro et al., 2017). In other words, it changes neural excitability. The exact neurobiological mechanisms that underlie tDCS effects are not yet completely understood. However, it has been hypothesized that tDCS effects

occur due to a modulation of membrane potentials, mediated through sodium and calcium channels (Liebetanz et al., 2002; Nitsche et al., 2003; Stagg and Nitsche, 2011). In addition, tDCS has been shown to exert effects by affecting neurotransmitters, such as the GABA, glutamate, acetycholine, serotonin and dopamine systems (Kuo et al., 2007; Nitsche et al., 2009; Stagg et al., 2009; Thirugnanasambandam et al., 2011; Medeiros et al., 2012). Since tDCS is easy to apply and presents a low risk for serious side effects, it has received a lot of interest in the last decade. A growing body of studies investigated the effects of online and offline stimulation of cortical areas on behavioral measures, including motor skills, language learning and response selection (Reis et al., 2009; Clark et al., 2012; Filmer et al., 2013; Iuculano and Kadosh, 2013; Harty et al., 2014a). Additionally, studies using tDCS to stimulate the dlPFC consistently report effects on working memory performance (Fregni et al., 2005; Boggio et al., 2006b; Nitsche et al., 2008; Andrews et al., 2011; Zaehle et al., 2011).

**Transcranial magnetic stimulation (TMS)**

Transcranial magnetic stimulation uses a different approach to stimulate the brain (Fig. 1B). Here, a copper-wire coil is positioned tangential to the participants' head above the area of interest (Hallett, 2000, 2007; Mills, 2017). Delivering a current to the coil results in the generation of a magnetic field that in turn inducts small currents in the brain. In contrast to tDCS, TMS actually induces action potentials in the underlying cells. One of the biggest advantages of TMS is its precision, due to the small size of the magnetic field, the spatial distribution of which being dependent on the shape of the coil (Wagner et al., 2004; Wagner et al., 2009; Mills, 2017). In combination with structural magnetic resonance images, TMS allows for very specific stimulation of cortical areas. TMS can be applied using single pulse (spTMS) or repetitive (rTMS) protocols (Hallett, 2007; Narayana et al., 2017). While single pulse TMS can be used to precisely interfere with cortical activity at a given point in time, rTMS allows for more long-lasting effects and, similarly to tDCS, can be applied to enhance or inhibit cortical activity (Chen et al., 1997; Berardelli et al., 1998; Romero et al., 2002; Sparing and Mottaghy, 2008). An rTMS protocol that has just recently become more broadly used is Theta Burst Stimulation (TBS; Huang et al., 2005; Di Lazzaro et al., 2008). TBS consists of three magnetic pulses at a frequency of 50Hz, repeated at a frequency of 5Hz. Studies show that a total number of 600 pulses

given in a continuous fashion (cTBS) lead to an inhibition of the motor cortex, while applying the same amount of pulses intermittently (iTBS) in trains of 2s-stimulation followed by an 8s-pause results in increased activity in the same area. An intermediate protocol (imTBS), applying 5s-stimulation-trains followed by a 10s-pause, did not change activity and is thus regarded as a sham condition. Although these initial findings refer to the motor cortex due to the advantage of a motor read-out (motor evoked potentials (MEP) of the first dorsal interossei muscle of the contralateral hand), there has been an increasing number of studies using TBS on prefrontal areas (Rounis et al., 2010; Verbruggen et al., 2010; Ott et al., 2011). While not many experiments used TBS to target the causal contribution of the prefrontal cortex specifically to flexible cognition, it presents a promising tool to do so.

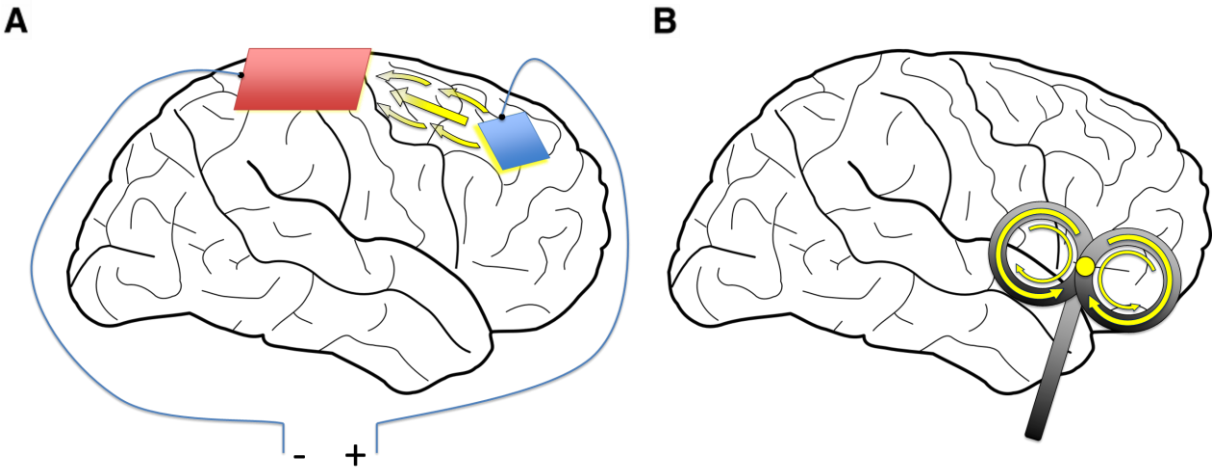


**Figure 1.** Schematic overview of transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) procedures. **(A)** With tDCS, a weak electric current is applied to the participant's head via two electrodes, the positively charged anode and the negatively charged cathode. The current flows from the anode to the cathode, leading to increased neural excitability in brain regions beneath the anode and decreased neural excitability in regions beneath the cathode. tDCS-effects are most pronounced directly below the electrodes and decrease with increasing distance to the electrodes. **(B)** With TMS, stimulation is delivered via a copper coil, positioned tangential to the participant's head. When a current is applied to the coil, it creates a magnetic field perpendicular to the coil, which in turn inducts an electric current in the brain tissue that flows opposite to the current in the coil. The strength and location of this current depend on the shape of the coil. Using a figure-eight coil, the magnetic field and consequently the induced current are strongest at the central conjunction point of the coil, allowing for very focal stimulation.

**Scope**

Although there has been much progress over the last few years in merging research traditions and identifying the large networks and network interactions underlying our ability to flexibly adjust our behavior, there is still a lack of evidence for causal involvement of the postulated brain areas in a lot of these processes. How do things such as abstract social norms influence the calculation of values when we make decisions? How exactly does stress undermine flexible cognition and are these effects preventable? While flexible and goal-oriented behavior is often seen as superior to habitual behavior, it consumes cognitive resources and there are numerous situations in which we are perfectly fine with relying on shallower processing. But how does the brain decide which behavioral system should be given control to? This thesis sets out to investigate these questions using NIBS (i.e. tDCS and TBS) to interfere with cortical processing in the lPFC, a structure presumably crucial for flexible cognition. In the following sections, I will give a short overview of three individual studies that make up the thesis (Fig. 2; for the complete manuscripts please see appendix A - C).

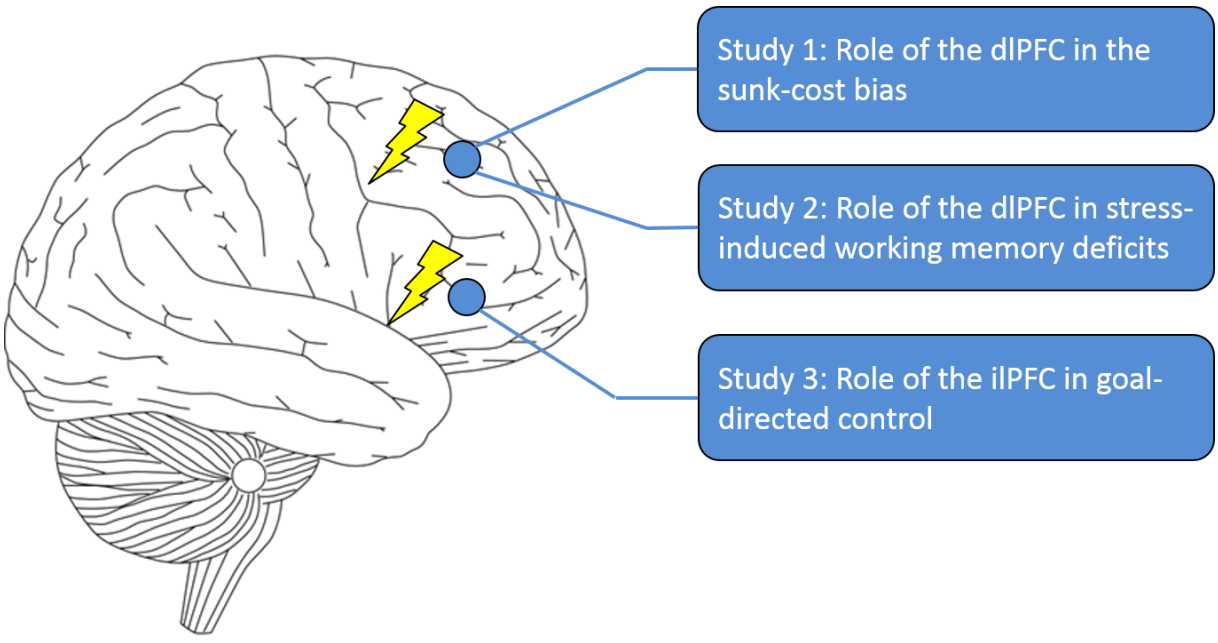


**Figure 2.** Brain stimulation locations in the presented studies. In study 1, we were interested in the causal role of the dorsolateral prefrontal cortex (dlPFC) in a well-known decision-bias, namely the sunk-cost effect. In study 2, we investigated the role of the dlPFC in stress-induced working-memory deficits. In both studies, we used tDCS to stimulate the right dlPFC (position F4 in the standard 10-20 system) either anodal, cathodal or with a sham protocol. In study 3, we used neuronavigated theta burst stimulation (TBS), a specific TMS protocol that allows for excitatory, inhibitory and sham stimulation, to test the role of the inferior lateral prefrontal cortex (ilPFC) in goal-directed behavioral control. TBS was applied to the right ilPFC (MNI coordinates: x = 48, y = 35, z = -2), based on previous neuroimaging data (Lee et al., 2014).

## Study 1: Social norms represented in the dlPFC influence value calculation in the vmPFC

Published in Cerebral Cortex as: Transcranial Stimulation Over the Dorsolateral Prefrontal Cortex Increases the Impact of Past Expenses on Decision-Making (Bogdanov et al., 2017)

**Background:** This study investigates the causal role of the dlPFC in the top-down modulation of economic decision-making via the implementation of social norms. As outlined above, rational decision-making should be guided by the prospective value of the expected outcome of an option and the probability with which choosing this option will actually lead to the outcome (Edwards, 1954; Frank and Bernanke, 2006; Cabantous and Gond, 2011). However, many studies and even everyday experience show that decisions are often not as rational as we might like them to be (Tversky and Kahneman, 1974; Samuelson and Zeckhauser, 1988; Kahneman et al., 1991; Shafir et al., 1993). While various simple situations or tasks do not require deliberate thought, many others are too complex to fully process. In this case, people rely on heuristics to guide decisions that, while often adequate, sometimes leave them prone to fall victim to cognitive biases (Kahneman et al., 1991; Gigerenzer and Selten, 2002). A common cognitive biases, the sunk-cost effect, has been of particular interest to researchers due to its potentially disastrous personal as well as economic consequences (Staw, 1976; Strube, 1988; Murnighan, 2002). The sunk-cost effect occurs when current decisions are impacted by past investments, such as money, time or work (Arkes and Blumer, 1985; Garland, 1990; Arkes and Hutzel, 2000; van Putten et al., 2010). Despite the fact that these prior expenses have been irrevocably lost, they are often considered in current choices and it has been argued that this is due to the influence of the social norm not to waste resources (Arkes and Ayton, 1999; Haller and Schwabe, 2014). The idea that their past investments have been in vain is aversive and individuals may hope to salvage these expenses by continuing to invest in options with results that are either less valuable than those of competing options or simply without value at all. The sunk-cost effect thus demonstrates how social norms, thought to be represented by the dlPFC (Sanfey et al., 2003; Baumgartner et al., 2011; Ruff et al., 2013), might influence decision-making processes that are usually thought to rely on the vmPFC (Kable and Glimcher, 2007; Grabenhorst and Rolls, 2011; Jocham et al., 2012). Indeed, prior expenses seem to increase connectivity between dlPFC and the vmPFC and to simultaneously decrease vmPFC activity for ongoing decisions (Haller and Schwabe, 2014). In this study, we built

upon this finding and set out to investigate whether dlPFC stimulation via tDCS might alter the magnitude of the sunk-cost effect. Since we did not stimulate the vmPFC dependent valuation processes directly, any impact of stimulation should arise due to altered connectivity between the dlPFC and the vmPFC, presumably due to changing the influence of the norm not to waste resources. This would imply a causal role of the dlPFC in the sunk-cost bias.

**Methods:** In this study, we tested sixty healthy participants (mean age ± SEM: 24.9 ± 3.6 years; 30 women) in a double-blind, sham-controlled, between-subject design using tDCS. Participants were randomly assigned to either receive anodal, cathodal, or sham stimulation of the right dlPFC while working on an investment task (Haller and Schwabe, 2014). This task presented participants with fictional projects characterized only by investment costs (low = 0.20 or 0.25 cents vs. high = 0.60 or 0.65 cents) and success probability (low = 40% vs. medium = 50% vs. high = 60%). Participants were instructed to choose whether they wanted to invest the displayed amount into a given project or not. To keep the participants motivated, they were told that a successful investment led to a win of two euros (minus the money invested) whereas a failed investment would lead to a loss of the invested money. The task consisted of 252 trials, a third of which would end after the participants invested once and received feedback about the success or failure of the project. However, in the remaining two thirds of the trials, participants were informed that in order to finish the project, more investments were needed, displaying the additional costs (again low vs. high) and updated success probability (low vs. medium vs. high) of the project. If participants chose rationally, their decision in these trials would be based only on the updated information instead of the amount already invested as these expenses had already been spent either way. However, if participants considered past expenses (i.e. if they fell victim to the sunk-cost effect), they would be more likely to invest again, even when the expected value of the outcome is relatively low (e.g. reinvestment costs are high and success probability is medium or low). This should be pronounced more if the initial investment has been large. In addition to the investment task, participants filled in questionnaires to control for interindividual differences in personality traits possibly interfering with the sunk-cost effect.

**Results:** When presented with a new project, participants' decisions were based on project costs and probability. As the expected value of the projects grew (i.e. lower costs

and higher success probabilities), participants were more likely to invest. However, when participants had already invested in a project and were asked whether they wanted to continue their investment, they fell for the sunk-cost effect, as they were more likely to invest into projects with a lower expected value. As expected, this was more pronounced for higher prior investments. While tDCS did not influence participants' choice on first time projects, anodal stimulation had a profound impact on choice behavior in decisions about continuing projects, i.e. when prior investments had been made. Specifically, when receiving anodal tDCS, participants showed a more pronounced sunk-cost effect compared to sham and cathodal tDCS, which did not differ (Fig. 3). This effect of anodal stimulation was strongest for trials with low expected value. Additional analyses revealed that this effect could not be explained by the outcomes of previous trials, participants' sex, or personality traits.

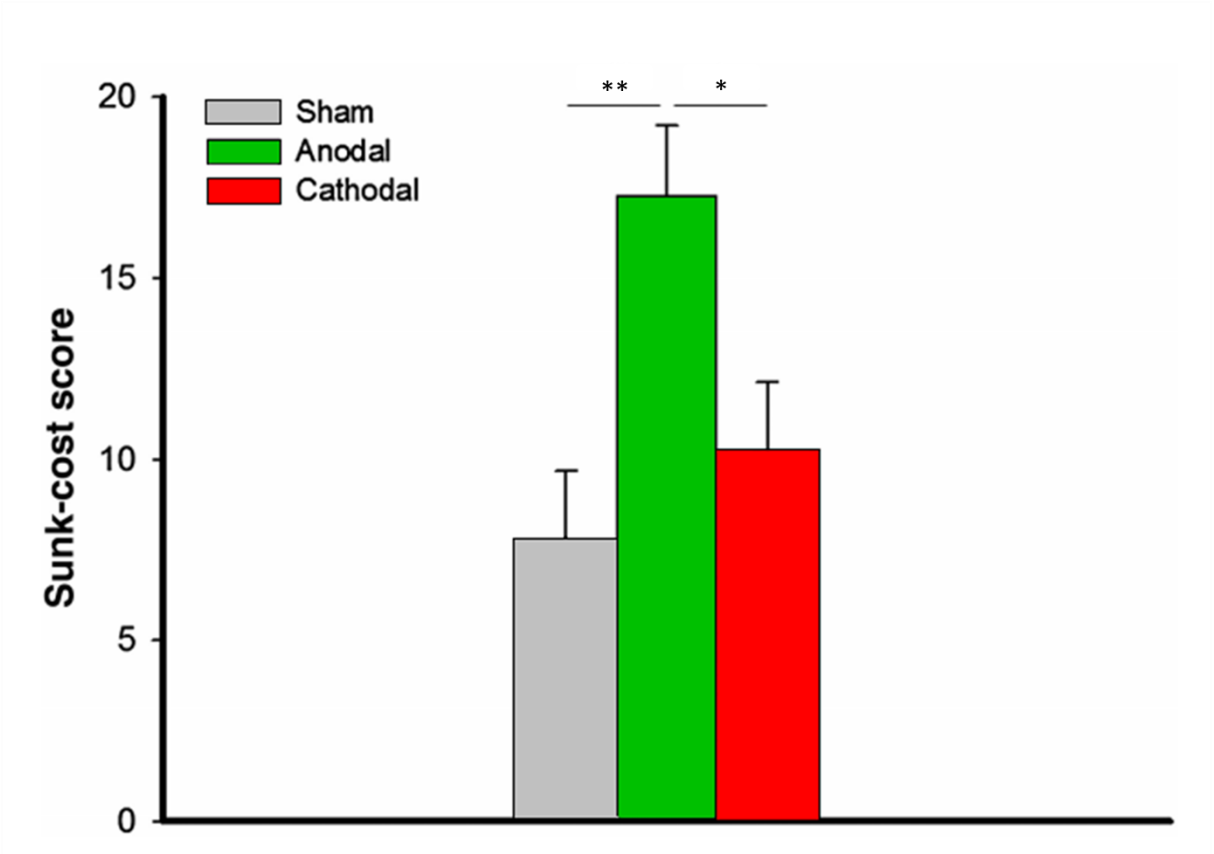


**Figure 3.** Impact of dlPFC stimulation on the sunk-cost score. The sunk-cost score was calculated as a single index of the subjects' tendency to consider past investments in current decisions. A higher score indicates a more pronounced sunk-cost effect. Anodal stimulation led to a higher sunk-cost score than both cathodal and sham stimulation. Error bars indicate SEM. *$p < 0.05$, **$p < 0.01$. P-values are corrected for multiple comparisons. Adapted from (Bogdanov et al., 2017).

**Discussion:** The choices we make do not only depend on their expected outcome but are also modulated by our personal point of reference, our emotions and social expectations (Kahneman and Tversky, 1979; De Martino et al., 2006; Ruff et al., 2013). While these influences are often useful, they sometimes lead to less adaptive choice behavior. The sunk-cost effect (i.e. considering unrecoverable past expenses in current decisions) is a well-known and consequential bias in human decision-making that occurs most likely due to the internalized norm not to be wasteful (Arkes and Blumer, 1985; Garland, 1990; Arkes and Ayton, 1999; van Putten et al., 2010). Previous studies have shown that this effect is associated with less activity in the vmPFC, a brain area thought to calculate values of decision options, and simultaneously with an increased connectivity between the vmPFC and the dlPFC, which is thought to represent social norms (Haller and Schwabe, 2014). Thus, we argue that stimulating dlPFC activity by anodal tDCS led to an increased top-down modulation of the decision-making process by increasing the impact of social norms, resulting in participants investing in less valuable options and therefore showing a more pronounced sunk-cost effect. This interpretation is supported by the fact that stimulation only altered decisions when participants already had invested into a project and the norm should be activated. In contrast, when participants made an initial investment, choices were only driven by the expected value. As the dlPFC plays a very well-known role in working memory (Fuster and Alexander, 1971; D'Esposito et al., 1995; Barbey et al., 2013), an alternative account for our data might be that tDCS alters choice behavior by strengthening the representation of prior investments in current decisions. We cannot fully disentangle the influence of working memory and social norms on the sunk-cost effect in this study. However, these alternatives are not mutually exclusive, as social norms, in order to guide our behavior, might need to be represented in working memory. Nonetheless, our study shows that the dlPFC plays a causal role in the sunk-cost effect and might influence decisions. Interestingly, this also illustrates that top-down control of behavior, in this case considering a social norm in decision-making, is not always beneficial, but might instead lead to unfavorable outcomes.

## Study 2: Stimulation of the dlPFC prevents stress-induced working memory deficits

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**Background:** Being able to flexibly adjust behavior is effortful. It requires continuous processing, updating and reorganization of information as well as inhibiting inappropriate or disadvantageous behavior, all of which are key aspects of executive functions supported by the lPFC (Aron et al., 2004; Hampshire et al., 2010; Barbey et al., 2013). Unsurprisingly, these effortful tasks are highly susceptible to interference, especially due to the experience of stressful events (Arnsten and Li, 2005; Lupien et al., 2007; Liston et al., 2009; Lupien et al., 2009; Qin et al., 2009; Plessow et al., 2012). As outlined above, acute psychosocial stress leads to a rapid increase in catecholamine concentration in the brain which leads to a deactivation of prefrontal areas and thus to a shift away from top-down control in favor of bottom-up processes (Arnsten, 2009; Hermans et al., 2014). This prefrontal deactivation is presumably supported by the non-genomic actions of cortisol, which binds to membrane-bound GRs and MRs, abundantly expressed in the prefrontal cortex (Barsegyan et al., 2010). Accordingly, prefrontal functions such as working memory are consistently reported to be impaired following stress. Given that working memory impairments are also at the heart of many stress related psychiatric disorders and that tDCS over the dlPFC has been shown to successfully modulate working memory processes (Fregni et al., 2005; Boggio et al., 2006a; Nitsche et al., 2008), it was tempting to investigate whether dlPFC stimulation could prevent or at least ameliorate functional decline after stress. Given that current treatment of disorders often involves medication, tDCS might also prove to be a promising alternative.

**Methods:** In this study, we tested 120 healthy participants (mean age ± SEM: 25.2 ± 0.31 years) in a two-day, double-blind, sham-controlled between-subject design using tDCS. Since we investigated salivary cortisol concentration as a marker for stress experience, exclusion criteria included medication intake, smoking, drug abuse, pregnancy and hormonal contraceptives. Women were not tested during their menses. Stress induction was achieved by using the Trier Social Stress Test (TSST; Kirschbaum et al., 1993; Dickerson and Kemeny, 2004; Smeets et al., 2012) that presents participants with a mock job interview consisting of a free speech and a difficult arithmetic task, performed in front of a panel of two unresponsive, non-reinforcing confederates. Participants were told that

their performance was rated and videotaped. Additionally, the participants saw their face on a flat screen TV for the whole duration of this task. In the control condition, participants gave a free speech about a topic of their choice and performed a simple counting task. There was neither a panel nor a camera present in the control condition. To assess successful stress induction, we measured blood pressure, heart rate, subjective mood ratings and salivary cortisol levels at several time points throughout the study. Participants were randomly assigned to either the stress or the control condition as well as either anodal, cathodal or sham stimulation of the right dlPFC. Working memory performance was assessed using the digit span backwards task and the corsi block span backwards task, two standard tasks probing verbal and spatial working memory, respectively. Both tasks require participants to hold information (i.e. a sequence of numbers or spatial positions) and then reproduce this information in reverse order. We assessed individual working memory performance on the first day. On the second day, participants underwent the stress or the control condition of the TSST before they completed both working memory tasks while simultaneously receiving either anodal, cathodal or sham tDCS. Since people differ greatly in their working memory performance, we calculated a difference score between performance of day one and day two as our primary measure of change in performance due to stress and stimulation. In addition to the working memory tasks, participants also filled in questionnaires to control for interindividual differences in personality traits, depressive symptoms and chronic stress level.

**Results:** Stress induction was successful as indicated by elevated blood pressure and heart rate during the stress manipulation and higher salivary cortisol levels 25 minutes after stress onset as well as higher subjective stress ratings in the stress condition compared to the control condition of the TSST. For the corsi block task (Fig. 4A), experiencing stress on day two resulted in an impaired working memory performance compared to performance on day one, while control participants performed better on day two. However, this expected stress-induced impairment was only seen in participants receiving sham and, although to a lesser extent, cathodal stimulation. In both groups, participants performed slightly worse or about as well as on day one. On the other hand, stressed participants in the anodal group performed better than those receiving sham or cathodal stimulation and equally well as participants in the control condition, indicating

that excitatory stimulation of the right dlPFC prevented stress-induced impairments in the corsi block task. Interestingly, tDCS had no effects on performance in control participants. For the digit span task (Fig. 4B), we observed a very similar pattern. Non-stressed participants performed slightly better on day two compared to day one independent of tDCS condition. Stressed participants, however, performed slightly worse on day two in the sham and cathodal stimulation condition, while this impairment did not occur after anodal stimulation. In fact, anodal tDCS led to much improved verbal working memory in stressed participants compared to sham and cathodal stimulation, on par with performance of non-stressed participants. Again, there were no tDCS effects for participants in the control condition. These results could not be explained by group differences in self-reported chronic stress levels, depressive symptoms or cortisol responses.

**Discussion:** Working memory is a core function of executive control and plays a key role in flexible cognition (Hofmann et al., 2012; Diamond, 2013). It enables us to hold information for a short period of time as well as to constantly update and manipulate this information (Baddeley and Hitch, 1974). As other functions primarily relying on the prefrontal cortex, working memory is known to be very sensitive to stress (Lupien et al., 1999; Schoofs et al., 2008; Qin et al., 2009; Gärtner et al., 2014).

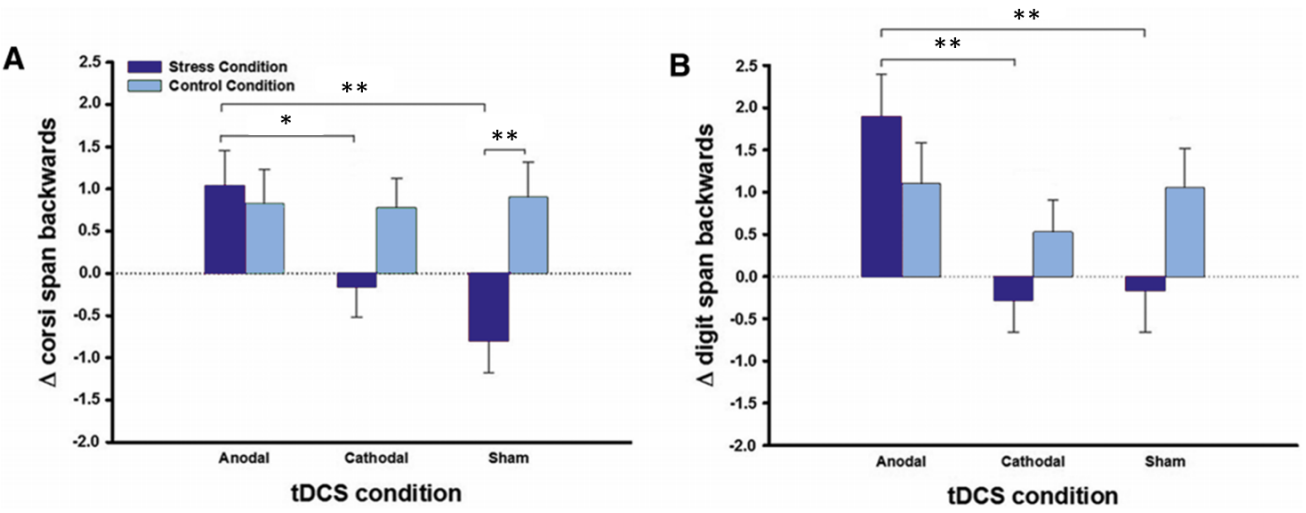


**Figure 4.** Anodal tDCS prevents stress-induced working memory impairments. **A**, Exposure to the TSST impaired Corsi block backwards performance, an indicator of visual-spatial working memory, in the sham and cathodal tDCS groups but not in the anodal tDCS group. **B**, Similarly, TSST exposure tended to reduce digit span backwards performance, an indicator of verbal working memory, in the sham and cathodal tDCS groups but not in the anodal tDCS group. In both tasks, working performance after stress was significantly better in participants that received anodal tDCS over the dlPFC than in those that received sham or cathodal stimulation. Error bars indicate SEM. *$p < 0.05$. **$p < 0.01$. Adapted from (Bogdanov and Schwabe, 2016).

The findings of the current experiment are in line with previous studies reporting working memory deficits after stress exposure, although we found these deficits to be more pronounced for spatial than for verbal material. In both modalities, however, anodal stimulation of the right dlPFC prevented the detrimental stress effects, resulting in performance levels comparable to non-stressed controls. This implicates a causal role of the dlPFC in stress-induced working memory impairments, previously indicated by neuroimaging data (Qin et al., 2009). We argue that tDCS might counter the decrease in synaptic and neuronal excitability that follows cortisol binding to glucocorticoid receptors in the prefrontal cortex after stress by negating the reduction of calcium influx in the presynaptic membrane (Liebetanz et al., 2002; Nitsche et al., 2003; Prager and Johnson, 2009). Although we cannot (and did not aim to) disentangle the exact sub processes of working memory affected by tDCS in this study, anodal tDCS has been shown to be an effective tool to counteract stress-induced working memory impairments. As such, it might also prove useful as an application to treat related symptoms in patients suffering from diverse stress-related psychiatric conditions, such as depression or post-traumatic stress disorder.

### Study 3: Causal contribution of the inferolateral prefrontal cortex to the balance of goal-directed vs. habitual behavioral control

Submitted as: Causal role of the inferolateral prefrontal cortex in the goal-directed control of action (Bogdanov et al., Submitted)

**Background:** Many studies using neuroimaging or lesion approaches reported distinct neural structures for habitual and goal-directed control over instrumental learning processes. Specifically, habitual behavior is associated with activity in the dorsolateral striatum or putamen in humans while goal-directed behavior is thought to rely on the orbitofrontal cortex and the dorsomedial striatum or caudate nucleus in humans (Balleine and Dickinson, 1998b; Coutureau and Killcross, 2003; Yin et al., 2004; Yin et al., 2005; Yin and Knowlton, 2006; Valentin et al., 2007; Tricomi et al., 2009; Balleine and O'Doherty, 2010; Schwabe et al., 2012a). Successful behavioral adaptation depends on both of these systems as they provide a balance between effortful but deliberate and efficient but more automatic behavior (Adams and Dickinson, 1981; Dickinson and Balleine, 1993; Dolan and Dayan, 2013; Dayan and Berridge, 2014). Research has identified several conditions that lead to a shift from goal-directed to habitual control, e.g. extensive training, distraction or

stress (Foerde et al., 2006; Tricomi et al., 2009; Schwabe et al., 2010b; Plessow et al., 2011; Plessow et al., 2012; Schwabe and Wolf, 2012). However, the mechanism with which the brain allocates control to one of the systems remains elusive. One possibility put forward in recent studies is that there might be an arbitration mechanism handing control to either system depending on the reliability of their prediction of current states and rewards. It has been proposed that the right ilPFC might subserve these computations (Lee et al., 2014). However, first evidence for this proposal stems from neuroimaging findings, restricting claims of causality. The current study thus aimed to investigate the causal role of the ilPFC in the balance of goal-directed vs. habitual behavioral control by using neuronavigated Theta Burst Stimulation.

**Methods:** In this study, we tested 48 healthy, right-handed participants (mean age ± SEM: 25.19 ± 0.43 years; 24 women) in a double-blind, sham-controlled between subject design using TBS. Exclusion criteria included contraindications for MRI and TMS, such as a history of epilepsy. Participants were randomly assigned to receive either (inhibitory) cTBS, (excitatory) iTBS, (sham) imTBS or no stimulation at all. For the stimulation groups, we located the individual position of the ilPFC in each participant using a previously acquired anatomical MR image and a neuronavigation system. The exact coordinates (MNI: x = 48, y = 35, z = -2) were chosen based on the location of the potential arbitrator reported in a previous study. Stimulation was delivered at 80% individual resting motor threshold using a 70mm figure-of-eight coil, following the standard protocol for TBS. After stimulation, participants completed an instrumental learning task (ILT), designed to differentially asses the employment of habitual vs. goal-directed behavioral control (de Wit et al., 2007; Gillan et al., 2011; de Wit et al., 2012b; de Wit et al., 2012a). This task consisted of three phases: an initial learning phase, a subsequent devaluation phase and the critical slips-of-action phase. In the learning phase, participants were asked to learn associations between discriminative cue stimuli (fruit pictures on top of a closed box), correct responses (pressing the left or right arrow key on a keyboard) and outcome stimuli (fruit pictures inside an open box) by trial and error. Importantly, associated fruit pairs belonged to one of three discrimination conditions: (I) standard, in which different fruits served as discriminative cue and outcome stimulus; (II) congruent, in which the outcome stimulus following a correct response was the same fruit as the discriminative stimulus and (III) incongruent, in which cue and outcome were different fruits but reversed their

roles for opposite responses (i.e. a banana cue leading to an strawberry outcome by pressing the left arrow key and a strawberry cue leading to a banana outcome by pressing the right arrow key). While congruent and incongruent trials are best learned by using simple S-R associations that are indicative for habitual behavior, learning in the standard trials can either be supported by S-R or more goal-directed S-O-R associations. In the following devaluation phase, participants were presented with two outcome stimuli one of which was marked as devalued by a superimposed red cross. Participants were asked to press the response button that they had learned to be associated with the still valuable outcome. In the critical slips-of-action phase, participants saw an overview of all previously encountered outcomes, two of which were devalued. Afterwards, participants were again presented with discriminative cue stimuli similar to the learning phase. They were instructed to press the correct response button but only if the associated outcome was still valuable as indicated by the initial overview. If the outcome was devalued, participants were told to refrain from pressing any button. If participants behaved in a goal-directed manner, they would adjust their behavior according to the changed outcome value. If they behaved habitually, they would respond according to the initially learnt associations regardless of value changes. After participants had completed the ILT, they filled in three questionnaires testing their explicit knowledge about the learned contingencies (S-R; S-O; O-R). To control for personality traits that could potentially influence our results, participants filled in several questionnaires before stimulation. In addition, all participants receiving TBS were familiarized with the ILT prior to stimulation to avoid potential TBS influences on task comprehension. Participants in the non-stimulation condition also received this training shortly before starting the ILT.

**Results:** Theta Burst Stimulation did not alter learning performance, as participants across all groups learned the associations equally well. As expected, learning in the difficult incongruent discrimination condition was worse than trials in the standard and especially in the congruent discrimination condition. The same pattern was seen in the devaluation phase. All groups performed equally well. Again, performance was best for trials with stimuli belonging to the congruent discrimination condition, followed by standard and then incongruent trials. In the slips-of-action phase, participants showed less slips (i.e. responses to stimuli associated with devalued outcomes) for trials belonging to the congruent discrimination condition compared to both the standard and the incongruent

discrimination condition. Importantly, participants in the cTBS condition were much more likely to show slips, indicating less goal-directed behavior in this group compared to all other experimental groups, which did not differ (Fig. 5). Interestingly, this increase in slips in the cTBS group was specific to trials in the standard discrimination condition, the only trial type that could be under both habitual and goal-directed control. No TBS effects were observed for congruent or incongruent trials. There were also no group differences for the declarative knowledge about the learned contingencies. These results could not be explained by any personality traits or initial learning performance, as controlled by reanalyzing our data using mediation analysis and ANCOVA.

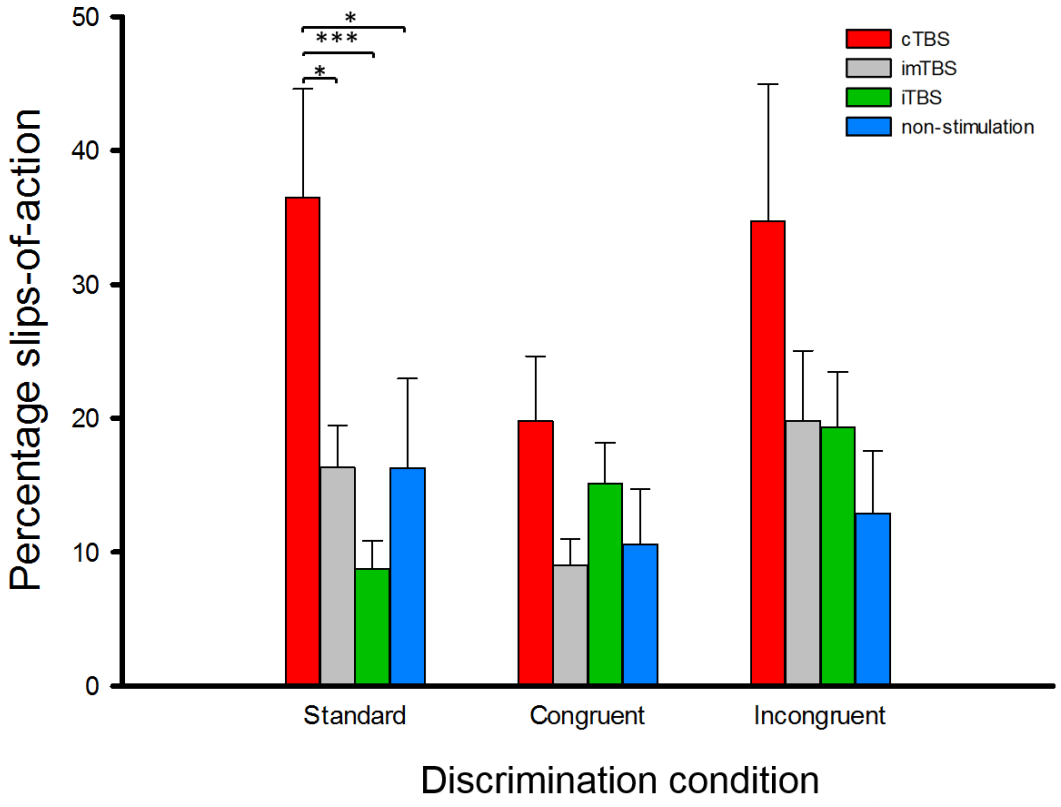


**Figure 5.** Performance in the slips-of-action phase in the Instrumental Learning Task (ILT). Inhibitory stimulation via continuous theta burst stimulation (cTBS) led to a significant increase in the percentage of slips-of-action compared to the sham intermediate (imTBS) and excitatory intermittent theta burst stimulation (iTBS) groups as well as compared to the non-stimulation group. Inhibition of the ilPFC favored the use of the habitual system, in particular in the standard discrimination condition that could be completed using either the habitual or the goal-directed system. Error bars indicate SEM. *p < 0.05. ***p < .001. Adapted from (Bogdanov et al., Submitted).

**Discussion:** Goal-directed and habitual behavior have been associated with distinct neural structures, namely the orbitofrontal cortex and dorsomedial striatum or caudate nucleus vs. the dorsolateral striatum or the putamen, respectively (Adams and Dickinson, 1981; Dickinson, 1985; Balleine and Dickinson, 1991; Valentin et al., 2007; Dolan and Dayan, 2013). How the brain allocates behavioral control to either one of these systems is not yet clear. Here, we used neuronavigated TBS to investigate the causal contribution of the ilPFC, a structure recently proposed to play a role in the balance of goal-directed vs. habitual behavior (Lee et al., 2014). Receiving inhibitory cTBS, participants showed considerably less goal-directed behavior in an instrumental learning task compared to those receiving excitatory, sham or no stimulation of the ilPFC.This was specifically seen in trials in which both goal-directed and habitual behavior could be used. These results indicate a critical role of the ilPFC in goal-directed behavior. Since this region is consistently associated with inhibition processes (Konishi et al., 1999; Aron et al., 2004; Hampshire et al., 2010), it is important to note that our results do not fit with the interpretation of altered inhibition. First of all, a general impairment in inhibition due to cTBS would have resulted in slips-of-action across all trial discrimination conditions, especially in those that were learned best and thus would be most difficult to suppress. This was not the case, as slips primarily appeared in standard and incongruent trial types that were learned worse than congruent trials which were mostly spared by slips. Second, cTBS selectively impaired associations in the standard discrimination condition, where both systems compete for control (de Wit et al., 2012a). In relation to previous findings, our results could also indicate a role of the ilPFC in the arbitration process between goal-directed and habitual control, possibly by interfering with its ability to downregulate the habitual system (Lee et al., 2014). This would also explain why we did not see an increase in goal-directed behavior after iTBS compared to the sham or non-stimulation groups. In this case, normal functioning of the ilPFC is sufficient to regulate the habit system, rendering the effects of additional excitation fruitless. Since performance was already close to optimum after sham or without stimulation, this seems rather likely.

## General discussion

Why do we always buy the same brand of orange juice and what do we do when it is sold out? Why do we constantly look in the wrong direction when crossing the street in a country in which people drive on the different side of the road? Why is it that we can walk into the kitchen to grab something and immediately forget what it was? Why does this happen more when we experience stress? In short, what factors determine how we act in a given situation? One of Psychology's fundamental questions, the mechanisms behind our brain's ability to enable adaptive adjustment of our behavior to environmental demands has attracted researchers from various backgrounds over the last decades (Dickinson, 1985; Evans, 2008; Rangel et al., 2008; Dolan and Dayan, 2013; Dayan and Berridge, 2014; O'Doherty et al., 2017). While some asked how experience shapes future behavior and how we react to changes in learned regularities, others were interested in how we ascribe values to different consequences of our behavior or how we protect our goals from distracting influences. Despite this diversity, recent integrative accounts postulate similar dual-process hypotheses of behavioral control, namely that adaptive behavior relies on a delicate balance of a stimulus-driven, efficient but slow to change habitual system depending on the dorsolateral striatum/putamen and a cognitively demanding, deliberative and flexible top-down system depending on the dorsomedial striatum/caudate nucleus, the hippocampus and prefrontal cortical structures (Dickinson, 1985; Balleine and O'Doherty, 2010; Daw et al., 2011; Delgado and Dickerson, 2012). Historically, research has emphasized the importance of the lPFC for complex cognitive control processes that allow us to act deliberately, overcoming reflexive and automatic tendencies arising from stimulus properties (Kane and Engle, 2002; Aron et al., 2004; Arnsten and Li, 2005; Buschman and Miller, 2007; Diamond, 2013). However, much of the existing evidence concerning the fundamental role of the lPFC in flexible behavioral control in human subjects stems from neuroimaging work, thus forbidding any causal interpretation. The studies presented in this thesis aimed to improve this situation and provide causal evidence for the role of lateral prefrontal structures in diverse forms of top-down modulation of behavior and its relation to the proposed balance of behavioral systems.

In the first study (Bogdanov et al., 2017), we probed the role of the dlPFC in a well-known bias in value-based decision-making, the sunk-cost effect (Arkes and Blumer, 1985;

Haller and Schwabe, 2014). Enhancing dlPFC activity by anodal tDCS led to a more pronounced sunk-cost bias. Participants were more likely to invest money in fictional projects with low expected values when they were asked to make a continuous investment compared to a first time investment. Prior studies have shown that the sunk-cost effect is associated with the social norm not to waste resources as well as decreased vmPFC activity and increased connectivity between vmPFC and dlPFC (Haller and Schwabe, 2014). Given that social norms are thought to be represented by the dlPFC and that the dlPFC is known to modulate the value signal computed by the vmPFC (Hare et al., 2009; Baumgartner et al., 2011), we argue that stimulation of the dlPFC intensified the social norm which in turn led to less optimal decisions due to an overreliance of this top-down influence. This implicates a causal role of the dlPFC in incorporating abstract rules into our choice behavior (Ruff et al., 2013).

In the second study, we aimed to investigate whether the dlPFC has a causal role in working memory deficits induced by acute psychosocial stress and whether these deficits might be ameliorated by transcranial stimulation (Bogdanov and Schwabe, 2016). Indeed, participants undergoing a stress manipulation showed impaired performance in two verbal and spatial working memory tasks, which is in line with many studies reporting similar impairments of prefrontal functions after stress. It is argued that acute stress leads to a shift away from more flexible top-down controlled behavior towards elevated reflective bottom-up processing, an effect that in our study was seemingly equalized by anodal tDCS. As non-stressed participants usually did not show any enhancement in their performance following dlPFC stimulation, it might be argued that optimal balance of top-down and bottom-up processes was in place and could not be improved further.

In the third study, we set out to more directly investigate the mechanism underlying the balance of goal-directed and habitual control (Bogdanov et al., Submitted). As recent data suggested that the right ilPFC might act as an arbitrator, allocating behavioral control to the system providing the most reliable state and reward predictions, we employed neuronavigated TBS to test this hypothesis (Lee et al., 2014). Using a task specifically designed to selectively probe both forms of behavior (de Wit et al., 2012b; de Wit et al., 2012a), we found that inhibiting the ilPFC via cTBS resulted in less goal-directed behavior than sham stimulation via imTBS or excitatory stimulation via iTBS. This study thus provided first evidence for a causal role of the ilPFC in the balance of the goal-

directed and habitual behavior. As the ilPFC has never been directly associated with goal-directed behavior (in terms of instrumental learning approaches), we argue that it is indeed possible that this structure functions as the postulated arbitrator.

Each of these studies provided novel insight into how the lPFC may modulate behavioral adjustment to environmental demands and top-down processes necessary for flexible behavior. In the following, I will integrate these findings with the broader literature, followed by a general discussion of limitations and implications of the presented research.

**Integration of findings**

Our findings further strengthen the proposed role of the lPFC in exerting top-down behavioral control, specifically in the incorporation of social norms, in stress-induced working memory impairments as well as in, potentially, allocating behavioral control to the system best suited to guide behavior in a given situation.

***Social norms: automatic or reflective?***

Complying with social norms is important for individuals in order to interact with society in an unproblematic way. Respecting these norms when deciding how to act is thus usually regarded to be a form of top-down control, allowing us to flexibly adjust behavior to what is currently expected instead of what might maximize our own gain. In order to be effective, a social norm would arguably require to be retrieved in a fitting context and represented in working memory before it can modulate decision-making by lowering the intrinsic value of norm-violating options. However, as demonstrated by an increased sunk-cost effect in our study, this top-down influence is not always beneficial. While not wasting resources might be a good rule to follow in general, in this particular study, as well as in many real life situations, individuals would have been better off by not considering prior investments (Arkes and Blumer, 1985; Strube, 1988). Nevertheless, participants stuck to the norm, even more so when receiving excitatory stimulation of the dlPFC. This seemingly contrasts the notion that prefrontal top-down control results in better or more adaptive behavior. Instead, it rather seems to imply cognitive inflexibility of the participants' behavior, neglecting the goal to maximize profit in the task and thus resembling more habitual behavior. Indeed, there is research suggesting that social norm

compliance can be automatic and without deliberate thought (Aarts and Dijksterhuis, 2003; DeBono et al., 2011). Social norms are not innate, we learn to act accordingly by life-long reinforcement learning, being rewarded for compliance and punished for non-compliance by parents, teachers or the law. Thus, a certain context reliably associated with a social norm might elicit an automatic, norm-compliant response, such as speaking in whisper tone once entering a library (Aarts and Dijksterhuis, 2003) or not crossing the street at a red light signal, even though there is no car in sight. In our study, having already invested money in a project before could have thus automatically triggered the norm-compliant behavior of further investing money.

This line of thought may also fit with the concept of bounded rationality, as social norms might act as cognitive shortcuts or heuristics and might present a simplified decision rule that stops further investigation of alternative options to prevent complex and unnecessarily effortful calculations (Gigerenzer and Selten, 2002). Both of these mechanisms can generally be deemed adaptive, as they free cognitive resources and likely lead to adequate results in most situations. There are, however, some points arguing against a purely automatic influence of such norms on behavior. First, not all social norms are encountered so frequently and reinforced so consistently that automatization can occur. Second, compliance to more abstract social norms might not require a very specific, well-defined response but instead a precise adjustment to the current environment. Third, habitual behavior as investigated in reinforcement learning has been primarily associated with dopaminergic signals arising from the striatum, yet social norms exert their influence via the dlPFC, as shown in our own study as well in work of others (Ruff et al., 2013; Haller and Schwabe, 2014; Buckholtz, 2015; Bogdanov et al., 2017). As an alternative explanation, one could thus imagine that social norms might be automatically recalled and activated in a given context but depending on the complexity and familiarity of the current situation, flexible behavioral adjustment is needed to comply with the norm, which in turn requires deliberate top-down modulation of the value of behavioral alternatives. For the sunk-cost effect, this process might lead to more or less pronounced consideration of prior investments, depending on the subjective value an individual ascribes to norm-compliant behavior.

***The value of norm violation***

Although norm incorporation leads to more "irrational" decisions in our particular task, weighting social norms against the potentially highly valuable outcome of a decision is crucial for adaptive behavior in our society. Failure to comply with these norms may lead to deviant behavior, resulting in conviction and exclusion from society. Given these aversive consequences, why do some individuals violate these norms? A popular model of non-compliance with social norms conceptualizes antisocial behavior as a result of impaired prefrontal cognitive control, particularly impaired response inhibition. In line with this idea, studies found the reduced gray matter volume and cortical thickness in the dlPFC of antisocial individuals (Yang and Raine, 2009; Dolan, 2012). In addition to altered dlPFC activity in response inhibition tasks, antisocial individuals interestingly also show increased amygdalar and striatal activation after the presentation of threat or reward stimuli, respectively (Blair, 2004; Coccaro et al., 2007; Yang and Raine, 2009; Buckholtz et al., 2010; Hyde et al., 2014). This implicates an important role of affective processing in norm-violation behavior. Indeed, emotions have been shown to have a significant impact on decision-making as well as cognitive control processes (Bechara et al., 2003; Gray, 2004; Ochsner and Gross, 2005; Pessoa, 2008; Inzlicht et al., 2015). For example, emotions have been proposed to work as a domain specific stopping rule in the framework of bounded rationality, preventing the search for alternative behavioral options (Gigerenzer and Selten, 2002). The amygdala has been implicated in learning and predicting positive and negative outcomes, in extracting relevant emotional information from contextual cues and in biasing choices, for example due to its role in loss aversion (De Martino et al., 2006; Paton et al., 2006). Incorporating affective information in balancing behavioral control might be necessary to accurately predict emotional consequences of our actions. This concept has recently been integrated into the framework of model-free and model-based control, shifting the focus away from the specific process of response inhibition and emphasizing more general prefrontal modulation of (ventral) striatal value signals (Buckholtz, 2015). According to this idea, the context, the societal rules, as well as the prospective value associated with the compliance with social norms are represented in a model of our environment that modulates the influence of previously learned action-reward associations. Antisocial behavior thus might occur due to insufficient top-down control of affective stimuli or

stimulus associated reward (e.g. when the positive affect for non-compliant behavior outweighs the value of the potentially negative consequences of said behavior).

***Stress-induced PFC impairment and flexible cognition***

More direct evidence for detrimental consequences following insufficient or disrupted top-down regulation of decision-making processes potentially comes from studies investigating the effects of psychosocial stress on choice behavior (Porcelli and Delgado, 2009; Starcke and Brand, 2012; van den Bos et al., 2013; Buchanan and Preston, 2014; Gathmann et al., 2014; Kluen et al., 2017; Lenow et al., 2017; Porcelli and Delgado, 2017). Specifically, stress impacts the valuation process and accordingly affects neural activity in associated regions, such as the OFC and the vmPFC as well as the striatum and the amygdala (Ossewaarde et al., 2011; Porcelli et al., 2012). Interestingly, reward related activity in the striatum and the amygdala has been shown to be increased shortly after stress (Kumar et al., 2014). This might lead to a stress-induced overestimation of reward value due to a lack of top-down regulation (possibly due to the lPFC) of these structures which might in turn result in favoring less optimal or more risky choice options. Unfortunately however, there are still many open questions regarding the exact effects of stress on decision-making processes, as studies differ significantly in several methodological aspects, including methods of stress induction, stress-to-task latency and decision phase (e.g. anticipatory or receipt phase; Porcelli and Delgado, 2017). In contrast, stress effects on lPFC functions proved to be more consistent, as many studies report a detrimental impact of acute stress on top-down executive control and a general decrease in prefrontal brain activity (Arnsten and Li, 2005; de Kloet et al., 2005; Arnsten, 2009; McEwen and Morrison, 2013; Shansky and Lipps, 2013). These mechanism are thought to be adaptive, enabling us to react to potential threats in the environment as fast as possible, efficiently processing relevant incoming (bottom-up) information without wasting cognitive resources on slow, top-down control (van Marle et al., 2009; Hermans et al., 2011; Hermans et al., 2014). Our findings of decreased working memory performance after stress thus fit well with earlier studies reporting similar results, including stress-induced deficits in complex tasks, such as n-back (Schoofs et al., 2008; Qin et al., 2009; Gärtner et al., 2014) or Sternberg paradigms (Oei et al., 2006), as well as simpler span tasks (Elzinga and Roelofs, 2005; Schoofs et al., 2009), although there is

evidence that these effects are more pronounced for tasks requiring high working memory load or manipulation of information instead of pure maintenance (Oei et al., 2006; Schoofs et al., 2009; Shields et al., 2016). Interestingly, working memory has been proposed to play a central role in successfully employing model-based behavior (Collins and Frank, 2012; Otto et al., 2013b). While not many studies have yet investigated stress effects specifically in the framework of model-based and model-free behavior, first evidence implies that acute stress hampers with model-based behavior while leaving model-free contributions intact, an effect that is mimicked by depleting working memory capacity (Otto et al., 2013a; Otto et al., 2014; Radenbach et al., 2015). Interestingly, the stress effects seem to be less pronounced in individuals with high working memory capacity, indicating a protective effect (Otto et al., 2013b). These findings are in line with evidence for a more general stress-induced impairment in flexible cognition. In studies using outcome devaluation and contingency degradation, i.e. canonical tests to probe goal-directed and habitual behavior, participants become insensitive to changes in outcome value, rendering behavior more habitual after stress (Schwabe and Wolf, 2009, 2010a; Dolan and Dayan, 2013; Fournier et al., 2017). A similar shift from flexible to more rigid forms of behavior has been reported for probabilistic classification learning and spatial navigation tasks, with participants relying less on declarative strategies and allocentric cognitive maps and instead preferably use non-declarative and egocentric S-R associations, respectively (Kim et al., 2001; Schwabe et al., 2007; Schwabe and Wolf, 2012; Schwabe et al., 2013b; Vogel et al., 2017; Wirz et al., 2017). Again, these stress-effects seem to be mostly mediated by concurrent actions of noradrenalin and glucocorticoids in the basolateral amygdala (Wirz et al., 2018). Following amygdala activation after stress, structures implicated in goal-directed or model-based behavior such as the hippocampus, the caudate nucleus and the prefrontal cortex are decreased in activity, resulting in a shift in behavioral control in favor of the dorsal striatum/putamen. However, in order to understand exactly how stress induces this shift, it is important to investigate how both systems communicate under normal, non-stressful conditions.

***Communication between behavioral control systems***

Research in model-based and model-free learning and memory proposed an arbitration mechanism that may allocate control to either system (Daw et al., 2005; Wunderlich et al., 2012; Lee et al., 2014). As the ilPFC has recently been implied to play an important role in the arbitration process, we targeted this region in our third study (Lee et al., 2014). We, indeed, found that inhibition of the right ilPFC led to decreased goal-directed behavior. Interestingly, the arbitration process in the ilPFC has been described as asymmetrical, possibly downregulating the model-free system when the model-based system is deemed to be more reliable (Daw et al., 2005). Otherwise, the model-free system would be favored as its computations are more efficient. This idea would fit with theoretical accounts claiming that much of our daily behavior happens automatically and without much deliberate thought (Kahneman, 2003a). It also fits with the idea that, in animals and humans, newly learned actions initially depend more on prefrontal control, gradually shifting towards the striatum with continuous training (Adams, 1982; Coutureau and Killcross, 2003; Tricomi et al., 2009). As antisocial individuals seem to be impaired in tasks requiring response inhibition (Dolan, 2012), a process strongly associated with the ilPFC (Aron et al., 2014), it also seems possible that failure to comply with social norms might occur due to a disturbed arbitration mechanism. This might also explain the reported stress-induced shift towards habitual or model-free behavior, as stress heavily affects the lPFC (de Kloet et al., 2005; McEwen and Morrison, 2013). The model-based or goal-directed system and the model-free or habitual system have usually been thought of as two distinct and, most importantly, competing systems (Daw et al., 2005). On a biological level, they were seen as manifestations of an outcome related value signal represented by the vmPFC and a dopaminergic (temporal difference) reward prediction error represented by the ventral striatum, respectively (Gläscher et al., 2010; Lee et al., 2014; Otto et al., 2014; Gillan et al., 2015). Arbitration between the systems has been described as a multi-level computation process. Specifically, the model-based system is thought to acquire state-action-state-transition probabilities using a state-prediction-error, while the model-free system tracks the difference between actual and expected reward using a reward-prediction-error. Both prediction errors would then enter a weighted competition to determine which system is granted control. While it has long been assumed that the contributions of both systems to this competition are

independent, recent studies have also consistently found cooperative integration (Daw et al., 2011; Doll et al., 2012). In fact, both the striatal dopaminergic reward prediction error and the reward signal in the vmPFC code model-based as well as model-free signals (Daw et al., 2011). Thus, independent of which system is granted control in an individual trial, prediction errors fed forward to the next trials will contain information from both systems. This cooperation approach probably captures the biological reality of the heavily interconnected brain regions supporting both systems much better than a simpler all or nothing approach. A recent study presented evidence for a habitual-goal-directed spectrum by showing that both strategies can be used to varying degrees to solve a multi-step-decision task, depending on whether the task allows for longer deliberation or not (Keramati et al., 2016). Considering this more nuanced interplay between the systems, it is not surprising that disrupting ilPFC activation via TBS, goal-directed behavior in our study was not abolished completely but merely reduced.

Taken together, our results confirm the importance of the ilPFC in top-down modulation of behavior. They add to the existing literature by providing causal evidence for the role of the lPFC in decision-making processes, in stress-induced working memory deficits and in the allocation of goal-directed behavioral control.

**Limitations**

While the studies presented in this thesis provide valuable insight into the causal contributions of the lPFC to flexible cognition, there are some shortcomings to the approach of transcranial brain stimulation that need to be addressed. We used tDCS to investigate the role of the dlPFC in the sunk-cost effect and working memory impairments following acute stress. Compared to TMS the spatial specificity of tDCS is rather low (Nitsche et al., 2008; Sparing and Mottaghy, 2008; Sellaro et al., 2017). In fact, the electrodes used for tDCS are quite large with usual sizes ranging from 25cm² to 100cm². This indeed makes it impossible to specifically target specific areas of the cortex. For our studies, we thus chose a small electrode (25cm²) over the area of interest, the dlPFC. Although the dlPFC is a rather large structure, we cannot exclude that the stimulation might have affected adjacent areas lying inferior or posterior to the dlPFC. However, as the literature suggests that the dlPFC plays a central role in both working memory processes and the representation of social norms, we argue that the observed effects

most likely occur due to manipulation of dlPFC activity (Sanfey et al., 2003; Baumgartner et al., 2011; Barbey et al., 2013; Ruff et al., 2013; D'Esposito and Postle, 2015). A second common criticism directed at tDCS is that it is not clear how much of the applied current actually reaches the brain after permeating the participants' hair, skin, skull, meninges and liquor (Nathan et al., 1993). Attempts to model the current distribution computationally suggest that even under optimized electrode set ups more than half of the initial current is lost by shunting (Miranda et al., 2006). However, over the last decade, a respectable number of studies using tDCS to stimulate the dlPFC have reported behavioral effects (Fregni et al., 2005; Boggio et al., 2006a; Andrews et al., 2011; Zaehle et al., 2011; Ruff et al., 2013; Harty et al., 2014b; Weber et al., 2014; Zmigrod et al., 2014; Zwissler et al., 2014; Axelrod et al., 2015; Pope et al., 2015). It is thus reasonable to assume that at least some fraction of the current reached the brain in our studies, resulting in the observed effects. A final criticism of tDCS is that, as it uses two electrodes for stimulation, effects could potentially arise due to altered brain activity either at the location of the reference electrode or at structures affected by the current flow. To minimize these unwanted effects, we used a large electrode (100cm²) to serve as the reference. In this way, current density over the reference position was very low, rendering it functionally ineffective (Nitsche et al., 2008). At the same time, current density over the dlPFC was far higher, making effects of stimulation at this position much more likely. It is also unlikely that effects occurred due to stimulation of structures affected by the current flow, as computational modelling approaches show that current density is highest directly under the electrodes, decreasing with an increase in distance between them (Miranda et al., 2006). It should also be stated that some tDCS studies do not find stimulation induced effects (Horvath et al., 2015). In fact, in our working memory study, we too did not find an increase in working memory performance after anodal tDCS in non-stressed participants, an effect repeatedly reported in healthy participants (Fregni et al., 2005; Andrews et al., 2011; Brunoni and Vanderhasselt, 2014). This discrepancy compared to other studies might be explained by differences in stimulation parameters across studies, such as electrode placement (e.g. placing the reference electrode on the ipsi- or contralateral hemisphere), electrode size and current intensity that determine current density at the cortical area of interest as well as the size of the electric field and the depth of stimulation (Nitsche et al., 2008; Sellaro et al., 2017). In addition, we did not

find any effects of cathodal stimulation. This is less surprising, however, as cathodal tDCS effects seem to be far less consistent and may be more task-dependent than effects of anodal tDCS (Kincses et al., 2004; Marshall et al., 2005; Sparing et al., 2008; Jacobson et al., 2012).

While the stimulation target in our first two studies was relatively large, stimulation of the ilPFC in the third study required much more precision. Thus, we used a neuronavigated TBS approach. Depending on the exact protocol, TBS has been shown to successfully modulate neural excitability (Huang et al., 2005; Wischnewski and Schutter, 2015). However, the specific parameters of these protocols have been established in studies on the motor cortex where stimulation effects can be more easily quantified by observable changes in MEPs. It is still under debate whether these findings can be easily transferred to stimulation of brain regions other than the motor cortex. Nonetheless, more and more studies use a TBS approach on frontal brain regions (Grossheinrich et al., 2009; Rounis et al., 2010; Verbruggen et al., 2010; Ott et al., 2011). In contrast to tDCS, it is unlikely that TBS directly interfered with activity of brain regions adjacent to the ilPFC due to its specificity. However, since prefrontal structures are heavily interconnected, we cannot exclude that he observed effects might have occurred due to activation in regions connected to the ilPFC. Additionally, after-effects of TBS have to be considered. As we chose offline stimulation before task administration, we cannot be entirely sure that stimulation effects on the ilPFC remained throughout the task. Although TBS after-effects on MEPs have been shown to last for at least half an hour (Huang et al., 2005; Gamboa et al., 2011; Wischnewski and Schutter, 2015), there is no clear evidence yet for the possible duration of these effects on prefrontal structures (Grossheinrich et al., 2009). Finally, addressing a more ethical point, TMS innervates cells in all tissues located under the coil, resulting in participants usually experiencing more unpleasant sensations compared to tDCS. This is especially true at higher intensities and if stimulation is applied to prefrontal regions, where TMS affects face muscles, resulting in involuntary muscle contractions. Due to its more direct interference with cell activity, TMS also poses a bigger risk for inducing epileptic seizures (Grossheinrich et al., 2009; Rossi et al., 2009). As brain stimulation techniques remain to gain interest as a non-invasive measure to investigate causal contributions of cortical structures to cognition, many of these shortcomings will

get addressed. Our findings contribute to this process by demonstrating the usefulness of tDCS and TBS in neuroscientific research.

**Implications for future research**

The studies presented in this thesis add to the quickly growing literature on the neural mechanisms underlying flexible cognition and highlight the importance of the lPFC in this context. The ability to flexibly and adaptively adjust behavior to current environmental demands has traditionally been investigated in distinct research traditions using various paradigms (Dickinson, 1985; Robbins et al., 1996; Balleine and O'Doherty, 2010; O'Doherty et al., 2017). Recent approaches such as the field of neuroeconomics aim to integrate these diverse takes on learning, memory and decision-making by acknowledging the close link between these processes (Rangel et al., 2008). After all, our current choices heavily depend on our past experiences and every new decision made can be evaluated and used to guide behavior in the future. This dependency is not limited to complex real-life scenarios but also affects laboratory experiments. It is thus important that future studies further acknowledge the interplay between all subprocesses that enable flexible cognition on the behavioral as well as on the neural level. For example, despite being broader than earlier concepts, the idea of model-based/model-free behavior is still based primarily on reinforcement learning theory (Sutton and Barto, 1998; Daw et al., 2005). But how do other forms of learning and memory, such as observational learning and episodic memory, influence our choices? Are emotions beneficial or detrimental to model-based or goal-directed behavior? What are the distinct contributions of different top-down-processes to flexible behavior and how do we solve conflicts arising from these processes (e.g. when social norms stand against our own benefits)? Current research already tackles some of these questions. For example, the hippocampus, well known for its role in episodic memory and spatial navigation, has been recently proposed to be more directly involved in value-based decision making due to its abilities to update (Gupta et al., 2009; Rubin et al., 2014) and generalize associative memories (Wimmer and Shohamy, 2012; Gerraty et al., 2014; Gilboa et al., 2014; Wimmer et al., 2014) as well as to construct future episodes mentally (Johnson et al., 2007; Barron et al., 2013; Miller et al., 2017; for a review, see: Palombo et al., 2015). This is in line with the intuitive idea that choices do not depend solely on conditioning

processes but can be also supported by more declarative and episodic memory systems (Murty et al., 2016). A recent study found that model-based signals but not ventral striatal dependent model-free signals are involved in observational learning (Dunne et al., 2016). Does this mean that habitual behavior will never occur after mere observation of behavior, even if repeated abundantly? How do observational and self-experienced reinforcement learning interact? There is evidence that observational learning is guided by observational action and outcome prediction errors represented in the dlPFC and vmPFC respectively (Burke et al., 2010), pointing to the prefrontal cortex as a possible integration structure. As mentioned earlier, the amygdala is known to bias decision-making (Bechara et al., 1999; Bechara et al., 2003; De Martino et al., 2006; Hampton et al., 2007). While, in classical economic theory, affective contributions to our decisions might have been labeled as irrational, more contemporary accounts picture emotions as beneficial to guiding choice, for example by ascribing positive value to certain goals (Perugini and Bagozzi, 2001; Seymour and Dolan, 2008). In accordance with this idea, it has also been proposed that the amygdala codes the value of choosing a certain option and maintains this value representation over time until the chosen behavioral option is concluded (Zangemeister et al., 2016). However, it is not clear whether this influence can be considered to purely represent stimulus-driven or top-down modulation of behavior. Recent work tries to classify emotion regulation strategies as either model-based or model-free, which might help to understand amygdalar contributions to both systems (Etkin et al., 2015). Finally, the relation between these processes and prefrontal functions in goal-directed or model-based learning needs to be investigated more closely. For example, a recent conceptualization, suggests that the lPFC is involved in forming a cognitive map, providing an abstract contextual representation of higher-order task structures, possibly by coding state prediction errors (Gläscher et al., 2010; Pan et al., 2014; O'Doherty et al., 2017). These abstract maps might as well include information about the social context. Due to its numerous anatomical connections (Goldman-Rakic et al., 1984; Selemon and Goldman-Rakic, 1985; McDonald et al., 1996; Fuster, 2001; Longe et al., 2010), the lPFC is perfectly positioned to integrate this vast amount of information, to guide behavior by top-down processes and to delegate control to the habitual/model-free or goal-directed/model-based system.

As the contributions of these individual brain areas to flexible cognition have become clearer over time, the vast number of processes involved require future research to target the underlying neural network interactions that enable the integration of these processes. A very promising approach to tackle these interactions lies in combining brain stimulation and neuroimaging techniques. In this way, it is possible to causally manipulate brain processes and to simultaneously monitor stimulation effects at the stimulation site as well as in projection areas. As we could show that stress-induced working memory impairments can be ameliorated by prefrontal brain stimulation, it would be particularly interesting to test, whether lPFC-stimulation might also prevent shifts from flexible to rigid behavior following stress in different paradigms. However, while they are perfectly suited to stimulate superficial cortical areas, non-invasive brain stimulation such as tDCS, tACS and TMS cannot be used to stimulate structures more deeply in the brain. Even cortical areas such as the vmPFC are presumably out of reach for these techniques without increasing the risk for potentially harmful side effects of the stimulation (although some researchers have used rTMS for vmPFC stimulation (Lev-Ran et al., 2012). While a possible approach in theory, stimulation of the hippocampus, the amygdala or the striatum via deep brain stimulation (DBS) presents no practical alternative for research in healthy human individuals, due to its invasive nature. Thus, manipulation of these deeper structures in humans is still restricted to pharmacological interventions or paradigms known to influence activity in these regions such as induction of psychosocial stress. As these kinds of manipulation never affect one particular structure in isolation, it is even more important to take network interactions into account, ideally by combining these approaches with neuroimaging. Only by understanding the communication between all systems involved in adjusting behavior to our needs will we be able to answer questions of how subprocesses such as working memory might modulate behavioral control or how signals from all of these systems are integrated into one value that guides our decisions.

A second important aspect in understanding flexible cognition are individual differences in personality traits and general intelligence. Participants may show great diversity in many variables that might influence their learning and decision processes. For example, people might find it more valuable to end an exhausting experiment sooner than receiving the highest possible monetary reward, thus pressing buttons as fast as

possible instead of doing the task properly. Similarly, avoiding stimulus material that induces negative affect might be more valuable than a supposedly rewarding consequence following a response to it. Although this behavior would not be deemed goal-directed with respect to our experiment, it is very well so for the participant. These difference also affect real life behavior. For example, some people might choose to pursue a career in a high paid job, not allowing for much leisure time, while other people will choose freedom over money, settling for a less time consuming workspace. Indeed, there seems to be a close relation between personality traits, such as impulsivity and the way participants behave more flexible or habitual (Hogarth et al., 2012). On the other side, executive functions have been proposed to play a major role in general intelligence (Kane and Engle, 2002; Conway et al., 2003). It might thus be interesting to test, whether more intelligent participants would act more goal-directed in general and whether detrimental influences such as stress are less likely to cause a switch in these individuals (as has been shown for greater working memory capacity (Otto et al., 2013b). In this context, it would also be very interesting to investigate the role of dopamine. Dopamine has been associated with both personality traits, such as extraversion (Depue and Collins, 1999; Wacker et al., 2006) and fluid intelligence (Previc, 1999) and its secretion is heavily influenced by stress (Vaessen et al., 2015). In addition, the activity of both the striatum and the lPFC is significantly modulated by dopaminergic innervation (Arnsten, 1997; Smith and Kieval, 2000; Seamans and Yang, 2004; Haber and Knutson, 2010). Disentangling the differential contributions of dopamine to the interplay of these functions might thus lead to profound progress in our understanding of how the PFC shapes our behavior and it might also improve our knowledge about (and consequently the treatment of) dopamine associated disorders, such as schizophrenia.

A more theoretical question that needs to be answered in future studies is whether the relation between more flexible and more rigid behavior is best categorized as two competing systems, two cooperating systems or maybe even as more than just two systems closely interacting to guide behavior. As described earlier, model-free or habitual behavior is primarily associated with the ventral striatum and the putamen, while model-based signals have been found arising from many distributed structures that contribute in many different ways to support goal-directed behavior (Doll et al., 2012;

O'Doherty et al., 2017). Merging these diverse processes into a universal construct of "flexible cognition" might thus be too reductive.

Finally, on a more technical note, while our studies employed brain stimulation to investigate prefrontal contributions to flexible cognition, we also made the more general point that tDCS and TMS may indeed modulate prefrontal activity and even ameliorate stress-induced deficits. As many psychiatric disorders and stress related conditions are characterized by symptoms indicating an imbalance between more goal-directed and more habitual behavior (Gillan et al., 2011; Everitt and Robbins, 2016), brain stimulation might present a useful tool for therapeutic application. Indeed, there are already several studies showing positive results in psychiatric and neurological conditions, such as depression or stroke (Hummel et al., 2005; Hummel and Cohen, 2006; Kuo et al., 2014). Future research should further examine the potential of NIBS for treatment.

## Concluding remarks

The American psychologist G. Stanley Hall once wrote "Man is largely a creature of habit, and many of his activities are more or less automatic reflexes from the stimuli of his environment" (Hall, 1916). While a great portion of our behavior is indeed automatic and reflexive, our brain undoubtedly provides us with a lot of processes tailored to flexibly guide our behavior. Studies spanning several decades and research traditions have shed light on how these processes work and how they are implemented in the brain. To this day however, much evidence in humans is based on neuroimaging data, not suitable to investigate causal contributions. By using NIBS, the work presented in this thesis improves that situation and thus adds to a broader understanding of the role of the lPFC in modulating the balance of flexible, goal-directed behavior and more rigid, habitual behavior. Science works slowly but steadily and although these findings may only provide another small advance in the long quest to answer one of psychology's biggest questions, I hope they prove to be a step towards a greater goal.

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# Appendix A

Study 1: Transcranial Stimulation Over the Dorsolateral Prefrontal Cortex Increases the Impact of Past Expenses on Decision-Making

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ORIGINAL ARTICLE

# Transcranial Stimulation Over the Dorsolateral Prefrontal Cortex Increases the Impact of Past Expenses on Decision-Making

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## Abstract

Goal-directed choices should be guided by the expected value of the available options. However, people are often influenced by past costs in their decisions, thus succumbing to a bias known as the "sunk-cost effect." Recent functional magnetic resonance imaging data show that the sunk-cost effect is associated with increased activity in dorsolateral prefrontal cortex (dlPFC) and altered crosstalk of the dlPFC with other prefrontal areas. Are these correlated neural processes causally involved in the sunk-cost effect? Here, we employed transcranial direct current stimulation (tDCS) to examine the role of the dlPFC for biasing choices in line with the cost of past expenses. Specifically, we applied different types of tDCS over the right dlPFC while participants performed an investment task designed to assess the impact of past investments on current choices. Our results show a pronounced sunk-cost effect that was significantly increased by anodal tDCS, but left unaltered by cathodal or sham stimulation. Importantly, choices were not affected by stimulation when no prior investments had been made, underlining the specificity of the obtained effect. Our findings suggest a critical role of the dlPFC in the sunk-cost effect and thus elucidate neural mechanisms by which past investments may influence current decision-making.

**Key words:** brain stimulation, dlPFC, sunk-cost effect, tDCS, value-based decision-making

## Introduction

According to traditional economic theory, humans should base their decisions on the expected future value of the choice-relevant objects, investments, or experiences (Edwards 1954; Frank and Bernanke 2006; Cabantous and Gond 2011). Choices in everyday life, however, are often not that rational and smart (Tversky and Kahneman 1974; Samuelson and Zeckhauser 1988; Kahneman et al. 1991; Shafir et al. 1993). In particular, when people have invested time, money, or effort into an option, they are often reluctant to abandon it even though its expected value is not favorable anymore. This tendency to consider past costs that cannot be recovered in current decision-making is referred to as the "sunk-cost effect" (Arkes and Blumer 1985). The sunk-cost effect has been demonstrated in numerous studies (Garland 1990; Arkes and Hutzel 2000; van Putten et al. 2010) and it is among the most consequential biases in human decision-making: It can explain why people remain in a failing relationship (Strube 1988) or why they are unable to leave a dissatisfying job (Arkes and Blumer 1985), it may push up prices in auctions (Murnighan 2002), drive wars, or keep failing policies alive (Staw 1976).

The past decade has seen significant progress in our understanding of the neurobiological underpinnings of human decision-making (Gold and Shadlen 2007; Kable and Glimcher 2007; Rangel et al. 2008; Hare et al. 2009; Rushworth et al. 2011; Delgado and Dickerson 2012; Ruff and Fehr 2014). A large network of interconnected areas has been implicated in decision-making,

including the amygdala, the anterior cingulate cortex, the parietal cortex, and the ventral striatum (Bechara et al. 1999; Sanfey et al. 2003; De Martino et al. 2006; Kennerley et al. 2006; Leotti and Delgado 2014). For the representation of the expected value of an option, which lies at the heart of rational decision-making, the orbitofrontal cortex and the ventromedial prefrontal cortex (vmPFC) have been identified as crucial neural components (Kable and Glimcher 2007; Grabenhorst and Rolls 2011; Jocham et al. 2012). A recent study provided first insights into the neural signature of the sunk-cost effect (Haller and Schwabe 2014). This study showed that prior investments reduce the activity of the vmPFC during subsequent decisions and that this reduction in vmPFC activity correlates with the magnitude of the sunk-cost effect. Moreover, in line with previous behavioral studies (Arkes and Ayton 1999), the sunk-cost tendency was associated with the norm not to be wasteful. Social norms are thought to be represented in the dorsolateral prefrontal cortex (dlPFC; Sanfey et al. 2003; Baumgartner et al. 2011), and several aspects of the data were consistent with this: First, the norm not to waste resources correlated with the activity of the right dlPFC, and second, the right dlPFC showed increased connectivity with the vmPFC when participants had already made an investment into a certain course of action, compared with when not. Thus, these data suggest a model for the neural origins of the sunk-cost effect in which the dlPFC, representing the norm not to waste resources, is activated once an investment has been made and overrides the vmPFC, thus hampering rational choices based on expected values.

One obvious weakness of the model proposed above is that it is based solely on functional magnetic resonance imaging (fMRI) data, which are correlational by nature and therefore not informative about causal relationships between brain activity and behavior. To formally test for such a causal relationship, we employed transcranial direct current stimulation (tDCS), a method for noninvasive stimulation of the human brain by means of weak electric currents (Nitsche and Paulus 2000) that has already successfully been used for demonstrating the involvement of a brain area in decision-making processes (Fregni et al. 2005; Ruff et al. 2013; Davis et al. 2014). In the present study, we examined how tDCS applied over the dlPFC affects the biasing influence of past, irrecoverable costs on current decision-making. To this end, participants performed an investment task that was recently introduced to examine the sunk-cost effect (Haller and Schwabe 2014). While participants performed this task, we applied anodal, cathodal, or sham stimulation over the right dlPFC, as our previous fMRI data showed that, in particular, the activity of the right dlPFC was linked to the sunk-cost effect (Haller and Schwabe 2014). Anodal and cathodal tDCS are known to increase or decrease the resting potential and therefore neural excitability in the targeted regions, respectively (Nitsche and Paulus 2000), whereas sham tDCS mimics the peripheral effects (i.e., tactile sensations) associated with tDCS while not affecting neural processing (Nitsche et al. 2008). We therefore expected that anodal stimulation over the dlPFC would increase dlPFC activity (and possibly other connected areas), thereby enhancing the impact of previous investments on decision-making compared with sham stimulation, whereas cathodal stimulation might even have the opposite effect of reducing the sunk-cost effect.

## Materials and Methods

### Participants and Experimental Design

Sixty healthy men and women between 18 and 32 years of age participated in this experiment (mean age ± SEM: 24.9 ± 3.6 years; 30 women). Exclusion criteria for participation were checked in a standardized interview prior to testing and comprised current illness, medication intake, a life-time history of any neurological disorders, as well as any contraindications for tDCS. Participants gave written informed consent before the start of testing and received a compensation of 12 Euros plus what they won in the investment task at the end of the experiment. The study was approved by the ethics committee of the German Psychological Association (DGPs).

In a double-blind, sham-controlled, between-subject design, participants were randomly assigned to 1 of 3 stimulation conditions (10 men and 10 women per group): Anodal, cathodal, or sham stimulation of the dlPFC. The stimulation lasted for as long as the individual participant worked on the investment task but not longer than 30 min.

### Questionnaires

To control for personality traits and behavioral tendencies that are relevant within the context of the sunk-cost effect and decision-making in general, participants filled out several questionnaires at the beginning of the experiment. In particular, participants completed the German versions of the Behavioral Inhibition/Behavioral Activation System scales (BIS/BAS scales, Carver and White 1994), the NEO Five-Factor Inventory (NEO-FFI, McCrae and Costa 2004), the Barratt Impulsiveness Scale (BIS-15, Spinella 2007), and a short questionnaire that assessed the individual sunk-cost tendency and the desire not to appear wasteful (Haller and Schwabe 2014). The latter consists of 8 items that should be answered on a scale from 1 ("I do not agree") to 11 ("I completely agree"). Example items were "I finish a started project, no matter the cost" or "People who know me think I am wasteful." A sum score for both the sunk-cost tendency and the desire not to appear wasteful was calculated by summing up the scores for the 4 items of each scale.

### Investment Task

The sunk-cost effect was examined with a modified version of a recently developed investment task (Haller and Schwabe 2014) that was adapted to the time constraints associated with the safe use of tDCS. In total, participants performed 252 trials of this investment task (average duration: 28 min). On each of these trials, participants were presented with a project characterized by its costs and probability of success (Fig. 1). The costs were either low (0.20 or 0.25 cents) or high (0.60 or 0.65 cents). The probability of success was low (40%), medium (50%), or high (60%), and corresponded to the actual probability of success implemented in the program. These probabilities were chosen based on a pilot study, showing that probabilities that were higher than 60% or lower than 40% result in ceiling and floor effects, respectively (Haller and Schwabe 2014). Participants were instructed to decide whether or not they wanted to invest the indicated amount of money in the project, by pressing either the right or left arrow key on a keyboard. If the participants did not respond within 5 s or if they decided not to invest, the trial was aborted. If the participants decided to invest, they either received immediate feedback about the success of the project (as determined by the computer program based on the given probability), or they were informed that further investments would be necessary. If a second investment decision was required, participants were presented with the additional costs and the updated probability of success; again the costs could be low or high and the probability of success could be low, medium, or high. Participants had again

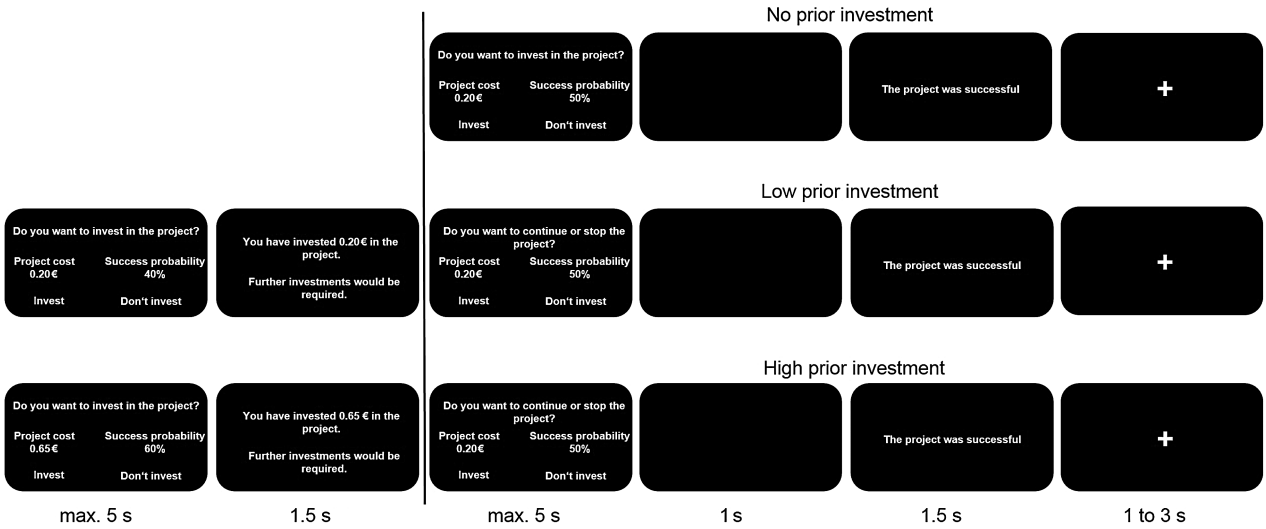


**Figure 1.** The investment task. On each trial, participants were presented with a project characterized by its costs (low vs. high) and its probability of success (low vs. medium vs. high). Participants were instructed to decide whether they want to invest the depicted costs in the project. If they decided to invest, they either received immediate feedback about the project's success (no prior investment trials) or were told that additional investments would be necessary (low and high prior investment trials). In the latter case, participants were presented with the additional costs and the updated probabilities of success for the project. The no, low, and high prior investment trials differed only in whether and how much participants had already invested in the project.

5 s to decide whether they wanted to invest the additional money in the project or whether they wished to abort it. Thus, the only difference between the first and second investment scenario was whether or not participants had already invested in the project. If participants decided to continue to invest, they were given immediate feedback about the success of the project, that is, there was a maximum of one follow-up investment.

For the initial investment trials, each of the 6 combinations of costs (low vs. high) and probability of success (low vs. medium vs. high) were presented 42 times (252 trials in total). In one-third of the trials, no second investment decision ensued ("no prior investment trials"). In the rest of the trials, participants were asked to decide whether they wanted to make a second investment required for the possible success of the project they had already invested in. This was done to ensure that there were sufficient trials to investigate the influence of past investments on current decisions. Trials in which a follow-up decision was required were subdivided into those in which the initial investment was low and those in which the initial investment was high ("low prior investment trials" and "high prior investment trials," respectively). Apart from the size of the previous investment (none, low, and high), the 3 types of trials were identical, as all possible costs × probability combinations were presented equally often in these trials. The different trial types were presented in a random order. Between trials, a fixation cross was presented for 1–3 s (random jitter: 2 s).

Critically, participants were told that they would gain 2 Euros for every project that was completed successfully, but that they would have to pay all investments made regardless of the success of a project. It was made clear that, in "prior investment trials," the probability of the first and second decisions was independent and that the initial investments were lost, irrespective of the follow-up decision. Participants were further instructed that the computer would randomly choose 10 trials at the end of the experiment and calculate their associated gains or losses. These would then be added to or subtracted from the participants' compensation. To make sure that participants fully understood the decision-making task, we asked them to repeat the essential features of the task after they had received the task instructions. Possible misconceptions were clarified. In particular, we emphasized that, in prior investment trials, the probabilities in the initial and follow-up decision scenarios are independent and that any initial investment is lost, irrespective of the follow-up decision.

## Transcranial Direct Current Stimulation

Brain stimulation was applied in a double-blind, sham-controlled manner using a Neuroconn stimulator (Neuroconn, Germany). In line with previous tDCS studies that focused on the dlPFC (Harty et al. 2014; Zwissler et al. 2014; Axelrod et al. 2015; Pope et al. 2015), we used an EEG cap and the standard 10–20 system to determine electrode positions individually for each participant. The smaller electrode (5 × 5 cm) was positioned over the right dlPFC (position F4). The larger electrode (10 × 10 cm), which served as a reference (Nitsche et al. 2007), was fixed centrally on the head (position CZ according to the EEG 10–20 system). Different electrode sizes were chosen so that a higher, functionally more effective current density was applied over the dlPFC (the area of interest) than over the central regions underlying the large electrode. Both electrodes were covered in sponges soaked with a sodium chloride solution to improve conductivity and to reduce skin irritation. For active stimulation, we applied a current of 1.075 μA, leading to a current density of 0.043 mA/cm² for the electrode over the dlPFC and 0.011 mA/cm² for the reference electrode, making it much less likely for the larger electrode to induce functional effects on the underlying brain tissue. The electrode setup was identical in all conditions. In the anodal condition, the electrode over the dlPFC served as the anode, whereas the reference electrode served as the cathode. In the cathodal condition, the polarity of the electrodes was reversed. Active brain stimulation lasted 30 min at most and was stopped once the participant had finished the investment task. In all conditions, the current was applied with an 8-s fade-in- and a 5-s fade-out-window at the beginning and the end of the stimulation. In the sham condition, no current was delivered after the initial fade-in-period, to prevent participants from being able to tell to which condition they had been assigned to. The investment task started

immediately after the fade-in-period. Blinding of the investigator and the participant was accomplished by using preprogrammed codes of the Neuroconn stimulator. Since the stimulation condition was unknown to the investigator and the participant, all participants were asked to guess in which condition they had been. At the end of the experiment, participants were debriefed.

### Data Analysis

Investment decisions were analyzed using a mixed-design ANOVA with prior investment (no vs. low vs. high), costs (low vs. high), and probability of success (low vs. medium vs. high) as within-subject factors and stimulation condition (anodal vs. cathodal vs. sham) as a between-subject factor. Significant main or interaction effects were further pursued by Bonferroni-corrected post hoc tests. In addition to the ANOVA model, we performed a logistic regression analysis including the stimulation condition, the costs, probability of success and prior investment in the current trial as well as the choice, investment and outcome in the previous trial as regressors. All reported *P*-values are two-tailed.

#### *Sunk-Cost Score*

In line with our previous study (Haller and Schwabe 2014), we calculated a sunk-cost score for each participant based on their investment decisions. We calculated the individual differences in the percentage of investment decisions between "no prior investment trials" and "low prior investment trials" as well as the difference between "low prior investment trials" and "high prior investment trials" for all 6 combinations of project costs and probability of success. The average of these difference scores was used as a single estimate for the individual "sunk-cost tendency." A high sunk-cost score indicates large differences between the trial types and thus a stronger sunk-cost tendency.

## Results

Overall, participants were unable to distinguish the different stimulation types. Treatment guesses were at chance level (58%) and did not differ between stimulation conditions ($\chi^2_2 = 1.78$, $P = 0.41$).

### Anodal Stimulation Over the dlPFC Boosts the Sunk-Cost Bias

As expected, participants' investment decisions were strongly influenced by the expected value of an option, as indicated by significant main effects of costs ($F_{1,57} = 78.44$, $P < 0.001$, partial $\eta^2 = 0.58$) and probability of success ($F_{1.41,80.58} = 160.75$, $P < 0.001$, partial $\eta^2 = 0.74$) as well as a costs × probability of success interaction ($F_{1.33,76.05} = 12.68$, $P < 0.001$, partial $\eta^2 = 0.18$). Critically, our data also demonstrate a pronounced sunk-cost effect: participants' decisions to invest or not invest were significantly influenced by whether they had already made an investment or not (main effect prior investment: $F_{1.79,102.00} = 93.16$, $P < 0.001$, partial $\eta^2 = 0.62$). This tendency to invest more after a prior investment held for both trials where the prior investment was low or high (low vs. no prior investment and high vs. no prior investment: both $P < 0.001$; low vs. high prior investment: $P = 0.99$). As shown in Figure 2*a*–c, the impact of prior investments was strongest for options with a low expected value and the influence of the expected value on decision-making was significantly modulated by prior investments (costs × probability of success × prior investment interaction: $F_{3.23,183.89} = 4.10$, $P = 0.003$, partial $\eta^2 = 0.07$).

Most importantly, however, the tendency to continue investing in a project that had already been invested (i.e., the sunk-cost effect) was significantly affected by tDCS over the dlPFC (stimulation × prior investment: $F_{3.58,102.00} = 5.99$, $P < 0.001$, partial $\eta^2 = 0.18$). When participants had not yet invested in a project, stimulation over the dlPFC did not alter their decision-making (main effect of stimulation in no prior investment trials: $F_{2,57} = 0.44$, $P = 0.65$, partial $\eta^2 = 0.02$) and choices were exclusively driven by the expected value of the current project (see an increase in bars in Fig. 2*a* from left to right; cost × probability of success interaction for no prior investment trials only: $F_{1.78,57} = 5.87$, $P = 0.004$, partial $\eta^2 = 0.09$). However, when participants had already made a low investment, stimulation over the dlPFC altered their decision behavior significantly (main effect of stimulation in low prior investment trials: $F_{2,57} = 4.81$, $P = 0.012$, partial $\eta^2 = 0.14$): Anodal stimulation led to higher investment rates than sham stimulation ($P < 0.009$), but there was no such effect for cathodal stimulation ($P = 0.36$). When participants had already made a large investment, anodal stimulation over the dlPFC led to higher investment rates (main effect of stimulation in high prior investment trials: $F_{2,57} = 6.96$, $P = 0.002$, partial $\eta^2 = 0.20$) compared with both sham stimulation ($P = 0.006$) and cathodal stimulation ($P = 0.007$), whereas the latter 2 conditions did not differ ($P = 0.99$).

The costs × probability of success × prior investment × stimulation interaction did not reach statistical significance ($F_{425.59,183,89} = 1.20$, $P = 0.31$, partial $\eta^2 = 0.04$). However, the data displayed in Figure 2 clearly suggest that anodal stimulation over the dlPFC affected most strongly choices about options with a low expected value. We therefore performed an additional post hoc ANOVA with the factors expected value (high costs/low probability of success vs. low costs/high probability of success) × prior investment × stimulation, for the options with the lowest and highest expected value only. This analysis confirmed that the modulatory influence of anodal stimulation, indeed, depended on the expected value of the option (expected value × prior investment × stimulation interaction: $F_{3.94,110,99} = 2.79$, $P = 0.03$, partial $\eta^2 = 0.09$). Specifically, anodal stimulation increased the impact of prior investments for options with a low expected value (prior investment × stimulation interaction: $F_{3.97,113,02} = 3.96$, $P = 0.005$, partial $\eta^2 = 0.12$) but not for projects with a high expected value (prior investment × stimulation interaction: $F_{4,114} = 0.56$, $P = 0.69$, partial $\eta^2 = 0.02$), perhaps reflecting that most participants decided to invest in these projects anyway.

Additionally, we calculated a sunk-cost score as a single parameter that reflected the individual sunk-cost tendency. As displayed in Figure 3, stimulation over the dlPFC significantly affected participant's sunk-cost tendency ($F_{2,57} = 6.68$, $P = 0.002$, partial $\eta^2 = 0.19$): Anodal dlPFC stimulation resulted in a significantly higher sunk-cost score than both cathodal ($P = 0.034$) and sham stimulation ($P = 0.003$), which did not differ ($P = 0.99$).

The analyses reported so far only focused on the expected value and the investments in the current trial. To test whether choices, investments, and outcomes in previous trials had an influence on decisions in the current trial, we performed a logistic regression analysis in which the parameters from the "previous" trials (i.e., previous choice, previous amount invested, and previous outcome) were included as regressors, in addition to the costs, probability, and prior investment in the current trial as well as the stimulation condition and the prior investment × stimulation condition interaction. This analysis showed that participants' decisions were indeed influenced by choices ($B = 0.58$, $P < 0.001$), investments ($B = 0.11$, $P = 0.03$), and outcomes ($B = -0.12$, $P = 0.01$) on the previous trial: When participants had invested in the previous trial, they were more likely to invest in the current trial; when they had made a larger investment in the previous trial, they were more likely to accept higher costs

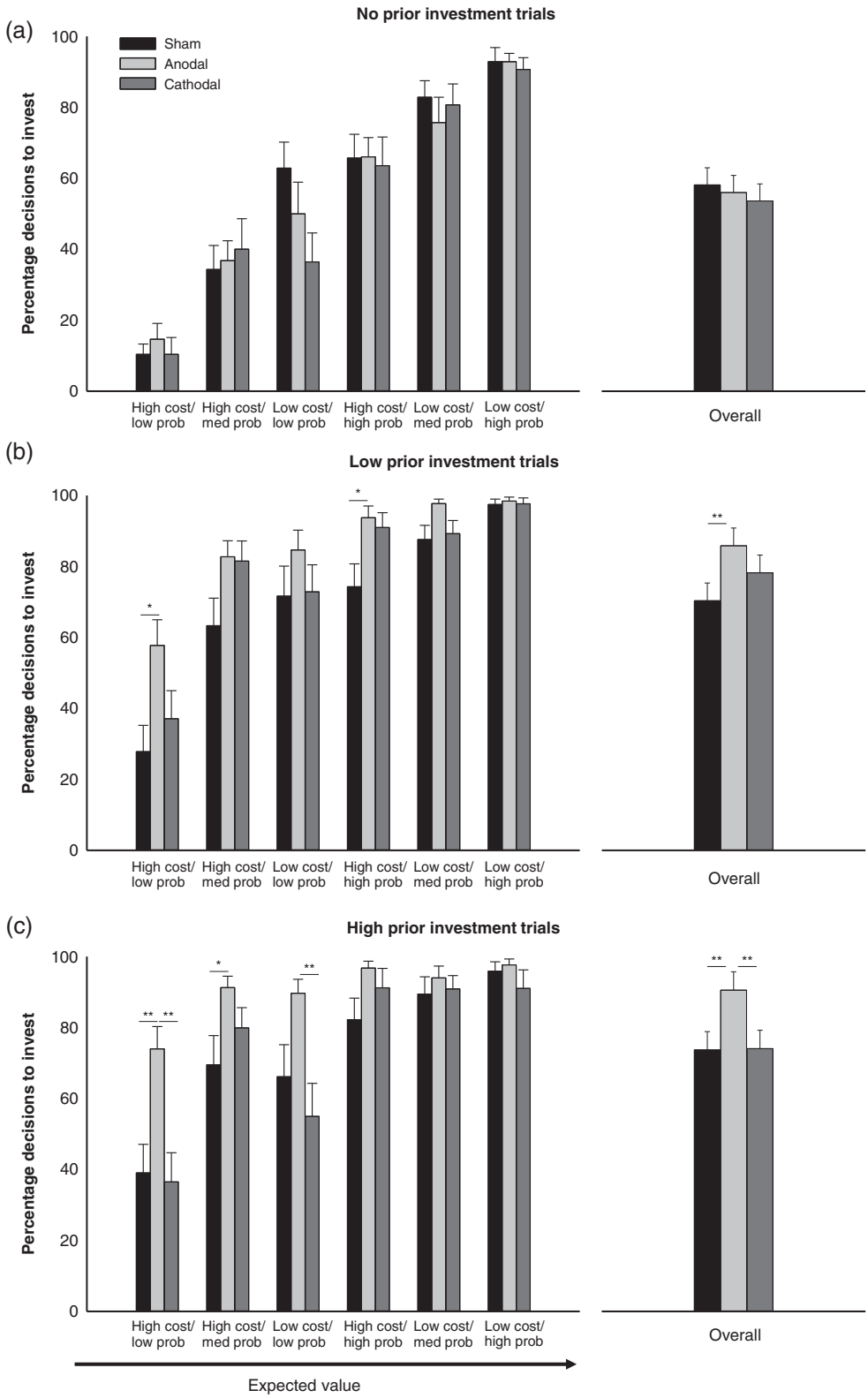


**Figure 2.** Participants' investment decisions depend on prior investments and dlPFC stimulation. Participants' decisions to invest generally reflected the expected value of an option. However, the influence of the expected value decreased significantly when participants had already made an investment (*b* and *c*), indicating a sunk-cost effect. Anodal stimulation of the dlPFC led to a more pronounced sunk-cost effect, as evident in significantly more choices to invest in trials with low or high prior investments; this effect appeared to be most pronounced for projects with a low expected value. When participants had not yet invested in a project (*a*), anodal stimulation did not alter decision behavior. Cathodal or sham stimulation did not alter decision-making. $^{*}P < 0.05$, $^{**}P < 0.01$. *P*-values are corrected for multiple comparisons.

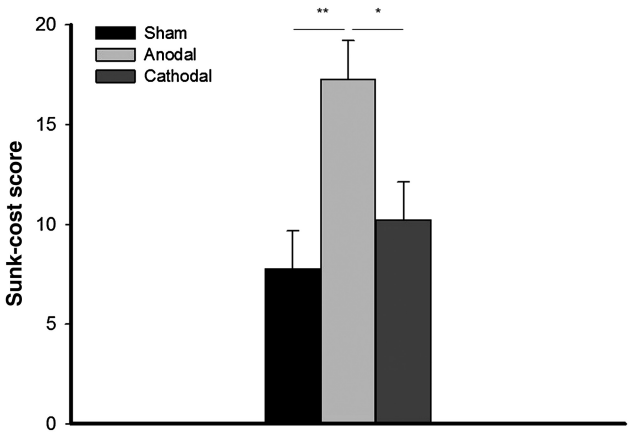


**Figure 3.** Impact of dlPFC stimulation on the sunk-cost score. The sunk-cost score was calculated as a single index of the subjects' tendency to consider past investments in current decisions. A higher score indicates a more pronounced sunk-cost effect. Anodal stimulation led to a higher sunk-cost score than both cathodal and sham stimulation. $^{*}P < 0.05$, $^{**}P < 0.01$. *P*-values are corrected for multiple comparisons.

in the current trial; and losses on the previous trial appeared to motivate participants to invest in the current trial. Critically, however, the effect of the prior investment in the current trial (i.e., the sunk-cost effect) and the prior investment × stimulation condition interaction remained significant (both $B > 1.34$, both $P < 0.001$) when the parameters of the previous trial were included in the analysis, indicating that the specifics of the previous trial cannot explain the observed effects.

### Control Variables

We compared participants in the 3 stimulation groups in a whole range of control variables, to ensure that they did not differ with respect to their behavioral inhibition, drive, fun seeking and reward responsiveness (as measured by the BIS/BAS), their neuroticism, extraversion, openness, and agreeableness (as measured by the NEO-FFI), their impulsiveness (as measured by the BIS-15), or their desire not to appear wasteful (as measured by the sunk-cost questionnaire). There were no such differences for all but one variable (all $F < 2.9$, all $P > 0.05$): Only for the NEO scale conscientiousness, there was a significant group difference ($F_{2,57} = 5.81$, $P < 0.01$, partial $\eta^2 = 0.17$), indicating that participants in the anodal group were less conscientious than those in the cathodal and sham condition (both $P < 0.05$). Thus, we performed our analyses again with conscientiousness as a covariate. Importantly, however, including conscientiousness did not alter our findings, indicating that group differences in conscientiousness could not explain our results. In particular, the significant prior investment × stimulation interaction remained ($F_{3.61,100.96} = 6.82$, $P < 0.001$, partial $\eta^2 = 0.20$) and none of the effects including the covariate conscientiousness approached significance (all $P > 0.14$). Note that we did not find any correlations between the individual norm not to waste resources and the sunk-cost effect (all $r > -0.08$ and $<0.11$, all $P > 0.65$), which is most likely due to the fact that we externally manipulated the brain area representing this norm using tDCS, thus changing its influence on choice behavior but not necessarily the participant's awareness of the norm (Knoch et al. 2006; Ruff et al. 2013).

Finally, given that previous studies reported sex differences in cognitive functions (Cahill 2006), we tested for possible gender effects by including the participants' gender as an additional factor in our analyses. Yet, we did not find any significant main or interaction effects (all $F < 1.95$, all $P > 0.12$), indicating that men and women did not differ in task performance, the sunk-cost tendency, or the impact of tDCS. Moreover, including participants' gender as a factor did not change any of the other significant results reported above.

## Discussion

The sunk-cost effect is one of the most fundamental biases in human decision-making and has been proposed to underlie a wide range of behaviors, including the decisions to stay in a failing relationship (Strube 1988), not to leave a dissatisfying job (Arkes and Blumer 1985), or to adhere to failing policies (Staw 1976). In the present experiment, we sought to elucidate the neural mechanisms underlying the sunk-cost effect. More specifically, we employed tDCS over the right dlPFC during an investment task in order to assess the role of the stimulated brain area in people's tendency to consider prior investments during decision-making. We found that anodal stimulation over the right dlPFC, indeed, increased the impact of past investments on current decision-making, thus leading to a more pronounced sunk-cost effect. This effect could not be attributed to individual differences in personality traits, such as impulsiveness, and it did not occur after sham or cathodal stimulation.

Our data are consistent with the view that the dlPFC plays an important role in the sunk-cost effect. In addition, the present findings support a model in which the dlPFC implements the norm not to be wasteful, which then counteracts decision-making based solely on expected values. The dlPFC is generally thought to influence decision-making by bringing abstract rules and norm-based behavior into action (Sanfey 2003; Koechlin and Summerfield 2007; Baumgartner et al. 2011; Crockett et al. 2013; Ruff et al. 2013). In line with this view, recent fMRI data showed that the activity of the dlPFC is related to the individual norm not to waste resources, which is one of the major sources of the sunk-cost effect (Arkes and Blumer 1985) and which is itself associated with an increased sunk-cost tendency (Haller and Schwabe 2014). Alternatively, the increased sunk-cost effect after anodal stimulation over the dlPFC may have been due to a more general influence on working memory processes required for the present task. In primates, dlPFC cells code for both choices and outcomes not only of the current trial, but also of past trials (Seo et al. 2007), and the key role of the dlPFC in working memory in general has been well established (Fuster and Alexander 1971; Jonides et al. 1993; Curtis and D'Esposito 2003). Stimulation over the dlPFC might thus have led to a more pronounced sunk-cost effect by amplifying representations of previous investments in working memory. On the other hand, implementing social norms such as the norm not to waste resources may resemble a resourceful top-down control process that helps us to incorporate the rules of our social environment in our decisions. Anodal stimulation over the dlPFC may have overactivated this abstract rule, thus impeding value-based decision-making. However, these alternatives are not mutually exclusive. After all, in order to be an effective top-down influence, any social norm needs to be represented in working memory.

Importantly, however, anodal stimulation over the dlPFC did not affect decision-making when participants had not yet invested in a project. Moreover, if participants had not yet made an investment, decision-making in the anodal tDCS group was mainly based on the expected value of an option, exactly as for the other experimental groups. Thus, our findings clearly show that dlPFC stimulation neither affected decision-making in general nor rendered decision-making based on expected values

impossible. Rather, the impact of anodal stimulation over the dlPFC was specific to situations when prior investments had triggered top-down regulation processes, presumably related to activating the norm not to waste resources or working memory processes.

Although anodal stimulation over the dlPFC had a critical impact on the strength of the sunk-cost effect, it is in our view unlikely that the dlPFC drives this effect in isolation. Instead, our data are consistent with the hypothesis that dlPFC stimulation may have altered the crosstalk of the dlPFC with other areas critical for decision-making, in particular the vmPFC. The vmPFC is a key structure for value-based decision-making (Tom et al. 2007; Grabenhorst and Rolls 2011) and our previous data indicate that prior investments enhance the interaction between dlPFC and vmPFC, resulting in a decrease of vmPFC activity (Haller and Schwabe 2014). When activated by relevant past investments, the dlPFC may override vmPFC activity and thus hamper decision-making based on the current value of an option. Such a modulating influence of the dlPFC on vmPFC activity has also been suggested by other studies examining other types of decisions (Hare et al. 2009; Baumgartner et al. 2011). Thus, our data lead to the interesting proposal for future studies that anodal stimulation targeting at the dlPFC may modulate the interplay of prefrontal areas with areas involved in valuation, in a manner that biases decision-making toward rather abstract norms at the expense of "rational" decision-making based on the actual value of an option. Importantly, while previous findings related this modulatory influence of the dlPFC on the vmPFC to self-control, fostering advantageous decision-making (Hare et al. 2009), the present findings suggest that "top-down" influences on decision-making are not necessarily beneficial. More specifically, our findings may imply that the overactivation of norms or past investments, represented in the dlPFC, may impede value-based decision-making, depending on the specific demands of a situation.

As expected, the sunk-cost effect was most pronounced for options with a low expected value, that is, for rather disadvantageous options in which participants invested only when they had already made an investment. Moreover, anodal stimulation over the dlPFC increased the influence of prior investments specifically for low expected value options, thus rendering decision-making even more unfavorable. Previous research has suggested that the sunk-cost effect may also be dependent on the amount of resources invested, with higher prior investments leading to a stronger sunk-cost effect (Haller and Schwabe 2014). At least for the option with the lowest expected value, this pattern was also obtained in the present experiment, both after sham and anodal dlPFC stimulation.

tDCS is a safe, noninvasive method that allows assessing the role of cortical brain areas in cognitive processes such as decision-making. It is, however, important to note that the spatial resolution of this method is limited due to the size of the electrodes. Based on our previous fMRI results that identified the dlPFC as the critical area for the sunk-cost effect (Haller and Schwabe 2014), we chose an electrode position (F4 in the standard EEG 10–20 system) that has been used in previous studies that targeted the dlPFC (Fregni et al. 2005; Harty et al. 2014; Zmigrod et al. 2014; Zwissler et al. 2014; Axelrod et al. 2015; Pope et al. 2015). Studies that combined tDCS with fMRI confirmed that stimulation over this (or the contralateral F3) site led to changes in dlPFC activation (Stagg et al. 2013; Weber et al. 2014). Note, however, that the changes in activation were not limited to the dlPFC, but also included neighboring and other connected areas. While it cannot be ruled out from a physiological perspective that the stimulation affected also cortices adjacent to the dlPFC, it is important to note that none of these adjacent cortices was activated in our previous fMRI study (Haller and Schwabe 2014). The tDCS effects on the sunk-cost bias observed here are thus highly likely to reflect modulation of task-relevant activity in the dlPFC, rather than in adjacent structures that are known not to be involved in this effect. Finally, it is important to note that in spite of the evidence for physiologically inhibitory influences of cathodal stimulation (Nitsche and Paulus 2000), we did not obtain an effect of cathodal dlPFC on the sunk-cost effect. This lack of behavioral effects for cathodal stimulation appears generally consistent with a whole range of other studies that did not find differences between sham and cathodal stimulation (e.g., Kincses et al. 2004; Marshall et al. 2005; Sparing et al. 2008), and with proposals that the effect of cathodal stimulation may be task-dependent and less reliable than that of anodal stimulation [for a review, see Jacobson et al. (2012)]. Alternatively, the lack of cathodal effects in our study may reflect a floor effect, as the options with a low expected value were rarely chosen even in the sham condition. This may have made it difficult to bias choice toward choosing these options even less often. In any case, the lack of behavioral effects in the cathodal condition perfectly controls for any unspecific nonneural effects of the ongoing tDCS and clearly demonstrates that the enhancements of the sunk-cost effect during anodal tDCS reflect the specific neural effects of this intervention.

To conclude, we show here that anodal stimulation over the right dlPFC boosts people's tendency to consider past expenses during current decision-making, suggesting that the stimulated brain area may play a critical role in the sunk-cost effect. Given that this effect leads to increased investments in rather disadvantageous options, these data show that anodal stimulation does not always improve decision-making, but may also counteract optimal choices by enhancing a decision-making bias [see also Xue et al. (2011)]. The present findings shed light on the brain mechanisms underlying the well-known human tendency to continue to "throw good money after bad," which may have considerable consequences for understanding maladaptive decisions in politics (Staw 1976), financial markets (Murnighan 2002), and in our everyday lives (Arkes and Blumer 1985; Strube 1988).

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# Appendix B

Study 2: Transcranial Stimulation of the Dorsolateral Prefrontal Cortex prevents stress-induced Working Memory Deficits

Behavioral/Cognitive

# Transcranial Stimulation of the Dorsolateral Prefrontal Cortex Prevents Stress-Induced Working Memory Deficits

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**Stress is known to impair working memory performance. This disruptive effect of stress on working memory has been linked to a decrease in the activity of the dorsolateral prefrontal cortex (dlPFC). In the present experiment, we tested whether transcranial direct current stimulation (tDCS) of the dlPFC can prevent stress-induced working memory impairments. We tested 120 healthy participants in a 2 d, sham-controlled, double-blind between-subjects design. Participants completed a test of their individual baseline working memory capacity on day 1. On day 2, participants were exposed to either a stressor or a control manipulation before they performed a visuospatial and a verbal working memory task. While participants completed the tasks, anodal, cathodal, or sham tDCS was applied over the right dlPFC. Stress impaired working memory performance in both tasks, albeit to a lesser extent in the verbal compared with the visuospatial working memory task. This stress-induced working memory impairment was prevented by anodal, but not sham or cathodal, stimulation of the dlPFC. Compared with sham or cathodal stimulation, anodal tDCS led to significantly better working memory performance in both tasks after stress. Our findings indicate a causal role of the dlPFC in working memory impairments after acute stress and point to anodal tDCS as a promising tool to reduce cognitive deficits related to working memory in stress-related mental disorders, such as depression, schizophrenia, or post-traumatic stress disorder.**

*Key words:* brain stimulation; dorsolateral prefrontal cortex; glucocorticoids; stress; working memory

**Significance Statement**

**Working memory deficits are prominent in stress-related mental disorders, such as depression, schizophrenia, or post-traumatic stress disorder. Similar working memory impairments have been observed in healthy individuals exposed to acute stress. So far, attempts to prevent such stress-induced working memory deficits focused mainly on pharmacological interventions. Here, we tested the idea that transcranial direct current stimulation of the dorsolateral prefrontal cortex (dlPFC), a critical neural substrate of working memory, may prevent working memory impairments after stress. Our results indicate that anodal stimulation of the dlPFC may indeed preserve working memory performance under stress, suggesting that the dlPFC plays a causal role in stress-induced working memory deficits and pointing to a potential new avenue to prevent stress-induced cognitive impairments.**

## Introduction

Stress and major stress mediators, such as glucocorticoids and catecholamines, are well known to modulate a broad range of cognitive processes, ranging from attention and cognitive control to social cognition, decision-making, learning, and memory (Diamond et al., 2007; Lupien et al., 2007; Lupien et al., 2009; Roozendaal et al., 2009; Schwabe et al., 2012; Schwabe and Wolf, 2013; Sandi and Haller, 2015). Specifically, working memory processes are among those cognitive functions that are most sensitive to the effects of stress and stress hormones, with most studies reporting impaired working memory after stress (Diamond et al., 1999; Lupien et al., 1999; Roozendaal et al., 2004; Elzinga and Roelofs, 2005; Schoofs et al., 2009). Given that working memory deficits are also prominent in stress-related psychopathology (Goldman-Rakic, 1994; Snyder, 2013; Honzel et al., 2014), it is important to find reliable methods to reduce or prevent stress-induced working memory impairments.

Working memory processes are subserved by a large network of interconnected cortical and subcortical brain regions (Goldman-Rakic, 1987; Fuster, 1997; Rottschy et al., 2012; Sreenivasan et al., 2014), with the dorsolateral prefrontal cortex (dlPFC) playing a critical role in this network (Fuster and Alexander, 1971; Jonides et al., 1993; D'Esposito et al., 1995; McCarthy et al., 1996; Barbey et al., 2013). As the dlPFC is one of the most stress-sensitive brain areas (de

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Kloet et al., 2005; McEwen and Morrison, 2013), it is thought that neurotransmitters and hormones that are released in response to stressful encounters downregulate dlPFC activity and thus impede working memory performance. Previous studies using fMRI confirmed that acute stress reduces working memory-related activity in the dlPFC (Qin et al., 2009). Moreover, pharmacological alterations of catecholamine levels, specifically dopamine and noradrenaline levels, in the dlPFC were shown to impair working memory performance in rodents (Brozoski et al., 1979; Arnsten and Goldman-Rakic, 1985; Arnsten and Li, 2005; Arnsten, 2009). Based on these findings, attempts have been made to counteract stress-induced working memory impairments by pharmacologically blocking the action of stress mediators (Conrad et al., 1996; Murphy et al., 1996; Martin and Wellman, 2011). Although such pharmacological manipulations may be successful, drugs can have serious side effects, and identifying techniques to prevent stress-induced working memory deficits that can be used safely in humans is crucial.

Transcranial direct current stimulation (tDCS) is a safe, noninvasive technique to stimulate specific brain areas with low electric current that is delivered via anode and cathode electrodes (Nitsche and Paulus, 2000; Nitsche et al., 2008). Combinations of neuroimaging and tDCS demonstrated that anodal tDCS increases task-related dlPFC activation (Stagg et al., 2013; Weber et al., 2014). Moreover, anodal tDCS over the dlPFC has been shown to facilitate working memory processes (Fregni et al., 2005; Boggio et al., 2006; Nitsche et al., 2008), making tDCS a promising tool for the amelioration of stress-induced working memory impairments. Therefore, the aim of this study was to investigate whether anodal tDCS can be used to counteract working memory deficits after stress. To this end, we first determined the individual baseline working memory capacity using standardized working memory tasks that are often used in clinical settings (Corsi block backwards and digit span backwards). On the next day, we assessed the effect of stress on working memory: participants underwent the Trier Social Stress Test (TSST) (Kirschbaum et al., 1993) or a control manipulation before completing the two working memory tasks. Critically, while participants performed the tasks, anodal, cathodal, or sham tDCS was applied over the right dlPFC. We chose to stimulate the right dlPFC because neuroimaging data indicated that acute stress decreases working memory-related activity in the right dlPFC (Qin et al., 2009). We hypothesized that anodal, but not sham, dlPFC stimulation would reduce stress-induced working memory impairments. As cathodal tDCS is assumed to decrease neural excitability (Nitsche and Paulus, 2000), we speculated that cathodal tDCS might even potentiate the impairing effect of stress on working memory.

## Materials and Methods

*Participants and experimental design.* A total of 120 healthy, normal-weight volunteers between 18 and 32 years of age participated in this experiment (60 females; age, mean ± SEM: 25.2 ± 0.31 years; body mass index, 22.44 ± 0.24 kg/m$^2$). Participants did not have any current or acute illnesses or a lifetime history of any psychiatric or neurological disorder. In addition, exclusion criteria included medication intake, smoking, drug abuse, any contraindications for tDCS, and pregnancy or use of hormonal contraceptives in women. Women were not tested during their menses. Further, participants were asked to refrain from physical exercise, food and caffeine intake within the 2 h before testing. All participants provided written informed consent before the experiment and received a monetary compensation of 25 euros at the end of testing. The study protocol was approved by the ethics committee of the German Psychological Association.

We used a double-blind, sham-controlled, fully crossed, between-subject design with the factors stress condition (TSST vs control manipulation) and tDCS condition (anodal vs cathodal vs sham tDCS), resulting in six experimental groups to which participants were randomly assigned (10 men and 10 women per group). For the digit span backwards task, eight participants (one or two participants of each experimental group) appeared to have difficulties understanding the task and were classified as outliers based on canonical statistical criteria (i.e., >2 SD below the group average; Tabachnick and Fidell, 2005), thus leaving a sample of 112 participants for the digit span task analyses.

*Experimental stress induction.* In the stress condition, participants were exposed to the TSST (Kirschbaum et al., 1993), a standardized paradigm in experimental stress research that is known to lead to substantial increases of subjective stress levels, sympathetic activity, and cortisol concentrations (Kirschbaum et al., 1993; Dickerson and Kemeny, 2004; Smeets et al., 2012). In the TSST, participants underwent a mock job interview, comprising a free speech about why they are the ideal candidate for the job and a rather difficult mental arithmetic task, each lasting 5 min, in front of a panel of two rather cold, nonreinforcing experimenters (1 male, 1 female). Furthermore, participants were videotaped during the TSST. In the control condition, participants gave a 5 min speech about a topic of their choice (e.g., last holiday) and performed a simple arithmetic task for 5 min while being alone in the experimental room; no video recordings were taken. During the control condition, the experimenter waited in front of the door outside the room where he/she was able to hear whether the participants complied with the instructions. In retrospect, all participants in the control condition complied with the instructions.

To evaluate the successful stress induction, subjective and physiological measurements were taken at several time points across the experiment. More specifically, participants completed a German mood scale (Multidimensional Mood Questionnaire; Eid et al., 1994) that assesses subjective feelings on three bipolar dimensions (elevated vs depressed mood, wakefulness vs sleepiness, calmness vs restlessness; higher scores indicating more depressed mood, higher sleepiness, and higher restlessness) and rated the stressfulness, difficulty, and unpleasantness of the previous experience immediately after the TSST or control manipulation on a scale form 0 ("not at all") to 100 ("very much"). In addition, blood pressure and pulse were measured using a Dinamap system (Critikon) before, during, immediately after the TSST/control manipulation, and before and after the working memory tasks. To quantify cortisol concentrations and elevations during the experiment, saliva samples were collected from participants using Salivette collection devices (Sarstedt) at several time points before and after the TSST/control manipulation. Saliva samples were stored at −18°C and subsequently analyzed for cortisol concentrations using a luminescence assay (IBL).

*tDCS.* tDCS was applied in a double-blind, sham-controlled manner using a Neuroconn stimulator. In line with previous tDCS studies that focused on the dlPFC (Harty et al., 2014; Zwissler et al., 2014; Axelrod et al., 2015; Pope et al., 2015), we used an EEG cap and the standard 10–20 system to determine electrode positions individually for each participant. The smaller electrode (5 × 5 cm) was positioned over the right dlPFC (position F4). The larger electrode (10 × 10 cm), which served as a reference (Nitsche and Paulus, 2000), was fixed centrally on the head (position CZ). Different electrode sizes were chosen so that a higher, functionally effective current density was applied over the dlPFC (the area of interest) than over central regions underlying the functionally ineffective, large electrode. Both electrodes were covered in sponges soaked with a sodium chloride solution to improve conductivity and to reduce skin irritation. Based on recent findings suggesting that tDCS of 1 mA may be most efficient (Hoy et al., 2013), we applied a current of 1.075 mA for active stimulation. Given the different electrode sizes of 25 and 100 cm$^2$, respectively, this leads to a current density of 0.043 mA/cm$^2$ for the electrode over the dlPFC and 0.011 mA/cm$^2$ for the reference electrode, making it much less likely for the larger electrode to induce functional effects on the underlying brain tissue. The electrode setup was identical in all conditions. In the anodal condition, the electrode over the dlPFC served as the anode, whereas the reference electrode served as the cathode. In the cathodal condition, the polarity of the electrodes was reversed. Active brain stimulation was stopped once the participant had finished the working memory task. In all conditions, the current was applied with an 8 s fade-in and a 5 s fade-out-window at the beginning

**Table 1. Subjective and physiological data on day 1[a]**

| | MDBF | | | Blood pressure | | | |
|---|---|---|---|---|---|---|---|
| | Elevated mood | Wakefulness | Calmness | Systolic | Diastolic | Pulse | Salivary cortisol |
| Stress condition | | | | | | | |
| Anodal group | 32.75 ± 0.89 | 27.75 ± 0.94 | 30.55 ± 0.96 | 129.35 ± 2.46 | 80.30 ± 1.45 | 79.15 ± 3.14 | 5.52 ± 1.00 |
| Cathodal group | 32.95 ± 1.04 | 27.00 ± 0.93 | 32.55 ± 0.65 | 135.80 ± 2.65 | 80.75 ± 1.99 | 75.65 ± 2.56 | 6.12 ± 0.74 |
| Sham group | 32.75 ± 1.05 | 26.50 ± 1.03 | 31.85 ± 1.12 | 134.60 ± 3.62 | 76.70 ± 1.80 | 74.85 ± 2.23 | 5.75 ± 0.92 |
| Control condition | | | | | | | |
| Anodal group | 32.90 ± 1.05 | 26.60 ± 1.22 | 30.85 ± 0.86 | 137.68 ± 4.04 | 79.30 ± 2.44 | 76.50 ± 2.94 | 7.69 ± 1.50 |
| Cathodal group | 32.50 ± 1.38 | 27.25 ± 1.21 | 31.10 ± 1.25 | 131.78 ± 3.60 | 78.23 ± 1.80 | 81.42 ± 3.28 | 6.11 ± 1.02 |
| Sham group | 32.00 ± 1.02 | 27.25 ± 0.92 | 31.20 ± 1.16 | 128.45 ± 2.62 | 75.90 ± 2.46 | 78.98 ± 3.13 | 4.34 ± 0.54 |

[a]Data are mean ± SEM. MDBF, Multidimensional Mood Questionnaire. Systolic and diastolic blood pressure is given in mmHg, pulse in beats-per-minute (bpm), and salivary cortisol in nmol/l.

and the end of the stimulation, respectively. In the sham condition, the initial fade-in-period was immediately followed by the fade-out-period. Thereafter no current was delivered in the sham condition. This setup prevented participants from explicitly understanding to which condition they had been assigned. Investigator and participant were oblivious to the condition applied, through the use of preprogrammed codes of the Neuroconn stimulator.

*Working memory tasks.* Working memory was assessed using two standardized tasks that are frequently used to assess working memory capacity in clinical settings: the Corsi block backward task assessing visuospatial working memory and the digit span backward assessing verbal working memory (Wechsler, 1997, 2008). In the Corsi block backwards task, the experimenter tapped on a number of squares, one after the other, on a sheet of paper lying in front of the participants. Participants were asked to memorize the sequence and to subsequently reproduce it in reversed order. The experimenter started with a sequence consisting of three squares and extended the sequence by one square every second trial. The task was stopped when participants were not able to reproduce at least one sequence for a given span correctly. In the digit span backwards task, the experimenter read a sequence of one-digit numbers aloud and participants were required to reproduce the digits in reversed order. The digit span task started with a sequence of four one-digit numbers and the digit span was increased by one digit every second trial. The task was stopped when participants were not able to reproduce at least one of the two presented spans correctly. In both tasks, one point was given for each correctly reproduced trial, and overall task performance was expressed as the score reached (Busch et al., 2005; Kessels et al., 2008; Wechsler, 2008). We chose to administer backward versions of both working memory tasks because our sample consisted of healthy university students and the forward versions would have been most likely to easy for this sample, leading to ceiling effects. Because participants completed each task on both experimental days, we used parallel versions to avoid potential carryover effects.

*Procedure.* Participants were tested between 1:00 P.M. and 6:00 P.M. on two consecutive days. On day 1, participants completed the Trier Inventory for the Assessment of Chronic Stress (Schulz and Schlotz, 1999) before ratings of subjective feeling, blood pressure, and pulse measurements and a saliva sample were taken, to control for potential group differences in the stress level before the baseline measurement of working memory performance. Participants then completed the Corsi block backward and digit span backward tasks, with task order being counterbalanced across participants. The working memory tests on day 1 served to familiarize participants with the tasks and to provide a "baseline" measurement of the individual working memory capacity.

On day 2, participants completed the Beck Depression Inventory (Beck et al., 1996) to control for interfering influences of depressive symptoms. Subsequently, baseline measurements of subjective and physiological stress parameters were taken (i.e., Multidimensional Mood Questionnaire, blood pressure, pulse, and cortisol). Depending on the experimental condition, participants then performed the TSST or the control manipulation. After the TSST or control manipulation, subjective and physiological stress measurements were taken again and electrodes were applied to the head for tDCS. Twenty minutes after the TSST/control manipulation, subjective and physiological stress levels were measured again before tDCS was applied. Shortly after the beginning of anodal, cathodal, or sham dlPFC stimulation, participants completed the Corsi block backwards and the digit span backwards tasks (task order counterbalanced across participants; different items than on day 1). Task instructions were given to the participants after the initial 8 s fade-in period to allow for maximum stimulation intensity during the tasks; behavioral testing started ~15–20 s after the fade-in period. The interval of ~30 min between stressor onset and start of testing was chosen because stress-induced cortisol elevations were expected to peak at that time (Kirschbaum et al., 1993). All participants completed the tasks within 6–10 min (average duration: ~8 min), thus resulting also in a stimulation duration of 6–10 min. After participants had finished both tasks, brain stimulation was stopped and electrodes were removed. At the end of the experiment, subjective and physiological measures were taken again. Participants were asked to guess what type of tDCS they had received and were then debriefed.

*Data analysis.* Subjective and physiological parameters were analyzed using a mixed-design ANOVA with time point of measurement as within-subject factor and stress condition (stress vs control) and tDCS condition (anodal vs cathodal vs sham) as between-subject factors.

The critical behavioral parameter was the change in working memory performance from day 1 to day 2 because this change takes differences in individual working memory capacities into account and allows the assessment of working memory changes due to stress and dlPFC stimulation, respectively, independent of the individual "baseline" working memory capacity. This difference score was subjected to an ANOVA with stress condition (stress vs control), tDCS condition (anodal vs cathodal vs sham), and sex (female vs male) as between-subject-factors. Participants' sex was included as an additional factor because previous evidence suggested that stress effects on memory processes may differ in men and women (Cahill, 2006; Andreano and Cahill, 2009; Guenzel et al., 2014). Significant main or interaction effects were further pursued by appropriate *post hoc* tests that were corrected for multiple comparisons, if required. Critical $p$ values were set to $p < 0.05$. All reported $p$ values are two-tailed.

## Results

### Indicators of successful stress induction

There were no group differences in subjective and physiological parameters on day 1, indicating that groups did not differ in their stress level before baseline working memory testing (all $p > 0.30$; Table 1).

Subjective and physiological data on day 2 verified the successful stress induction by the TSST. Although groups did not differ in their subjective ratings before the TSST/control manipulation (all $p > 0.13$; Table 2), participants who were exposed to the TSST reported lower mood and calmness compared with participants in the control group after the experimental manipulation (time × stress condition interaction effects for mood and calmness: both $F > 14.40$, both $p < 0.001$; Bonferroni-corrected *post hoc* tests: both $p < 0.001$); participants' wakefulness ratings remained unaffected by the TSST (time × stress condition interaction: $F_{(2.72,307.62)} = 1.16, p = 0.32$). Moreover, participants who underwent the TSST experienced the stress condition as signifi-

**Table 2. Subjective stress ratings on day 2[a]**

| | Stress condition | | Control condition | |
|---|---|---|---|---|
| | Mean | SEM | Mean | SEM |
| Elevated versus depressed mood (MDBF) | | | | |
| Before TSST/control manipulation | 33.58 | 0.57 | 32.55 | 0.68 |
| After TSST/control manipulation | 28.12*,** | 0.96 | 32.78 | 0.63 |
| Before working memory testing | 29.32** | 0.90 | 30.70** | 0.84 |
| After working memory testing | 31.30** | 0.79 | 31.98 | 0.67 |
| Calmness versus restlessness (MDBF) | | | | |
| Before TSST/control manipulation | 32.20 | 0.61 | 30.65 | 0.83 |
| After TSST/control manipulation | 24.47*,** | 0.94 | 30.65 | 0.71 |
| Before working memory testing | 27.71** | 0.89 | 29.05** | 0.87 |
| After working memory testing | 30.47** | 0.82 | 30.72 | 0.71 |
| Wakefulness versus sleepiness (MDBF) | | | | |
| Before TSST/control manipulation | 28.00 | 0.63 | 27.17 | 0.71 |
| After TSST/control manipulation | 28.03 | 0.52 | 26.47 | 0.68 |
| Before working memory testing | 28.10 | 0.56 | 27.05 | 0.67 |
| After working memory testing | 27.38 | 0.62 | 25.57** | 0.68 |
| Subjective rating of the TSST/control manipulation | | | | |
| Stressfulness | 65.17* | 3.49 | 33.33 | 2.89 |
| Difficulty | 72.50* | 2.75 | 29.33 | 3.04 |
| Unpleasantness | 67.67* | 3.72 | 28.33 | 3.05 |

[a]MDBF, Multidimensional Mood Questionnaire.

*Significant difference between stress and control condition ($p < 0.001$).

**Within-group differences compared with the baseline measurement ($p < 0.05$).

cantly more stressful, difficult, and unpleasant than participants who underwent the control manipulation (all $t_{(118)} > 7$, all $p < 0.001$). On the physiological level, exposure to the TSST led to significant increases in participants' pulse (time × stress condition interaction: $F_{(2.33,251.88)} = 84.00$, $p < 0.001$), diastolic blood pressure ($F_{(3.49,361.84)} = 36.92$, $p < 0.001$) and systolic blood pressure ($F_{(3.11,345.31)} = 19.09$, $p < 0.001$). As shown in Figure 1*A–C*, groups did not differ in their pulse and blood pressure before the TSST/control manipulation, yet participants who were exposed to the TSST had higher blood pressure and pulse during and shortly after the manipulation. Finally, the TSST caused also the expected rise in salivary cortisol; although the TSST and control groups did not differ in their baseline cortisol concentrations ($t_{(118)} = 0.31$, $p = 0.76$), cortisol increased after the TSST but not after the control manipulation (time × stress condition interaction: $F_{(2.11,238.11)} = 25.01$, $p < 0.001$; Fig. 2). Salivary cortisol concentrations were elevated in the TSST group, compared with the control group, at each time point of measurement after the TSST (all $p \leq 0.001$) and reached their maximum ~30 min after stressor onset, shortly before working memory testing started.

Critically, there were no differences between the tDCS groups in any of the subjective or physiological responses to the TSST (time × stress condition × tDCS condition interactions: all $F < 1.52$, all $p > 0.17$).

### Anodal stimulation of the dlPFC abolishes stress-induced working memory impairments

Groups did not differ in their working memory performance on day 1 (Corsi block backwards: $F_{(2,108)} = 0.72$, $p = 0.49$; digit span backwards: $F_{(2,100)} = 1.38$, $p = 0.26$; Table 3). Yet, as expected, there were considerable differences in working memory capacity between individual participants (range: 2–11 [Corsi span]; 1–12 [digit span]). To take these individual differences in working memory capacities into account and assess the impact of stress and/or tDCS on working memory independent of such baseline differences, performance on day 2 was expressed as Δ score relative to day 1 performance.

For the Corsi block task, we obtained a significant main effect of stress condition ($F_{(1,108)} = 7.13$, $p = 0.009$) and a trend for a main effect of tDCS condition ($F_{(2,108)} = 3.01$, $p = 0.054$). Most importantly, however, we found a significant interaction between stress condition and tDCS condition ($F_{(2,108)} = 3.36$, $p = 0.039$). Participants who underwent the TSST performed significantly better when they received anodal dlPFC stimulation than when they received sham ($p < 0.01$) or cathodal stimulation ($p < 0.05$; main effect tDCS condition in the stress condition: $F_{(2,60)} = 5.92$, $p = 0.005$); in the control condition, there was no effect of tDCS condition ($F_{(2,60)} = 0.24$, $p = 0.98$). As shown in Figure 3*A*, the exposure to the TSST resulted in a decline in Corsi block performance in the sham condition (main effect stress condition: $F_{(1,36)} = 9.80$, $p = 0.003$) and a trend toward impaired performance in the cathodal condition ($F_{(1,36)} = 3.92$, $p = 0.055$). Under anodal dlPFC stimulation, however, TSST exposure did not decrease Corsi block performance ($F_{(1,36)} = 0.15$, $p = 0.70$). Overall, men outperformed women in the Corsi block task ($F_{(1,108)} = 5.31$, $p = 0.02$), yet the influence of stress and tDCS condition did not differ in men and women (stress condition × tDCS condition × sex: $F_{(2,108)} = 2.08$, $p = 0.13$).

The pattern of results in the digit span backwards task was very similar to that observed in the Corsi block task. In addition to a main effect of tDCS condition ($F_{(2,100)} = 5.02$, $p = 0.008$), we obtained a marginally significant interaction of stress condition and tDCS condition ($F_{(2,100)} = 2.96$, $p = 0.057$). Importantly, after stress, participants in the anodal tDCS condition performed significantly better than those in the sham ($p = 0.002$) or in the cathodal condition ($p = 0.003$; main effect of tDCS condition in the stress condition: $F_{(2,55)} = 7.05$, $p = 0.002$), whereas there was no effect of tDCS condition after the control manipulation ($F_{(2,54)} = 0.52$, $p = 0.60$). As displayed in Figure 3*B*, stress tended to decrease working memory performance in the sham group ($F_{(1,35)} = 3.26$, $p = 0.08$) and in the cathodal group ($F_{(1,35)} = 2.27$, $p = 0.12$) but not in the anodal group ($F_{(1,36)} = 1.27$, $p = 0.23$). There was no main or interaction effect including the factor sex (all $p > 0.26$). For both tasks, performance on day 2 was (in the control condition) better than performance on day 1, which was most likely due to practice and familiarity effects.

Although the cortisol response to the stressor did not differ between the tDCS groups (see above), we wanted to make sure that the facilitating effects of anodal tDCS were not related to differences in cortisol responses; we performed an additional analysis in which we included the peak cortisol level (before working memory testing) as a covariate. There was, however, no main effect for this covariate in either task (both $F < 1.90$; both $p > 0.17$); and, importantly, the stress condition × tDCS condition interactions remained as described above, indicating that differential cortisol levels before testing cannot explain the impact of anodal tDCS.

### Control variables

There were no group differences in chronic stress level or depressive symptoms (all $F < 1.90$, all $p > 0.15$; Table 4), indicating that these factors could not explain our results.

When participants were asked to guess whether they had received active or sham tDCS, most participants (67%) assumed that they had received active stimulation, regardless of the actual tDCS condition. Participants were not able to discriminate between the different stimulation types ($\chi^2_2 = 3.57$, $p = 0.17$). Moreover, there were no side effects of stimulation.

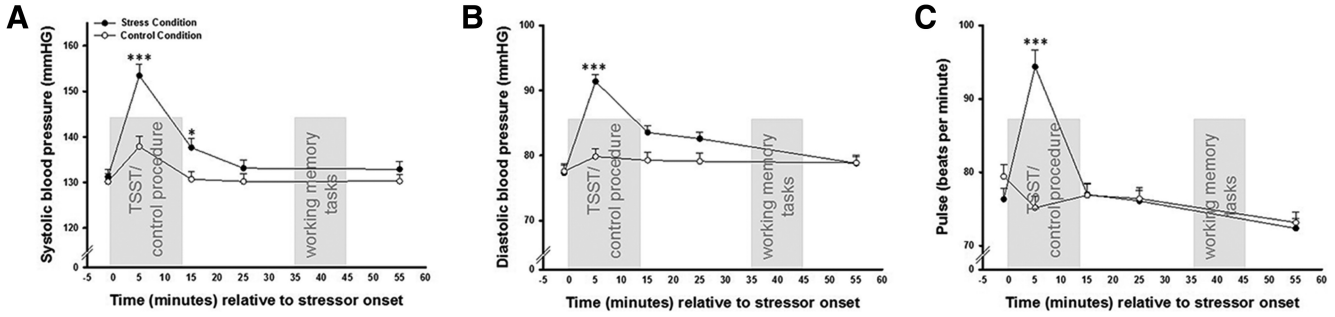


**Figure 1.** Sympathetic nervous system responses to the TSST. Exposure to the TSST, but not to the control manipulation, led to significant increases in systolic blood pressure (***A***), diastolic blood pressure (***B***), and pulse (***C***). Stress and control groups differed in these parameters during the TSST/control manipulation and shortly thereafter but not before the TSST/control manipulation or before working memory testing started. Error bars indicate SEM. $*p < 0.05$. $***p < 0.001$.

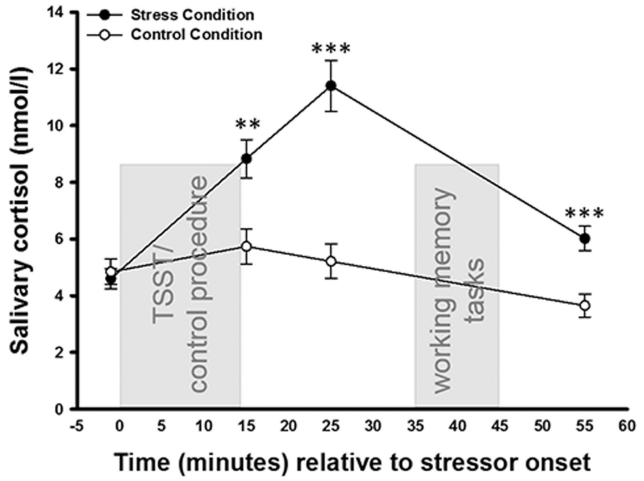


**Figure 2.** Salivary cortisol responses to the TSST. Cortisol concentrations increased in response to the TSST but not in response to the control manipulation. Peak cortisol concentrations were reached shortly before working memory testing started. Error bars indicate SEM. $**p < 0.01$. $***p < 0.001$.

**Table 3. Performance in working memory tasks on day 1[a]**

| | Corsi block backwards | Digit span backwards |
|---|---|---|
| Stress condition | | |
| Anodal group | 6.35 ± 0.36 | 3.90 ± 0.58 |
| Cathodal group | 6.50 ± 0.46 | 4.50 ± 0.50 |
| Sham group | 7.05 ± 0.43 | 4.05 ± 0.61 |
| Control condition | | |
| Anodal group | 6.05 ± 0.46 | 4.25 ± 0.44 |
| Cathodal group | 6.25 ± 0.41 | 4.25 ± 0.66 |
| Sham group | 5.90 ± 0.37 | 3.10 ± 0.44 |

[a]Data are mean ± SEM.

## Discussion

Working memory deficits are a characteristic feature of stress-related disorders, such as major depression, schizophrenia, or post-traumatic stress disorder (Goldman-Rakic, 1994; Snyder, 2013; Honzel et al., 2014). Here, we tested whether transcranial stimulation of the dlPFC, the key locus of working memory in the brain (Fuster and Alexander, 1971; D'Esposito et al., 1995; D'Esposito et al., 1998), could prevent the disruptive influence of acute stress on working memory performance. The present findings show that dlPFC stimulation with anodal tDCS may indeed prevent stress-induced working memory impairments. Compared with cathodal and sham stimulation, anodal dlPFC stimulation led to significantly better performance after stress, in two separate working memory tasks. Because we controlled for "baseline" differences in working memory, these effects cannot be attributed to individual differences in working memory capacity.

Corroborating earlier studies, we show that acute stress disrupts working memory performance (Diamond et al., 1999; Lupien et al., 1999; Schoofs et al., 2009), although this effect appeared to be stronger for visual spatial working memory (Corsi span) than for verbal working memory (digit span). Most importantly, however, our findings suggest a critical role of the dlPFC in this stress-induced working memory impairment. This finding is in line with fMRI evidence showing a stress-related decrease in dlPFC activity during a working memory task (Qin et al., 2009). However, fMRI data are correlational, not causal; and, in addition to brain lesions, only brain stimulation techniques, such as tDCS, allow conclusions about causal relationships between brain and behavior. Although we propose a causal role of the dlPFC in working memory deficits after stress, other brain areas also need to be taken into account. It is well established that complex cognitive functions, such as working memory, rely on a network of interconnected brain areas (Smith and Jonides, 1997; Pessoa, 2008). More specifically, it was shown in rats that working memory deficits after stress hormone administration are mediated by the basolateral amygdala interacting with the medial PFC (Roozendaal et al., 2004). Altered medial PFC activity has been directly linked to impaired working memory after glucocorticoid administration (Barsegyan et al., 2010). Medial and dorsolateral prefrontal areas are thought to belong to functionally distinct networks (Fox et al., 2005; Gerlach et al., 2011), and their activity is often negatively correlated (Baumgartner et al., 2011; Haller and Schwabe, 2014). Hence, we suggest that stress results in altered crosstalk of limbic and prefrontal areas that ultimately leads to reduced dlPFC activation and impaired working memory. Anodal stimulation of the dlPFC targeted this "endpoint" and could thus abolish the stress-induced working memory impairment.

However, how exactly may anodal tDCS have prevented the impairing effect of stress on working memory? Rapid effects of acute stress on working memory are thought to be mediated by glucocorticoids, in concert with catecholamines, acting via membrane-bound glucocorticoid receptors (Barsegyan et al., 2010). Activation of membrane-bound glucocorticoid receptors decreases synaptic and neuronal excitability by reducing calcium currents through NMDA receptors and voltage-gated calcium channels via protein kinase A and G-protein-dependent mechanisms (Prager and Johnson, 2009). In contrast to these stress hormone effects, anodal tDCS increases neuronal excitability. These excitability increases are eliminated by a sodium channel blocker as well as by a calcium channel blocker (Liebetanz et al.,

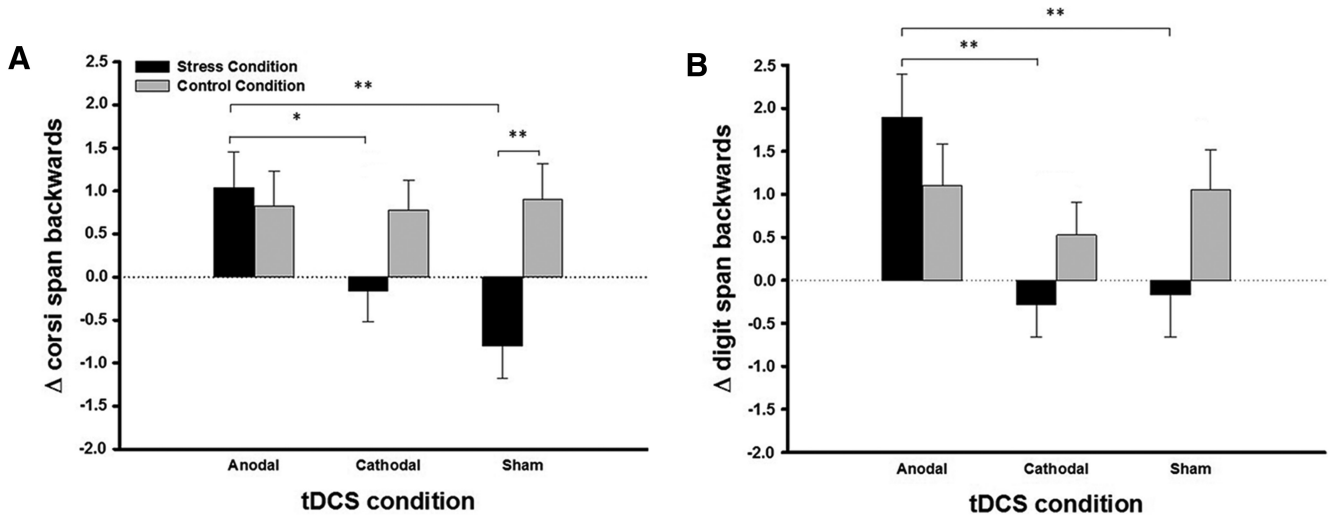


**Figure 3.** Anodal tDCS prevents stress-induced working memory impairments. ***A***, Exposure to the TSST impaired Corsi block backwards performance, an indicator of visual-spatial working memory, in the sham and cathodal tDCS groups but not in the anodal tDCS group. ***B***, Similarly, TSST exposure tended to reduce digit span backwards performance, an indicator of verbal working memory, in the sham and cathodal tDCS groups but not in the anodal tDCS group. In both tasks, working performance after stress was significantly better in participants that received anodal tDCS over the dlPFC than in those that received sham or cathodal stimulation. Error bars indicate SEM. $*p < 0.05$. $**p < 0.01$.

**Table 4. Depression and chronic stress scores**[a]

| | Stress | | | Control | | |
|---|---|---|---|---|---|---|
| | Anodal | Cathodal | Sham | Anodal | Cathodal | Sham |
| BDI | 8.90 ± 1.55 | 6.55 ± 1.03 | 6.15 ± 1.21 | 6.25 ± 1.00 | 7.85 ± 1.89 | 8.45 ± 1.16 |
| TICS scales | | | | | | |
| Work overload | 13.42 ± 1.51 | 13.75 ± 1.44 | 13.75 ± 1.85 | 13.75 ± 1.72 | 14.35 ± 1.54 | 12.10 ± 1.30 |
| Social overload | 8.58 ± 1.14 | 8.16 ± 0.91 | 7.00 ± 0.99 | 6.70 ± 0.98 | 8.79 ± 1.09 | 7.33 ± 0.89 |
| Performance pressure | 16.85 ± 1.61 | 14.75 ± 1.58 | 16.05 ± 1.52 | 16.04 ± 1.57 | 17.10 ± 1.28 | 16.25 ± 1.17 |
| Work discontent | 14.90 ± 0.80 | 10.74 ± 1.36 | 13.40 ± 1.50 | 12.35 ± 1.07 | 12.35 ± 1.35 | 15.21 ± 1.09 |
| Excessive workload | 8.37 ± 0.71 | 7.58 ± 0.93 | 6.85 ± 1.18 | 7.16 ± 1.12 | 6.44 ± 0.90 | 8.79 ± 1.05 |
| Lack of social recognition | 5.58 ± 0.60 | 5.72 ± 0.99 | 5.50 ± 0.80 | 4.68 ± 0.65 | 4.37 ± 0.56 | 6.00 ± 0.71 |
| Social tension | 9.80 ± 0.95 | 8.85 ± 1.07 | 9.79 ± 1.18 | 8.70 ± 1.15 | 9.47 ± 1.09 | 11.53 ± 0.96 |
| Social isolation | 8.60 ± 0.89 | 7.56 ± 0.95 | 8.94 ± 1.38 | 7.68 ± 1.02 | 7.74 ± 1.12 | 9.95 ± 1.02 |
| Chronic worrying | 8.37 ± 0.88 | 6.95 ± 0.85 | 6.70 ± 0.92 | 7.20 ± 0.82 | 6.50 ± 0.89 | 7.63 ± 0.81 |
| TICS screening scale | 19.84 ± 2.01 | 18.05 ± 2.04 | 17.30 ± 2.36 | 17.25 ± 2.11 | 16.15 ± 1.85 | 17.85 ± 1.87 |

[a]Data are mean ± SEM. BDI, Beck Depression Inventory; TICS, Trier Inventory of Chronic Stress.

2002; Nitsche et al., 2003), suggesting that cortical excitability changes during tDCS require membrane polarization, mediated through sodium and calcium channels. Moreover, tDCS induces aftereffects in neuroplasticity that are mediated by NMDA receptors (Liebetanz et al., 2002; Nitsche et al., 2003). Based on these data, we propose that stimulation of the dlPFC using anodal tDCS prevented decreases in working memory performance after stress by counteracting stress-induced decreases in neuronal excitability.

Whereas anodal dlPFC stimulation improved working memory performance after stress, we obtained no effect of cathodal dlPFC stimulation. Although there is some physiological evidence for an inhibitory influence of cathodal tDCS (Nitsche and Paulus, 2000), a number of studies failed to find differences between cathodal and sham stimulation (e.g., Kincses et al., 2004; Marshall et al., 2005; Sparing et al., 2008), and it is argued that the effect of cathodal stimulation might be less reliable and more task-dependent than that of anodal stimulation (Jacobson et al., 2012). For anodal dlPFC stimulation, several studies reported enhancing effects on working memory performance (Fregni et al., 2005; Andrews et al., 2011; Zaehle et al., 2011). In the present experiment, however, we observed no working memory enhancement during anodal dlPFC stimulation in the control condition, which would have been expected based on previous studies showing working memory enhancements during and after tDCS over the dlPFC (Fregni et al., 2005; Andrews et al., 2011; Zaehle et al., 2011). This discrepancy with earlier reports might be due to stimulation parameters, such as the intensity, timing, and duration of stimulation or the chosen stimulation site. For example, we stimulated the right dlPFC because neuroimaging data showed a robust decrease in working memory-related activity in this area after stress (Qin et al., 2009). Previous studies that reported enhanced working memory during tDCS over the dlPFC, however, typically stimulated the left dlPFC (Fregni et al., 2005; Boggio et al., 2006).

Finally, it is important to note that working memory is a complex, high-level cognitive function, composed of different subprocesses (Baddeley, 2003; Nee et al., 2013) (e.g., attention, processing speed), and from our data we cannot conclude exactly which of these processes were modulated by tDCS. We used two tasks that are frequently used to assess working memory performance in both healthy and clinical individuals (Harvey et al., 2004; Castaneda et al., 2008). However, these tasks did not allow us to measure subprocesses of working memory. Although we did not aim to examine the specific processes of working memory that are affected by stress and/or tDCS but rather to assess

whether tDCS over the dlPFC could modulate the stress-induced impairment of working memory, targeting the specific cognitive processes involved in the stress-induced working memory deficit and its modulation by dlPFC stimulation is a challenge for future studies. In these studies, it should also be tested how specific the tDCS effect is (i.e., whether tDCS may also be used to modulate stress-induced changes in other cognitive processes, such as memory or decision-making). A further limitation of the present study is related to the relatively low spatial resolution of tDCS. It is possible that cortical areas adjacent to the dlPFC have also received stimulation. In addition, it is unclear how much of the current was shunted through the skull or CSF and thus not reaching the brain at all. Indeed, computational modeling approaches indicate that only a minor portion of the current reaches the brain, especially when the electrodes are placed relatively close to each other (Miranda et al., 2006). Yet, the setup we applied has been used in several previous studies to successfully target dlPFC-dependent cognitive functions (Harty et al., 2014; Zwissler et al., 2014; Axelrod et al., 2015; Pope et al., 2015) and to stimulate the dlPFC (Stagg et al., 2013; Weber et al., 2014). Furthermore, it has been shown recently that the brain current density is highest in cortical areas that are directly below the stimulation electrode and decreases with increasing distance from the electrodes (Miranda et al., 2006; Wagner et al., 2014). Finally, the fact that we obtained a behavioral effect of tDCS over the dlPFC may be taken as indication that at least part of the stimulation actually reached the brain. It is thus plausible to assume that the dlPFC was stimulated in the present study. The stimulation of the dlPFC, however, may well have changed activity in other (e.g., medial prefrontal) areas that are intimately linked to the dlPFC and could have played a role in the observed behavioral effects. Although not spatially focused, our findings suggest a potential use of tDCS to improve cognitive performance under stress. Combining brain stimulation with neuroimaging techniques for more precise, individual localization of the electrodes might even enhance these beneficial effects.

In conclusion, our findings show that anodal tDCS over the right dlPFC may prevent working memory impairments induced by acute stress. These findings not only aid our understanding of the functional localization of the impact of stressful experiences on working memory processes but may also have important clinical implications. Anodal tDCS has already been successfully used to improve cognitive functioning in stroke or Alzheimer's patients (Fregni and Pascual-Leone, 2007; Ferrucci et al., 2008; Brunoni et al., 2012). Although the duration and intensity of the stress experienced in clinical conditions are certainly different from the stress experienced in this experiment, our findings suggest that stimulation of prefrontal areas with tDCS could also be a safe, noninvasive tool to alleviate working memory deficits in stress-related psychopathologies, such as depression or anxiety disorders.

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# Appendix C

Study 3: Causal role of the inferolateral prefrontal cortex in the goal-directed control of action

# Causal role of the inferolateral prefrontal cortex in the goal-directed control of action

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Successful adaptation to complex environments depends on the balance of at least two systems: a flexible but slow goal-directed system encoding action-outcome associations and an efficient but rigid habitual system linking responses to preceding stimuli. Recent evidence suggests that the inferolateral prefrontal cortex (ilPFC), a region well known to contribute to cognitive control processes, may play a crucial role in the balance of goal-directed and habitual responding. This evidence, however, comes mainly from correlational data and whether the ilPFC is indeed causally involved in the goal-directed vs. habitual control of behavior is unclear. Here, we used neuro-navigated theta-burst stimulation (TBS) to either inhibit or enhance right ilPFC functionality before participants completed an instrumental learning task designed to probe goal-directed vs. habitual behavioral control. TBS did not affect overall learning performance. However, participants that had received inhibitory TBS were less able to adapt their behavior to altered task demands, indicating a shift from goal-directed towards more habitual control of behavior. Sham or excitatory TMS groups showed no such effect and were comparable in their performance to an unstimulated control group. Our findings indicate a causal role of the ilPFC in the balance of goal-directed vs. habitual control of behavior.

Successful adaptation to varying environments requires an intricate balance of thoughtful deliberation and efficient responding. To achieve this balance, behavior can be controlled by distinct systems, a goal-directed or model-based system encoding the relationship between actions and their consequences and a habitual or model-free system involved in the formation of stimulus-response associations[1-3]. Converging lines of evidence from lesion studies in rodents and human neuroimaging studies implicated mainly the orbitofrontal cortex and dorsomedial striatum in goal-directed action[4-8], whereas the dorsolateral striatum was identified as a key locus of habitual responding[9-12].

Very recent evidence points to another region that may be critical for the goal-directed vs. habitual control of behavior, the inferolateral prefrontal cortex (ilPFC)[13]. Classically, the ilPFC has been associated with cognitive control processes, including the maintenance and release of inhibitory control[14-17]. While these functions are closely linked to goal-directed behavior, the ilPFC has recently been argued to act as an arbitrator that determines to what extent goal-directed and habit systems can govern behavior, primarily through the modulation of the habit system[13]. The claim that the ilPFC is critically involved in the balance of goal-directed and habit behavior is based on correlational neuroimaging data and whether the ilPFC plays a causal role in the goal-directed vs. habitual control of behavior is currently unknown.

To test whether the ilPFC is indeed causally involved in the goal-directed vs. habitual control of behavior, we employed neuro-navigated, sham-controlled Theta Burst Stimulation (TBS), a non-invasive technique that uses magnetic fields to directly decrease (continuous TBS) or increase (intermittent TBS) brain activity in the targeted region[18]. TBS was applied over the right ilPFC, exactly over the location postulated to modulate the balance of goal-directed and habitual action[13], before participants completed an instrumental learning task (ILT), designed to test the degree of habitual vs. goal-directed control of behavior[19,20]. Throughout the ILT, participants were presented with fruit

stimulus pairs, serving either as discriminative stimuli or as outcomes. The stimulus pairs were linked by responses that, if correct, led from a discriminative stimulus to an outcome stimulus. Goal-directed action is indicated by the formation of stimulus-outcome-response (S-O-R) associations, whereas habitual behavior is reflected in simpler stimulus-response (S-R) associations. Stimulus pairs belonged to one of three different discrimination conditions (Fig. 2a): congruent, incongruent, and standard. In the congruent condition, the same fruit served as discriminative stimulus and outcome. Thus, participants could rely on simple O-R associations in these trials[20]. In the incongruent condition, stimulus pairs reversed their status as discriminative stimulus or outcomes across different trials. To avoid response conflict, participants in the incongruent condition usually rely on habitual S-R associations[19]. Finally, in the standard condition, correct responses towards discriminative stimuli lead to unique outcome stimuli. The relative goal-directed vs. habitual control of behavior was tested in a subsequent 'slips-of-action test' requiring participants to abstain from responding to devalued actions. We hypothesized that, compared to sham or intermittent TBS, continuous TBS interfering with ilPFC functioning would result in less goal-directed behavior and hence more slips of action, either due to a direct impairment of the goal-directed system or indirectly via an impaired arbitrator mechanism, hindering the downregulation of the habit system. This impairment should be particularly pronounced in standard trials that can be controlled both by the goal-directed and the habitual system[20,21]. Although data on behavioral facilitation after magnetic brain stimulation in healthy subjects are not very consistent[22-26], we predicted that increased brain activity through intermittent TBS might even facilitate the goal-directed control of action. Even though intermediate TBS is considered to be a sham condition[18,27], we also included a no-stimulation control group to control for general effects of TBS.

## Results

### *Learning phase*

In the initial *learning phase* of the ILT, participants were asked to learn associations between fruit pairs and responses (Fig. 2b). Participants learned these associations very well, as indicated by a significant increase in correct responses across blocks ($F_{(4.749, 199.472)} = 54.423$, $p < .001$, $\eta^2 = .56$). Although there was a marked increase in performance across trials in all discrimination conditions (all $F > 15.968$, all $p < .001$), performance differed, as expected, for the three discrimination conditions ($F_{(2, 84)} = 17.116$, $p < .001$, $\eta^2 = .29$): stimulus pairs in the congruent condition were learned best (vs. standard: $p = .085$, vs. incongruent: $p < .001$) and stimulus pairs in the incongruent condition were learned worst (vs. standard: $p = .005$). Learning performance was generally comparable in the four experimental groups (main effect: $F_{(3, 42)} = 0.901$, $p = .449$, $\eta^2 = .06$), both across discrimination conditions (discrimination condition × TBS interaction ($F_{(6, 84)} = 1.125$, $p = .355$, $\eta^2 = .07$) and across trials (block × TBS interaction: $F_{(14.248, 199.472)} = 0.795$, $p = .676$, $\eta^2 = .05$). All groups performed well and reached about 85% correct responses in each of the three discrimination conditions at the end of the learning session. TBS groups did also not differ in their reaction times ($F_{(3, 41)} = 1.679$, $p = .186$, $\eta^2 = .11$), thus ruling out any differences in speed-accuracy trade-offs between groups.

### *Devaluation phase*

Participants performed also well in the devaluation phase, with each group reaching at least 73% correct responses (Fig. 3b). Again, performance depended on the discrimination condition ($F_{(1.5,62.985,)} = 14.638$, $p < .001$, $\eta^2 = .26$), with better performance in the congruent condition compared to both the standard and the incongruent condition ($p = .030$ and $p < .001$, respectively) and in the standard compared to the incongruent condition ($p = .012$). TBS condition did not affect task performance ($F_{(3, 42)} = 1.354$, $p = .270$, $\eta^2 = .09$)

and did not interact with the discrimination condition ($F_{(4.449, 62.985)} = 0.260$, $p = .919$, $\eta^2 = .02$).

***Slips-of-action phase***

The predominance of goal-directed action vs. habitual responding was revealed in the slips-of-action phase. Overall, participants showed less slips of action in the congruent condition than in the standard condition ($p = .027$), which can be under both habitual and goal-directed control[20,21], or in the incongruent condition ($p = .02$; main effect discrimination condition: $F_{(2, 84)} = 5.715$, $p = .005$, $\eta^2 = .12$), which is assumed to rely mainly on the habit system [20]. Most importantly, however, there was a main effect of TBS condition on the slips of action ($F_{(3, 42)} = 3.005$, $p = .041$, $\eta^2 = .18$). Participants in the cTBS condition showed a significantly higher percentage of slips compared to participants in the imTBS ($p = .024$), the iTBS ($p = .022$) or the no-stimulation condition ($p = .014$), with all other groups being comparable in performance (all $p > .780$). As shown in Fig. 3c, cTBS doubled the percentage of slips compared to the other groups. Moreover, there was a strong trend for a TBS condition × discrimination condition interaction ($F_{(6, 84)} = 2.254$, $p = .054$, $\eta^2 = .14$), suggesting that TBS primarily affected performance in the standard discrimination trials ($F_{(3, 42)} = 4.492$, $p = .008$, $\eta^2 = .24$), with a significantly higher percentage of slips in those trials in the cTBS condition compared to the imTBS, iTBS and no-stimulation conditions (all $p < .017$; imTBS vs. iTBS: $p = .348$; imTBS vs. no-stimulation: $p = .997$; iTBS vs. no-stimulation: $p = .360$). In contrast, we found no effects of TBS in the congruent ($F_{(3, 42)} = 1.806$, $p = .161$, $\eta^2 = .12$) or incongruent discrimination trials ($F_{(3, 42)} = 1.913$, $p = .142$, $\eta^2 = .12$).

In addition to the mere percentage of slips, we also calculated a difference score reflecting the relative use of goal-directed vs. habitual behavior[20,21,28]. The patter of results for the differences score generally resembled the pattern observed for the percentage of slips (see supplementary results).

Although groups did not differ in their learning performance, we ran mediation and ANCOVA analyses to rule out that altered learning could account for the observed differences. These analyses confirmed that the increase in slips-of-action after cTBS was not due to altered learning (see supplementary results).

***Contingency questionnaires***

The different TBS conditions did neither affect participants' ability to explicitly reproduce the contingencies between the fruit stimuli and the button responses (all $F$s < 1.187, all $p$s > .326) nor the certainty of their answers (all $F$s < 1.395, all $p$s > .257; see Table 1).

***Control variables***

Importantly, the TBS groups did not differ in mean stimulation intensity ($F_{(2, 32)} = 0.047$, $p = .954$, $\eta^2 < .01$) or perceived discomfort after stimulation ($F_{(2, 32)} = 0.793$, $p = .461$, $\eta^2 = .05$).

The four experimental groups did further not differ in most of the measures of personality traits and behavioral tendencies associated with decision-making processes which were measured at the beginning of the experiment, i.e. before the TBS manipulation (all $F$s < 3.170; all $p$s > .05; see Table 2), with the exception of Extraversion ($F_{(3, 42)} = 3.207$, $p = .033$, $\eta^2 = .19$), indicating a lower score in the imTBS group compared to the no-stimulation group ($p = .049$). Importantly, this difference could not explain our findings, as revealed by reanalyzing the data using the Extraversion-score as a covariate (see supplemental results).

## Discussion

Extensive evidence from human and rodent studies demonstrates that behavior can be controlled by a deliberative, goal-directed system or a more reflexive, habitual system[2,4,29-32]. Over the past decades, a number of studies identified a network of brain areas relevant for the goal-directed vs. habitual control of behavior, including the orbitofrontal cortex, striatal and thalamic areas as well as the amygdala[8,11,12,33-37]. However, only very recently the ilPFC, a region which has previously been implicated in cognitive control processes[38-40], has been linked to goal-directed and habitual behavioral control[13]. Using neuronavigated TBS, we show that the ilPFC indeed plays a causal role in the goal-directed control of behavior. Specifically, our findings show that cTBS over the ilPFC leads to a breakdown of the goal-directed control of action, paralleled by an increase in habitual responding. This effect could not be explained by differences in initial learning performance, speed-accuracy trade-offs, or personality traits relevant for decision-making.

The predominance of the goal-directed vs. the habitual system was reflected in the slips of action in an instrumental learning task. Previous studies using this task showed that goal-directed action relies on the ventromedial PFC and its connection with the dorsomedial striatum, whereas habitual responding, indicated by a higher number of slips, was linked to the connection between premotor areas and the dorsolateral striatum[19,20]; in line with rodent studies and neuroimaging studies using other tasks to investigate the neural basis of goal-directed and habit behavior[4,5,9,10,12,41]. However, the focal TBS applied here was not directed at one of those areas but specifically at the ilPFC. Thus, our results point to a direct involvement of the ilPFC in goal-directed behavior. The ilPFC is directly connected to areas involved in goal-directed action[42,43]. Moreover, the role of the lateral PFC in inhibition and executive control, i.e. in cognitive functions that are essential for goal-directed behavior, is well established[14,38-40]. It is, however, important to underline that our findings cannot be interpreted as a simple modulation of inhibitory control. If this were

the case, we should see slips-of-action in all discrimination trials and in particular in those for which acquisition performance was best (and responses therefore most difficult to suppress). However, slips of action were mainly observed in incongruent trials, thought to rely mainly on the habit system[20], although acquisition performance was worse in those trials than in congruent or standard trials. Moreover, cTBS did not affect performance in congruent or incongruent trials but specifically in standard discrimination trials, in which goal-directed and habitual systems compete for control[19]. This specificity of our effects argues against a modulation of general inhibitory control but instead suggests a specific alteration of the goal-directed control of behavior.

In addition to a direct role of the ilPFC in goal-directed action, there is an intriguing alternative based on recent data suggesting that the ilPFC acts as an arbitrator that allocates behavioral control to the goal-directed vs. habit system[13]. More specifically, the ilPFC has been postulated to track the reliability of the goal-directed and habit systems and to allocate control by modulating the degree to which the habit system can guide behavior[13]. We chose the stimulation site exactly according to the recent study showing such a role of the ilPFC. Thus, although the task used here does not allow a direct assessment of the arbitration process, the observed increase in slips-of-action after cTBS may be due to a modulation of this arbitrator region. Whereas the previous evidence linking the ilPFC to the balance of goal-directed action and habitual responding was based on correlational data[13], our data provide evidence for a causal role of the ilPFC in the modulation of goal-directed and habitual behavior. Because the ilPFC was suggested to allocate behavioral control mainly via the modulation of the habit system[13], we further suggest that cTBS may have interfered mainly with the capacity of the ilPFC to downregulate the habit system when behavior should be under goal-directed control.

Assuming that the arbitration mechanism works mainly through the modulation of the habit system when the ilPFC deems behavior should be driven by the goal-directed

system, this could explain why we did not find an effect of iTBS. In contrast to cTBS, iTBS should have led to increased activity of the ilPFC[18]. Yet if intact ilPFC functioning is already sufficient to control the habit system and if the ilPFC does not strengthen goal-directed control, one would not necessarily expect a further increase in goal-directed action after iTBS of the ilPFC. In line with this idea, there were only relatively few slips-of-action after sham imTBS and in the no-stimulation control group, suggesting that there was not much room for further improvement of goal-directed control by iTBS.

Since we applied TBS before the ILT, it could have affected both the initial acquisition of the associations and the goal-directed vs. habitual control in the slips-of-action test. Because standard and congruent trials can be solved by both systems equally well and performance in the incongruent trials is thought to rely on the habit system anyway[19,20,28], performance should be comparable no matter which system guides behavior. Nevertheless, a differential recruitment of the goal-directed and habit systems during acquisition may translate into more slips in the slips-of-action test and we cannot conclude that cTBS affected exclusively the performance in the slips-of-action test. Future studies using fMRI in combination with TBS may be helpful to assess the contribution of goal-directed and habit systems during task acquisition and tests of behavioral flexibility. It is, however, important to note that there were no differences in learning or devaluation performance between groups.

In sum, we show that cTBS directed specifically at a region of the ilPFC, previously implicated in cognitive control processes and in balancing the allocation of behavioral control between the goal-directed and the habit system[13], renders behavioral responding less goal-directed. Although the ilPFC is most likely not acting in isolation, but communicating extensively with other regions supporting goal-directed or habitual behavior, our findings demonstrate a causal role of the ilPFC in the goal-directed control of behavior. These findings shed light on the neural mechanisms underlying the balance of

deliberate, goal-directed action and efficient but rather rigid habitual responding. Moreover, our findings provide novel insights into how goal-directed action may break down in disorders such as addiction or OCD that are characterized by impaired goal-directed control[28,44,45].

## Materials and Methods

### *Participants and Experimental Design*

Forty-eight healthy men and women between 19 and 32 years of age participated in this experiment (mean age ± SEM: 25.19 ± 0.43 years, 24 women). Exclusion criteria were checked in a standardized phone interview prior to testing and included current physical or mental conditions, medication or drug intake, a life-time history of any neurological disorder and pregnancy in women as well as any contraindications for MRI and TMS, including a history of epilepsy. All participants gave written informed consent prior to testing and received a moderate monetary compensation. The study protocol was in line with the Declaration of Helsinki and approved by the ethics committee of the Faculty of Psychology and Human Movement Sciences of the University of Hamburg (26 2015 Bogdanov).

We used a double-blind, sham controlled, between-subjects design, in which participants were randomly assigned to one of four experimental conditions (6 men and 6 women per group): continuous, intermediate, or intermittent theta burst stimulation (TBS) of the right ilPFC or a no- stimulation control condition. Two participants (one in the intermittent TBS group and one in the no-stimulation group) had difficulties understanding the task and were thus excluded from analysis, leaving a sample of eleven participants in these groups.

***MRI acquisition***

For each participant, a high-resolution T1-weighted anatomical MRI image was acquired using a 3T Skyra scanner (Siemens) equipped with a 32-channel head coil with the following parameters: TR=2.5s, TE=2.12ms, 256 slices, voxel size=0.8x0.8x0.9mm.

***Neuronavigated TMS application***

Using the anatomical MRI image, the individual position of each participant's right ilPFC for the application of TMS was determined using a stereotaxic frameless Brainsight neuronavigation system (Rogue-Reseach, Canada). First, a 3D-reconstruction of each participant's brain was built. We then specified the right ilPFC as the stimulation target. The exact stimulation site (MNI coordinates: x = 48, y = 35, z = -2) was chosen based on fMRI evidence pointing to the ilPFC as a critical structure in balancing goal-directed and habitual control of behavior[13] (Fig. 1a). Finally, the coil position was adjusted according to the target and marked for later stimulation.

In order to obtain optimal stimulation intensity, we determined participants' individual resting motor threshold (RMT). Therefore, the coil was moved over the hand area of the left motor cortex. Motor potentials were recorded from the first dorsal interosseus muscle of the right hand using disposable Ag/AgCL surface electrodes and a micro 1401-mkII data acquisition unit with a 1902 pre amplifier by Cambridge Electronic Design (UK). RMT was defined as the stimulator intensity necessary to evoke muscle responses greater than 50µV in at least 5 of 10 consecutive pulses. Depending on the individual stimulation intensity, TBS was delivered at 80% RMT using either a Magstim Super Rapid² or a Magstim Super Rapid² Plus stimulator (The Magstim Company Ltd, UK) and a 70mm figure-of-eight coil. Following the standard protocols for TBS established for the motor cortex[18], participants received a series of bursts of 3 magnetic pulses (pulse triplets) at a frequency of 50Hz which were repeated at a rate of 5Hz (i.e., 5 pulse triplets per second).

In total, each participant received 600 magnetic pulses. Depending on the experimental condition, these pulse triplets were delivered using one of three different stimulation protocols (Fig. 1b). In the continuous stimulation protocol (cTBS), pulses were delivered continuously for a duration of 40s. In the intermittent stimulation protocol (iTBS), pulses were delivered in intervals of 2s-stimulation-trains followed by a 8s-pause for a total of 190s. In the intermediate stimulation protocol (imTBS), pulses were delivered in intervals of 5s-stimulation-trains followed by a 10s-pause for a total of 110s. It has been shown, that cTBS leads to a deactivation of the targeted brain region for up to 60 minutes, whereas iTBS leads to an activation. ImTBS, however, has no such effect and represents thus a sham stimulation[18,27]. The coil was positioned tangential to the previously marked location on the head and manually held throughout the stimulation. Noticeable side effects consisted of muscle twitching in the face and neck, which participants reported to be moderately unpleasant.

***Instrumental Learning Task***

About 15 minutes after TBS, participants completed a modified instrumental learning task (ILT)[20,21,28,46] that allowed us to assess the goal-directed vs. habitual control of behavior. This task consisted of three phases: the learning phase, the devaluation phase, and the slips-of-action phase. During these phases, participants were presented with six different stimulus pairs consisting of fruit pictures (Fig. 2). These fruit pictures could serve either as discriminative cue stimuli (when depicted on top of a closed box) or as outcomes (when depicted within an open box). The stimulus pairs were linked by responses (button presses) that, if correct, would lead from a cue to an outcome. If participants acted in a goal-directed manner, they would be able to form stimulus-outcome-response (S-O-R) associations whereas habitual behavior would be reflected in the formation of simpler stimulus-response (S-R) associations. There was a total of six stimulus pairs with two pairs

belonging to one of three different discrimination conditions (Fig. 2a): congruent, incongruent, and standard. In the *congruent* condition, cue and outcome were the same fruit. Participants would thus only need to associate one fruit stimulus with the according response. In the *incongruent* condition, cue and outcome were different fruits. However, these stimulus pairs reversed their role across trials, demanding opposite responses depending on which fruit served as the cue (e.g., if a banana cue led to an orange by pressing the left arrow-key then an orange cue would lead to a banana by pressing the right arrow-key). It is argued that in this condition, goal-directed behavior leads to a response conflict because the two fruit stimuli are associated with opposite responses. For example, a banana should activate the "banana-orange-left" (S-O-R) association. In this case, however, the banana would additionally activate the "banana-right" (O-R) association learnt in trials in which the orange served as a cue. To avoid this response conflict, participants should rely on simple S-R ("banana-left", "orange-right") associations. Thus, the incongruent discrimination condition is usually used as a baseline measure of habitual behavior[19,28,46]. Finally, in the *standard* discrimination condition, a correct response towards the cue would lead to a distinct outcome fruit that was not otherwise used in the experiment. Participants could use either the habitual or the goal-directed system to form associations in these trials[20,47]. However, flexible adaption of behavior in the later slips-of-action phase critically depends on functional S-O-R associations (i.e. goal-directed behavior).

In the initial *learning phase* (Fig. 2b), participants were asked to learn associations between the discriminative cue stimulus, the appropriate response and the outcome for each stimulus pair by trial and error. In each trial, they were presented with a picture of a fruit on top of a closed box and were asked to open the box by pressing either the left or the right arrow-key on a keyboard. If the response was correct, the box opened to reveal the fruit outcome. If incorrect, the open box was empty. Correct responses also earned

points depending on reaction times (5 points for reaction times within 0-1 second; 4 points for 1-2 seconds; 3 points for 2-3 seconds; 2 points for 3-4 seconds; 1 point for 4-5 seconds). Participants were explicitly instructed to respond as fast as possible and had 5 seconds to respond before the trial was terminated and the next trial started. They were informed that a higher total score would convert into a higher monetary reward in order to motivate proper task performance. Importantly, participants could use both systems to complete the learning phase, forming either simple S-R (i.e. habitual) or more complex S-O-R (i.e. goal-directed) associations. In total, participants completed 9 learning blocks with each block consisting of 12 trials (4 trials per discrimination condition).

In the subsequent *outcome devaluation phase* (Fig. 2c), participants saw two open boxes containing fruits that were previously shown as outcomes but were associated with opposite responses (i.e., one of the depicted fruits followed a right button press, the other fruit followed a left button press). However, one of these formerly rewarded fruits was now devalued, as indicated by a red cross covering it. Participants were informed that the devalued fruit would no longer earn any points and that they should press the arrow-key that was associated with the other, still valuable fruit, only. There was a total of 12 trials, each former outcome was devalued twice. No feedback was shown to the participants in this phase. This outcome devaluation phase was included primarily to get the participants used to responding to former rewards instead of discriminative cue stimuli and to familiarize participants with the devaluation.

The critical *slips-of-action phase* (Fig. 2d) consisted of 6 blocks of 24 trials each. At the beginning of each block, participants were presented with an overview depicting 6 open boxes showing all fruits that served as rewarded outcomes in the learning phase. Importantly, two of these fruits were now marked with a red cross indicating that they were now devalued. This overview was shown for 10 seconds. Similar to the learning phase, participants were then presented with single closed boxes with fruits on them. They were

instructed to earn points by pressing the correct button associated with the fruit cue on the box only when the outcome fruit that would appear in the box was still valuable. If, however, the response would lead to a devalued outcome, participants should refrain from pressing any button at all. Any response towards a cue leading to a now devalued fruit would result in a subtraction of 2 points from the total score. Again, no feedback was provided to the participants. If participants responded in a goal-directed manner (i.e. relying on S-O-R associations), responses in each trial should be adapted to the value of the associated outcome fruit. If, however, participants responded more habitually (i.e. relying on S-R associations), they should show slips of action (i.e., responses to stimuli even when the outcome fruit is devalued). When the participants had completed the ILT, they were asked to fill in three questionnaires that tested their explicit knowledge about the stimulus-response, response-outcome and stimulus-outcome contingencies for each fruit pairing. In addition, participants also had to indicate their response certainty.

***Procedure***

The individual MRI scan was acquired several days or weeks before behavioral testing. Upon their arrival at the lab on the testing day, participants signed the informed consent form before completing German versions of the Beck Depression Inventory[48], the Behavioral Inhibition/Behavioral Activation System scale[49], the Barratt Impulsiveness Scale[50] and the NEO Five-Factor Inventory[51]. These questionnaires allowed us to control for personality traits and behavioral tendencies that are relevant in decision-making processes. For participants in the TBS groups, individual stimulation site and resting motor threshold were determined. Participants then received the ILT instructions and completed a training sequence in which they were presented with all three phases of the ILT using different fruits than in the main experiment. This was done to familiarize participants with the task and to avoid possible stimulation-induced differences in task comprehension. After

training, the experimenter left the room while stimulation was applied over the right ilPFC by a different experimenter, ensuring double-blindness. Participants then completed the ILT, including the contingency questionnaires. For the no-stimulation group, the ILT began shortly after training. In general, participants completed the task within 30 minutes. At the end of the experiment, participants were asked to rate the unpleasantness of the stimulation procedure on a scale from 1 to 10. Finally, all participants were debriefed and received a monetary compensation.

***Data Analysis***

For the learning and the devaluation phase, we calculated the percentage of correct responses as the primary measure of task performance. Reaction times were analyzed for the learning phase only. For the slips-of-action-phase, we focused on the percentage of slips. In addition, we calculated a difference score that reflects goal-directed behavior more generally by taking into account, that goal-directed behavior is also reflected in correct responses to valuable outcomes. In line with previous studies[20], this score is calculated by subtracting incorrect responses (i.e., pressing a button when the outcome was devalued) from correct responses (i.e., correct button presses for valuable outcomes and no button presses for devalued outcomes). We also corrected for missing button presses for still valuable outcomes. This score ranges from -100 to 100 with higher numbers indicating more goal directed behavior and lower numbers more habitual responding[20]. Data were analyzed using a mixed-design ANOVA with number of blocks (9 for analyses of the learning phase only) and discrimination condition (standard vs. congruent vs. incongruent) as within-subject factors and TBS condition (continuous vs. intermediate vs. intermittent vs. no-stimulation) as between-subjects factor. If necessary, Greenhouse-Geisser correction was applied. Significant main or interaction effects were further pursued by appropriate

*post-hoc* tests that were corrected for multiple comparisons, if required. All reported *p* values are two-tailed. Effect sizes are reported as partial $\eta^2$.

**Data availability statement**

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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**Author contributions**

M.B. performed research, analyzed data and prepared all figures and tables. M.B. and L.S. drafted the manuscript. L.S. designed research. J.T. helped performing research. J.G. helped analyzing data. F.H. helped design research. All authors contributed to writing the manuscript.

**Competing financial interests**

The authors declare no competing financial interests.

## Figures

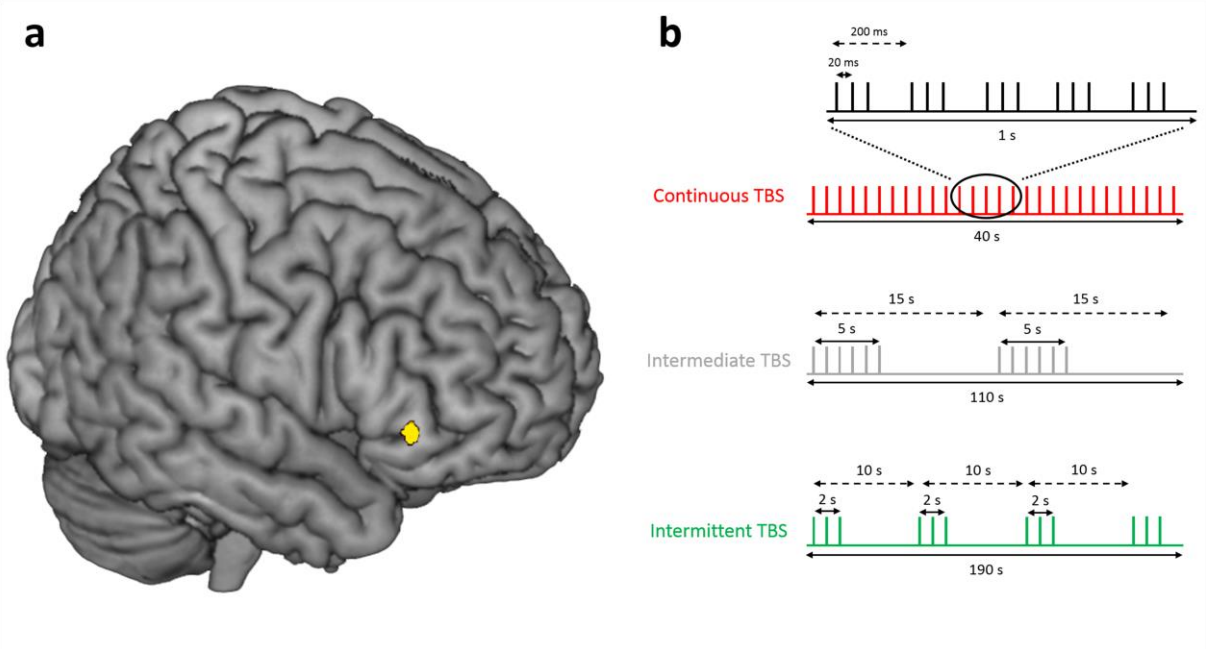


**Figure 1. Theta-burst stimulation protocol.** a, Using an individual anatomical MRI image and a stereotaxic frameless Brainsight neuronavigation system, theta burst stimulation (TBS) was applied over the right inferior lateral prefrontal cortex (MNI: x = 48, y = 35, z = -2). Coordinates were chosen based on former neuroimaging findings, suggesting that the ilPFC is involved in the interplay of habitual and goal-directed behavior[13]. b, TBS pulses were delivered in triple bursts, consisting of three magnetic pulses at an interval of 50Hz. Bursts were delivered at an interval of 5Hz. Participants received in total 600 pulses, in one of three TBS protocols that served as either inhibitory (cTBS), excitatory (iTBS) or sham stimulation (imTBS)[18]. Continuous (c)TBS consisted of 40 seconds continuous stimulation. Intermediate (im)TBS consisted of 5 second trains of active stimulation followed by a 10 second pause, lasting for a total of 110 seconds. Intermittent (i)TBS consisted of 2 second trains of active stimulation followed by an 8 second pause, lasting for a total of 190 seconds. In the no-stimulation control condition, participants did not receive any stimulation.

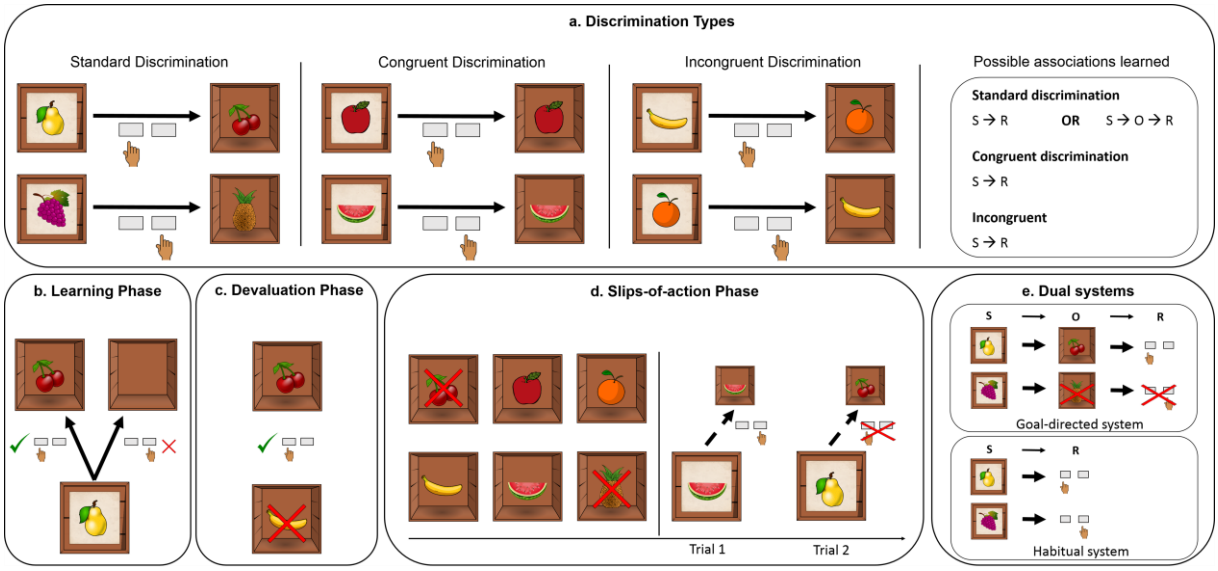


**Figure 2: Overview of the Instrumental Learning Task (ILT).** Participants were presented with 6 stimulus pairs consisting of fruit pictures. These pictures could serve as discriminative cue stimuli (depicted on top of a closed box) or outcome stimuli (depicted inside an open box). Stimuli pairs were linked by responses, which, if correct, would lead from cue to outcome. a, Stimuli pairs belonged to one of three discrimination conditions: standard, congruent, and incongruent. In the congruent condition, cue and outcome were identical. In the incongruent discrimination condition, different fruits served as cue and outcome. However, fruits reversed their role as cue and outcome across trials, demanding opposite responses depending on which fruit served as a cue. In the standard discrimination condition, discriminative cue stimuli and outcome stimuli were unique fruits. b, In the 9-block learning phase, participants were asked to learn the associations between the fruit stimulus pairs and the correct responses by trial-and-error. A correct response led to the outcome fruit and rewarded points. An incorrect response resulted in an empty box and no points. c, In the outcome devaluation phase, participants were presented with two formerly rewarded outcome fruits associated with opposite responses. However, one fruits was now declared devalued, indicated by a red cross. Participants were asked to press the button that was associated with the still valuable reward. d, In the 6-block slips-of-action phase,

participants were first presented with an overview of all formerly rewarded outcome stimuli at the beginning of each block, two of which were now devalued. Subsequently, they were again presented with the discriminative cue stimuli. Participants were instructed to only show the correct response to cues with still valuable outcomes. If the outcome had been devalued, participants should refrain from responding at all. e, If participants used the goal-directed system (i.e. S-O-R associations), responses should have been adapted to the actual value of the outcome stimuli. If, however, participants responded habitually (i.e. using S-R associations) they should show responses to stimuli with devalued outcomes (so-called slips-of-action). In this phase, correct responses would earn points whereas slips-of-action would lead to a subtraction of points. Pictures of fruits were taken from free online sources (pixabay.com and openclipart.org).

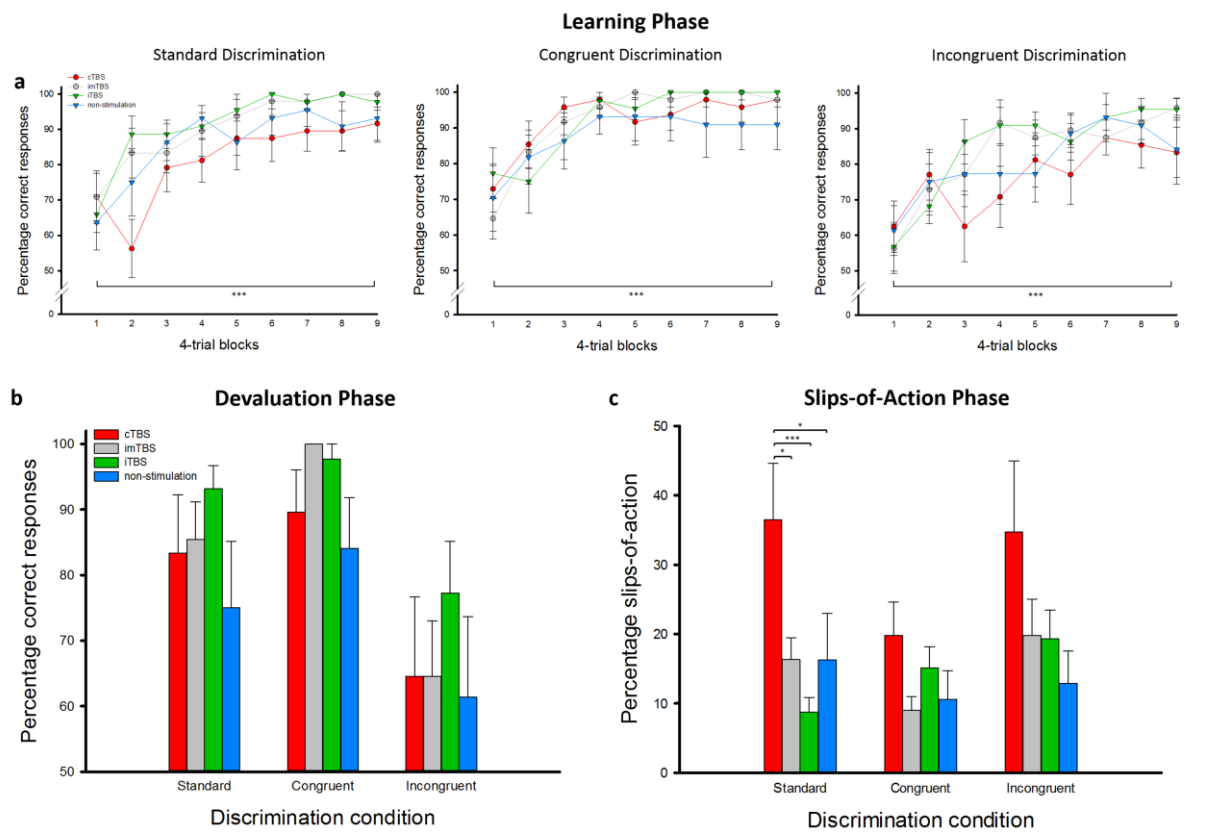


**Figure 3: Performance in the Instrumental Learning Task (ILT).** a, Participants learned the associations between the fruit stimulus pairs and the according responses very well, independent of TBS condition and across discrimination conditions. b, Performance in the devaluation phase was worse in the incongruent discrimination condition compared to the congruent and standard condition. TBS groups did not differ in their performance. c, In the critical slips-of-action phase, cTBS led to a significant increase in the percentage of slips-of-actioncompared to the imTBS and iTBS groups as well as the no-stimulation group. Inhibition of the ilPFC favored the use of the habitual system, in particular in the standard discrimination condition that could be completed using either the habitual or the goal-directed system. Error bars indicate SEM. *p < 0.05. ***p < .001.

**Table 1. Performance and certainty ratings in the contingency questionnaires**

| | cTBS | imTBS | iTBS | No-stimulation |
|---|---|---|---|---|
| Percentage correct responses | | | | |
| Standard discrimination condition | 91.67 ± 4.81 | 95.83 ± 2.99 | 98.48 ± 1.52 | 95.45 ± 0.05 |
| Congruent discrimination condition | 97.22 ± 2.78 | 98.61 ± 1.39 | 100 ± 0.00 | 92.42 ± 0.05 |
| Incongruent discrimination condition | 93.06 ± 3.82 | 97.22 ± 2.78 | 93.94 ± 6.06 | 90.91 ± 0.06 |
| Certainty ratings | | | | |
| Standard discrimination condition | 90.83 ± 5.30 | 93.47 ± 2.88 | 95.15 ± 3.03 | 84.84 ± 6.73 |
| Congruent discrimination condition | 98.89 ± 0.78 | 97.92 ± 1.05 | 98.33 ± 1.67 | 93.33 ± 3.89 |
| Incongruent discrimination condition | 90.83 ± 6.51 | 93.75 ± 2.89 | 96.06 ± 2.38 | 90.91 ± 5.36 |

Data represent mean ± SEM. cTBS, continuous theta burst stimulation; imTBS, intermediate theta burst stimulation; iTBS, intermittent theta burst stimulation.

**Table 2. Scores in the control measures**

| | cTBS | imTBS | iTBS | No-stimulation |
|---|---|---|---|---|
| TBS Intensity | 45.42 ± 2.13 | 46.08 ± 2.66 | 46.36 ± 1.77 | / |
| TBS Unpleasantness | 7.21 ± 0.39 | 6.25 ± 0.57 | 6.73 ± 0.67 | / |
| BDI | 4.33 ±1.26 | 4.08 ± 2.79 | 4.18 ± 2.38 | 6.18 ± 1.23 |
| NEO FFI | | | | |
| Neuroticism | 27.75 ± 1.77 | 28.42 ± 3.09 | 26.18 ± 2.93 | 31.55 ± 2.18 |
| Extraversion | 42.08 ± 1.15 | 37.42 ± 2.54 | 43.82 ± 1.55 | 44.45 ± 1.52 |
| Openness | 44.00 ± 1.33 | 43.75 ± 1.13 | 45.00 ± 1.45 | 43.64 ± 1.19 |
| Agreeableness | 43.92 ± 2.34 | 41.67 ± 1.44 | 45.64 ± 1.88 | 44.73 ± 2.12 |
| Conscientiousness | 43.92 ± 1.59 | 42.33 ± 1.96 | 45.09 ± 1.45 | 47.27 ± 1.92 |
| BIS/BAS scales | | | | |
| BIS | 16.33 ± 0.75 | 16.75 ± 1.59 | 16.91 ± 0.92 | 15.18 ± 0.736 |
| BAS overall score | 21.58 ± 1.22 | 24.58 ± 1.13 | 21.91 ± 0.58 | 20.73 ± 1.71 |
| BAS drive | 7.33 ± 0.38 | 7.75 ± 0.66 | 7.82 ± 0.46 | 6.73 ± 0.74 |
| BAS fun seeking | 6.42 ± 0.43 | 7.75 ± 0.48 | 6.91 ± 0.39 | 6.64 ± 0.53 |
| BAS reward responsiveness | 7.83 ± 0.63 | 9.08 ± 0.56 | 7.18 ± 0.44 | 7.36 ± 6.78 |
| BIS 15 | | | | |
| Non-planning | 10.67 ± 0.62 | 11.75 ± 0.91 | 11.09 ± 0.61 | 10.09 ± 1.06 |
| Motor | 11.50 ± 0.61 | 11.75 ± 0.82 | 11.45 ± 0.49 | 11.18 ± 0.44 |
| Attentional | 8.83 ± 0.71 | 9.75 ± 0.65 | 7.91 ± 0.58 | 10.18 ± 0.92 |
| Overall score | 31.00 ± 1.39 | 33.25 ± 1.64 | 30.45 ± 1.19 | 31.45 ± 1.73 |

Data represent mean ± SEM. cTBS, continuous theta burst stimulation; imTBS, intermediate theta burst stimulation; iTBS, intermittent theta burst stimulation; BDI, Beck Depression Inventory; NEO FFI, NEO Five Factor Inventory; BIS/BAS scales, Behavioral Inhibition/Behavioral Activation System scales; BIS 15, Barratt Impulsiveness Scale.

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