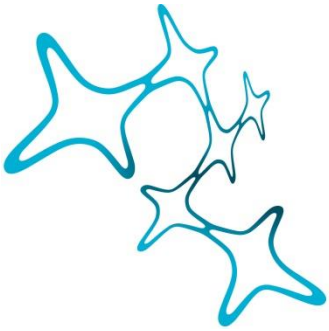
THE NEURAL BASIS OF SELF-CONTROL

PHARMACOLOGICAL, PHYSIOLOGICAL AND NEUROCOGNITIVE PERSPECTIVES

Georgia Eleni Kapetaniou



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Supervisor: Dr. Alexander Soutschek
General and Experimental Psychology
Faculty of Psychology and Educational Sciences
Ludwig-Maximilians-Universität München

First Reviewer: Dr. Alexander Soutschek
Second Reviewer: Prof. Dr. Ophelia Deroy
External Reviewer: Prof. Dr. Jan Peters

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Summary

Intertemporal choices, during which we have to decide between outcomes of different magnitude received at different points in time are pervasive in our everyday lives. Our ability to resist temptation in such situations and delay immediate gratification in favor of our long-term goals (i.e., self-control) is crucial. Self-control abilities have been correlated with better financial decisions, academic outcomes and overall well-being, while deficits in self-control have been frequently associated with psychiatric disorders, such as addiction, pathological gambling and obesity, often accompanied by relevant neural dysfunctions. It is therefore crucial to understand the mechanisms of self-control, not only at the theoretical, but also the empirical and more specifically, neural level. Understanding the underlying neurobiological mechanisms of self-control can provide unique insights into intertemporal decision making in health and disease. In this thesis, I investigate the neurobiological underpinnings of self-control taking a systemic and interdisciplinary approach. In more detail, I delved into pharmacological, oscillatory and neurocognitive dynamics contributing to intertemporal decision making, addressing key questions in the field.

The first project of the present thesis investigated the role of oxytocin in delay of gratification and flexibility in intertemporal choice. In contrast to a previously ascribed social role for oxytocin, growing evidence points to its domain-general beneficial effects in clinical samples. By testing these effects with healthy participants, we were able to show that oxytocin causally affects non-social decision making and leads to improved cognitive flexibility as well as enhanced delay of gratification in the intertemporal choice task.

The second project addressed the causal role of different oscillatory frequencies in the dorsolateral prefrontal cortex (dlPFC) for self-control. While previous correlational methods point to a link between specific brain oscillation frequencies and self-control, the causal implication of these frequencies in intertemporal choice was an open question. By using transcranial alternating current stimulation (tACS) over the left dlPFC, we were able to provide evidence for a causal involvement of alpha (10 Hz), beta (20 Hz) and gamma (30 Hz) oscillations in intertemporal choice.

Finally, with a combined high-definition (HD) tACS-fMRI paradigm, the third project investigated the brain network dynamics of metacognition during decision making. High intensity theta (5 Hz) HD-tACS impaired metacognitive sensitivity in the intertemporal choice task. Our results further revealed that the frontopolar cortex (FPC) actively implements metacognitive evaluations during decision making through functional connectivity with lateral prefrontal cortex (lPFC) and posterior parietal cortex (PPC), regions that were found to encode confidence and value information.

Taken together, this thesis provides new insights into the neural mechanisms underlying self-control, providing causal evidence for neurobiological, physiological and neurocognitive determinants of intertemporal decision making. The present findings can have important clinical implications, as they can potentially inform therapeutic interventions targeting different mechanisms of self-control.

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1. General Introduction

1.1. Self-control; past and present

Humans are faced constantly with multiple decisions between outcomes taking place at different points in time. Whether one has to decide whether to have another drink or head home to be well rested for the next day, indulge in overspending or saving up, or eat a burger instead of a salad, intertemporal decisions like these, where the mutually exclusive outcomes are received at different points in time and the delayed option has greater magnitude than the tempting, immediate reward are pervasive in our everyday lives. The ability to resist temptation and delay gratification for the sake of a long-term goal, therefore, or in other words our ability to self-control, is crucial for our well-being and can affect many aspects of our lives.

But despite the long-term benefits of going to sleep early, saving for retirement, or eating healthy, it is often the case that we would select the less beneficial option that would provide us with immediate gratification instead of the more beneficial but delayed one. Psychologists have tried for decades to understand and explain why despite having the needed skills, knowledge and opportunities, people are still struggling to adjust their behavior to their intentions (Metcalfe & Mischel, 1999; Mischel, Shoda, & Rodriguez, 1989; Muraven & Baumeister, 2000; Trope & Fishbach, 2000). Understanding this discrepancy between behavior and perceived self-interest has been characterized as one of the major but largely untackled theoretical challenges to decision theory (Loewenstein, 1996).

The study of the conflict between impulses and self-control can be traced to numerous historical accounts. An analogue of this conflict already appeared in the writings of Greek philosophers discussing “passion” versus “reason”. The paradox of self-control failure in particular, acting against our better judgement, was addressed as “weakness of will” by Socrates and Aristotle. As described in Plato’s Protagoras writings, Socrates reasoned that weakness of will cannot logically exist, as there is no individual that would willingly act against her better judgement. Rather, the judgement itself must be wrong, lacking the proper knowledge that a wise individual would have. Aristotle in turn, in his Nicomachean Ethics, argued that one could indeed

act against their better judgement, as that would mean that they were acting under the influence of their passions (Barnes, 1984; Hamilton, Cairns, & Jowett, 1997; Hofmann, Friese, & Strack, 2009).

In more recent history, Freud through his psychoanalytic theory defined such dilemmas as the conflict between primary processes and instincts (the impulse-driven and irrational id seeking immediate gratification) and secondary thinking (the patient, logical and goal-oriented ego striking the balance between the id and the morally guiding super-ego). In Freud's view, successful development was based particularly on developing the ego, in order for the child to learn to reject immediate satisfaction and pleasure (Duckworth, Gendler, & Gross, 2016; Freud, 1916–1917/1977).

Building on those early accounts, there has been extensive research on self-control from the viewpoints of different disciplines such as philosophy (e.g., Davidson, 1980), economics (e.g., Loewenstein & Elster, 1992; Thaler, 1994), and political science (e.g., Schelling, 1984). Notably, after Mischel and colleagues' seminal findings on children's delay of gratification ability (Mischel, Shoda, & Peake, 1988), a new framework was available to study self-control experimentally, giving rise to a great amount of work shedding light on this puzzling yet greatly important ability (Hofmann et al., 2009). Since then, several theoretical models provided accounts of self-control focusing on the behavioral and psychological aspects of failures of self-control and its consequences. Close to the Freudian concept, dual systems accounts suggested a dichotomy of hot/cool systems, where the "hot" system succumbs to all temptations and the "cool" system exerts self-control and controls the impulses (Metcalfe & Mischel, 1999), whereas the strength model postulated that self-control relies on a central resource that much like a muscle, once depleted, the individual is prone to self-control failures (Baumeister, Bratslavsky, Muraven, & Tice, 1998).

More recent accounts suggest a dual-motive concept where self-control plays a role in advancing distal over proximal motivations when the two are in competition (Fujita, 2008). These accounts depart from the previous notion that self-control reflects primarily the effortful inhibition of impulses in the effort to choose the "rational" larger but delayed reward, and rather suggest that impulse inhibition is one of many ways humans employ in pursuing motives for larger and more abstract rewards compared to proximal ones (Fujita, 2011). While other theoretical frameworks propose that self-control can be thought of simply as another instance of value-based decision making, where the decision maker selects an option between two or more alternatives based on

their subjective value (Berkman, Hutcherson, Livingston, Kahn, & Inzlicht, 2017), building on the abundance of empirical evidence available, there is recently a consensus from different theoretical viewpoints that delay of gratification and self-control depend on many more processes than a dual-system/dual-motive battle solely focused on inhibition of impulses. (Berkman et al., 2017)There is now clear evidence that self-control is a process affected by several contextual and incidental factors (Lempert & Phelps, 2016) and focus on the theoretical level seems to shift from impulse inhibition to simulation of the future self (O'Connell, Christakou, & Chakrabarti, 2015).

Across theoretical explanations, numerous empirical studies on self-control have been conducted to date, which provide a great amount of evidence on the importance of self-control for human well-being. The ability to delay gratification even early in life has been deemed a strong predictor of success later in life. The now seminal studies of Mischel, Shoda and Peake (1988; 1990) assessed the capacity of children to delay gratification at age 4 and showed after following up with them that the children with more successful delay of gratification at the time of the initial experiment had become young adults with better academic performance, pointing towards lasting and long-term benefits of self-control. Our ability to self-control reflects on aspects like financial planning (Angeletos, Laibson, Repetto, Tobacman, & Weinberg, 2001), consumer behavior (Baumeister, 2002) and higher probability of saving money (Strömbäck, Lind, Skagerlund, Västfjäll, & Tinghög, 2017). Deficits in self-control on the other hand, are linked to several disorders, such as substance abuse and addiction, obesity, pathological gambling and even ADHD (Amlung, Vedelago, Acker, Balodis, & MacKillop, 2017; Bickel et al., 2019; Bickel & Marsch, 2001; Critchfield & Kollins, 2001; Fujita, 2011) and have also been associated with a several poor health behaviors, including failure to attend to medical visits, exercise, wear a seat belt, engage in safe sexual behavior (Daugherty & Brase, 2010). Importantly, delay discounting (i.e., the rate of devaluation of the future reward) has been characterized and widely accepted as a trans-disease process underlying these maladaptive behaviors and calling for relevant interventions (Bickel et al., 2019; Bickel, Jarmolowicz, Mueller, Koffarnus, & Gatchalian, 2012).

As estimated by 2017, the societal costs of addiction in Europe alone were estimated to 8.7 billion euros for illicit drugs, with the same costs for tobacco and alcohol reaching 122 and 118 billion euros respectively (European Monitoring Centre for Drugs and Drug Addiction, 2017), whereas the social cost of obesity has been estimated at 70 billion euros per year (Erixon, 2016).

It is therefore clear, that understanding the mechanisms behind self-control in intertemporal choice is of paramount importance not only at the individual but also at the societal level. Given the crucial role that this faculty plays in our lives, well-being and prosperity, improving and fostering self-control could significantly reduce societal costs related to associated disorders, but also promote financial stability and prosperity.

Although extensive research has generated a great amount of empirical evidence at the behavioral level, understanding the neurobiological basis of self-control is an ongoing and relatively recently taken up endeavor. The importance of understanding the neurobiological mechanisms of this unique capacity is manifold. This type of evidence can allow us to clarify and provide support for theoretical accounts, distinguishing between competing models of self-control and contributing to our understanding of self-control at the theoretical and process levels. Most importantly, it is well known that self-control deficits in clinical disorders are associated with relevant neural dysfunctions (Baler & Volkow, 2006; Friederich, Wu, Simon, & Herzog, 2013; King et al., 2016; Norman et al., 2017; Norman et al., 2018; Sebastian et al., 2014). Thus, uncovering and understanding the neurobiological underpinnings of self-control is of paramount importance in order to pave the way towards new interventions and treatments for psychiatric disorders, core symptoms of which manifest with impairments of self-control.

Naturally, a discussion on the neurobiological underpinnings of any cognitive and behavioral ability cannot be single-faceted. With this dissertation, I took a systemic, interdisciplinary approach to investigate the neural mechanisms of self-control from different perspectives. For this, I investigated pharmacological, oscillatory, and neurocognitive dynamics contributing to intertemporal decision making, advancing the field in three directions, where lack of previous knowledge deserved investigation. In what follows, I briefly review theoretical models of self-control as a steppingstone for experimentation, followed by empirical evidence on the neurobiological mechanisms of self-control, including neuroimaging, pharmacological, neurostimulation and neurocognitive findings. For each, I identify core contributions and key unaddressed questions in the literature, introducing the rationale for the papers included in this dissertation.

1.2. Measuring and modeling intertemporal decision making

Through most of its research history, self-control has been defined as a preference for delayed but larger rewards over smaller but immediate ones (Ainslie, 1975; Fujita, 2011; Hoch & Loewenstein, 1991; Kirby & Herrnstein, 1995; Mischel et al., 1989; Rachlin, 1995). This conceptualization served and still does, as the basis for research on delay of gratification in intertemporal choice. The primary way that self-control is operationalized is by measuring individuals' time preferences and their ability to defer immediate rewards by preferring larger rewards delivered at a later time point. This is done through delay discounting tasks, measuring choice impulsivity, where participants are asked to make choices between rewards delivered at different points in time (Fujita, 2011). With this type of tasks, we are able to define the individual's discount function, which characterizes, the rate at which future outcomes are devalued the more delayed their delivery is in the future. Individual differences in discounting serve as a measure of impatience, with steeper discounting reflecting greater impatience and impulsivity.

Delay discounting is an early and widely accepted theoretical concept, stemming from the discipline of economics, that explains impatient decisions in intertemporal choice (Ainslie, 1975; Frederick, Loewenstein, & O'donoghue, 2002). It can be defined as the decrease of the subjective value of a reward the farther away its receipt is in the future, and it is established as a behavioral model of impulsive decision making in intertemporal choice and a core element of a broader impulsivity construct (Anokhin, Grant, Mulligan, & Heath, 2015). Discounting rate subsequently refers to the rate with which future rewards lose their present value and is often used as a measure of impatience. Early economic accounts of discounting, suggested that humans discount future rewards exponentially, decreasing the subjective value of a future reward by a fixed percentage for every time unit of delay, implying that a delay of one day now and one day more 10 days from now, will result to equal devaluation of the same reward (Samuelson, 1937).

Importantly, however, empirical evidence shows that when two rewards are both delayed, individuals are able to rationally select the larger reward. But when time has passed and one of the two is immediately available, the individual tends to have a stronger preference towards it, even if smaller. This would constitute a self-control problem, which, in contrast to the assumptions of the exponential discounting model, typically arises when individuals' preferences are inconsistent

across time or context (Ainslie, 1975; Loewenstein, 1996). This type of systematic preference reversal is ascribed to hyperbolic time discounting (Ainslie, 1975; Kirby, 1997), under which immediately available rewards have a disproportionate effect on preferences relative to more delayed rewards, causing a time inconsistent taste for immediate gratification (Ariely & Wertenbroch, 2002). Though other hyperbolic-like models have been proposed in the literature, as for example the quasi-hyperbolic discounting model (Laibson, 1997), which in parallel to dual systems theories, has two parameters for devaluing future rewards (one devaluing with a fixed percentage for every time unit as does the exponential model and one adding a present bias devaluing all future rewards by the same percentage), the hyperbolic discounting model has been widely validated and has shown to fit individuals' intertemporal choice and discounting behavior not only in humans, but across species (Kirby & Maraković, 1995; Mazur, 1987).

1.3. Neural mechanisms underlying self-control

Neuroimaging studies over the past decades have contributed greatly to understanding the mechanisms behind self-control and impulsivity. Using standard delay discounting tasks with a variety of primary and secondary rewards, research on the neural antecedents of self-control in intertemporal choice has yielded a set of converging results.

In one of the earliest neuroimaging studies in the field, McClure and colleagues found evidence for a set of brain regions consisting of ventromedial prefrontal cortex (vmPFC), ventral striatum and posterior cingulate cortex (PCC), involved with greater activation during impulsive choices. Conversely, a brain network composed of dorsolateral prefrontal cortex (dlPFC) and posterior parietal cortex (PPC) displayed greater activation during patient choices. This differential activity for impulsive and patient choices, replicated in a subsequent study (McClure, Ericson, Laibson, Loewenstein, & Cohen, 2007), led the authors to propose a dual systems model of intertemporal choice in the brain, in accordance with the quasi-hyperbolic discounting model, with two interacting systems: a system facilitating impulsive behavior (vmPFC, striatum and PCC) and a system facilitating patient behavior (dlPFC, PPC) (McClure et al., 2007; McClure, Laibson, Loewenstein, & Cohen, 2004).

Kable and Glimcher (2007) later reported similar brain areas involved in intertemporal decision making: vmPFC, ventral striatum and PCC during choice of immediate rewards, but with activation increasing hyperbolically as the value of the offer increased showing that these brain areas in reality track discounted subjective value and not just immediacy or present bias (Kable & Glimcher, 2007). These findings were further replicated (Kable & Glimcher, 2010), allowing for an alternative interpretation of neural mechanisms of intertemporal choice to that of the earlier studies. These brain areas are now considered to form the core of the brain's valuation system, which tracks the value of options across contexts and reward types, as replicated multiple times across groups (Hare, Malmaud, & Rangel, 2011; Kable & Glimcher, 2009; Levy & Glimcher, 2011; Levy & Glimcher, 2012; J. Peters & Büchel, 2009, 2010; Rangel & Hare, 2010).

Lateral brain regions on the other hand seem to make a different contribution to intertemporal decision making. More specifically, the dlPFC is suggested to interact with (rather than oppose) and modulate the subjective value signals of the vmPFC in order to promote self-control and patient choices (Figner et al., 2010; Hare, Camerer, & Rangel, 2009; J. Peters & Büchel, 2011). In addition, the left dlPFC has been found to be more active when individuals chose the delayed options and connectivity with the vmPFC increased at the time of choice, especially when they chose the delayed rewards (Hare, Hakimi, & Rangel, 2014). Additional studies provide evidence of greater prefrontal cortex involvement over striatal regions during patient choices, reflecting top-down cognitive control (J. Peters & Büchel, 2011), as reduced sensitivity to delay has been linked to lateral cortical activity (Ballard & Knutson, 2009). Lastly, it has been shown that structural and functional connectivity between the striatum and lPFC is linked to greater patience, whereas impulsivity was associated with connectivity between the striatum and subcortical areas (Van den Bos, Rodriguez, Schweitzer, & McClure, 2014).

With an Activation Likelihood Estimation meta-analysis of neuroimaging studies, Carter and colleagues show that despite the heterogeneity in methodology across groups and years, the findings of neuroimaging studies on delay discounting seem to largely overlap (Carter, Meyer, & Huettel, 2010). Moreover, in addition to brain areas involved in valuation and control, a typically reported set of regions involved in intertemporal choice is thought to reflect prospection, i.e. thinking about the future, (J. Peters & Büchel, 2011) as would be expected during intertemporal decision making. Those regions include inferior prefrontal cortex, medial prefrontal cortex,

temporoparietal cortex, and peri-splenial posterior cingulate (Carter et al., 2010). The medial orbitofrontal cortex (mOFC) in specific is thought to be involved in intertemporal choice in the preference for delayed rewards either through valuation, by computing the values of future outcomes, or through prospection, by enabling individuals to hold representations or imaginations of future rewards (Sellitto, Ciaramelli, & di Pellegrino, 2011).

These consistent and convergent findings from the neuroimaging literature, seem to not only resolve one of the early debates in neuroeconomics, but to have a strong impact both on psychology and economics. Findings from numerous studies clearly point to a common-currency valuation system across reward types, that in favor of self-control is modulated by a control network. This challenges the common assumption of dual process systems (e.g., hot/cool systems driving behavior) and rather provides support for unified accounts of self-control. With respect to economics, the neuroimaging findings are pointing towards a neurobiological system that reflects hyperbolic discounting across rewards, both at the behavioral and the neural level, whereas there is no strong evidence in support of the quasi-hyperbolic model at the neural level. Taken together, a great progress has been made over the past years in understanding the underlying brain mechanisms of self-control. This set of findings is a great steppingstone for a feedback loop between theory and evidence and for the development of further research to investigate the precise mechanistic involvement and computational role of these systems.

1.4. Pharmacological underpinnings of self-control

An important avenue of research on the neurobiology of self-control is that of neuropharmacology, an indispensable part of the neurobiological systems driving human behavior. In addition to important insights from neuroimaging research, whose findings are by nature correlational, pharmacological manipulations complement and advance this research providing novel insights into the mechanistic aspects of the nervous system, allowing simultaneously for causal evidence on the role of different neuromodulators (i.e., hormones, neurotransmitters and neuropeptides) in self-control. The main neuromodulators typically investigated for their involvement in decision making are the monoamine neurotransmitters dopamine, serotonin and norepinephrine, in addition to the hormones testosterone and oxytocin (Crockett & Fehr, 2014;

Serra, 2021). A great number of studies focusing on neuromodulation in monoaminergic corticostriatal systems have revealed the contribution of these neuromodulators to self-control and delay of gratification in intertemporal choice. This comes in agreement with neuroimaging evidence suggesting a strong contribution of corticostriatal connectivity in self-control (Van den Bos et al., 2014). Further, deficits in self-control have been linked to dysfunctions or dysregulations of these systems (Mitchell & Potenza, 2014). This stream of research can therefore be crucial in paving the way towards new treatment options targeting self-control deficits that are known to characterize several disorders (Amlung et al., 2017; Bickel et al., 2019; Bickel & Marsch, 2001; Critchfield & Kollins, 2001; Fujita, 2011).

Research to understand how dopamine modulates intertemporal and impulsive choice has been extensive, building on evidence that the frontostriatal circuits known to be involved in intertemporal choice are critically modulated by dopamine (Dagher & Robbins, 2009; Dalley, Mar, Economidou, & Robbins, 2008). While research on amphetamines (known to increase dopamine release) (Cardinal, 2006; Charrier & Thiebot, 1996; Floresco, Tse, & Ghods-Sharifi, 2008), and general increase of dopamine in the brain (Foerde et al., 2016; Kayser, Allen, Navarro-Cebrian, Mitchell, & Fields, 2012; Petzold et al., 2019; Pine, Shiner, Seymour, & Dolan, 2010) is inconclusive with regards to the precise effects or course of action, findings on more selective dopamine manipulations have shed light on dopamine's possible role in impulsive decision making. Some evidence from the animal literature points to increased impulsivity in rats after D1R (Van Gaalen, Van Koten, Schoffelmeer, & Vanderschuren, 2006) and D2R antagonist administration (Wade, De Wit, & Richards, 2000). In humans, contrary to D1R and D2R agonist administration showing no effects on self-control (Hamidovic, Kang, & De Wit, 2008; Soutschek, Gvozdanovic, et al., 2020), studies that manipulated dopaminergic activity with selective D2R antagonists, seem to converge to the finding that blocking D2R activity can lead to increased patience in intertemporal decisions (Soutschek et al., 2017; Wagner, Clos, Sommer, & Peters, 2020; Weber et al., 2016; though see Pine, et al., 2010). Although the exact role of dopamine in self-control is still the matter of controversial debate (Soutschek, Jetter, & Tobler, 2022), dopamine antagonist administration has been more clearly linked to increased patience in intertemporal choice, while findings for dopamine agonists seem to be mixed possibly due to baseline- and dose-dependent effects (Soutschek et al., 2022). Overall evidence suggests that dopamine may be involved in processes such as performing cost control and modulating sensitivity to reward

proximity (Soutschek et al., 2022), integrating both delay and reward magnitude for computing subjective value (Kheramin et al., 2004).

Serotonin is also considered well studied with respect to intertemporal choice and is known mostly from animal models to promote patient choices by increasing the ability to wait for delayed rewards (i.e., decreasing sensitivity to delay) (Mobini, Chiang, Ho, Bradshaw, & Szabadi, 2000; Schweighofer et al., 2008; Wogar, Bradshaw, & Szabadi, 1993; Xu, Das, Hueske, & Tonegawa, 2017). While a number of studies reported no effects on impulsivity following serotonin manipulations (Crean, Richards, & De Wit, 2002; Evenden, 1999; Evenden & Ryan, 1996, 1999; Winstanley, Dalley, Theobald, & Robbins, 2004), several other studies point to a clear direction of effects. Inhibition of serotonin synthesis has been shown to increase impulsivity (Bizot, Le Bihan, Puech, Hamon, & Thiébot, 1999; Denk et al., 2005; Schweighofer et al., 2008), and is suggested to do so possibly via altering striatal activity (Tanaka et al., 2007). Serotonin is also known to affect and modulate intertemporal decision making with decreases in 5-HT levels associated with increased impulsivity in rodents and humans (Mobini et al., 2000; Schweighofer et al., 2008; Winstanley et al., 2004), and deficits in the serotoninergic system correlated with impulsive behavior (Doya, 2008). Moreover, enhancement of serotoninergic activity through reuptake inhibitors or serotonin releasers showed to reduce impulsivity and enhance patient responding in rats (Bizot et al., 1999; Poulos, Parker, & Le, 1996). Finally, it has been posited that crucial to self-control abilities is the interaction between the dopaminergic and serotoninergic systems (Winstanley, Theobald, Dalley, & Robbins, 2005).

In contrast to dopamine and serotonin, studies on the role of norepinephrine in intertemporal choice are so far relatively limited and primarily adopt animal models. It has been reported that enhancing norepinephrine function is linked to reduced impulsivity in rodents (Bizot, David, & Trovero, 2011; Robinson et al., 2008), while stimulation specific to a2 receptors led to opposite results (Van Gaalen et al., 2006). Evidence from research on primates on the other hand, showed that administration of a selective a-2A receptor agonist led to reduced impulsivity (Kim, Bobeica, Gamo, Arnsten, & Lee, 2012). In humans, with a correlational and self-report study, it was found that the concentration of catecholamine levels correlated with drug use and steeper delay discounting (Brody et al., 2014), while the relationship between cocaine use and delay

discounting in a different study was modulated by the norepinephrine system (Havranek et al., 2017).

In contrast to pure neurotransmitters that have been studied extensively, the contribution of hormones like testosterone and oxytocin to self-control has received less attention in the literature. Testosterone has been investigated with relation to intertemporal choice, albeit in limited and mainly correlational studies. Previous research reports that elevated salivary testosterone levels in men correlated with higher patience (Takahashi, Sakaguchi, Oki, & Hasegawa, 2008), a finding replicated in a more recent study, however revealing an inverse relationship for female participants (Doi, Nishitani, & Shinohara, 2015). Testosterone levels were further found to be associated with lower integrity within the frontostriatal tract, in turn associated with higher impulsivity (Peper et al., 2013). Finally, active administration of testosterone was found to increase patience in rats (Wood et al., 2013), though causal evidence from human samples are mixed. Testosterone administration in healthy human males resulted in no significant difference in delay discounting between the testosterone and placebo groups (Ortner et al., 2013), whereas more recently significantly steeper discounting rates and increased impulsivity were reported as a result of a single dose administration of testosterone (Wu et al., 2020). A recent meta-analysis found a small but positive correlation between testosterone and impulsivity (Kurath & Mata, 2018) and mixed findings may again be accounted for by a suggested a baseline-dependent effect of testosterone on impulsivity (Takahashi, Sakaguchi, Oki, Homma, & Hasegawa, 2006).

In striking contrast with the previously discussed neuromodulators, oxytocin for a long time has been considered a social hormone, thought to critically modulate solely social behaviors, promoting prosociality (Kemp & Guastella, 2011; Shamay-Tsoory & Abu-Akel, 2016). Recent mounting evidence, however, points towards a domain-general role of this neuromodulator. In more detail, oxytocin has been found to reduce food intake in eating disorders and characterized previously as a potential target for treating obesity (Blevins & Ho, 2013; Giel, Zipfel, & Hallschmid, 2018; Lawson, 2017; Olszewski, Klockars, & Levine, 2017; Sabatier, Leng, & Menzies, 2013), suggesting a possible role of oxytocin in modulating phasic dopamine responses and altering dopaminergic neurotransmission (Love, 2014). Central administration of oxytocin in rats led to lower food seeking behavior, lower impulsivity and reduced dopamine neuron activity in food cue-evoked trials, affecting phasic dopamine responses in the ventral tegmental area. In

addition to food-related responses, oxytocin has been linked to reduced drug-seeking behavior (Cox et al., 2017; Kohtz, Lin, Smith, & Aston-Jones, 2018; S. T. Peters, Bowen, Bohrer, McGregor, & Neumann, 2017) and drug craving in addiction (Hansson et al., 2018; McRae-Clark, Baker, Maria, & Brady, 2013; M. A. Miller, Bershad, King, Lee, & De Wit, 2016), as well as reduced impulsivity in social anxiety disorder (Hurlemann et al., 2019). It has also been shown that oxytocin may modulate the neural response to ambivalence (Preckel, Scheele, Eckstein, Maier, & Hurlemann, 2015), risk aversion within and out of social context (Patel et al., 2015) and avoidance of negatively-valenced stimuli (Harari-Dahan & Bernstein, 2017).

Building on this evidence, recent theories on the function of oxytocin have taken into account its non-social effects (Harari-Dahan & Bernstein, 2014; Quintana & Guastella, 2020), with the most recent account positing a role of oxytocin for allostasis (i.e., a role for maintaining stability in changing environments) (Quintana & Guastella, 2020). The mechanistic role of oxytocin in non-social behavior, however, and in intertemporal decision making in specific is far from understood. One speculation could be that beneficial effects of oxytocin on delay of gratification could underlie the observed effects on addiction, while effects of oxytocin on reversal learning (re-learning dysfunctional cue-outcome associations) could underlie reported improvements of symptoms in schizophrenia (Gibson et al., 2014; Michalopoulou et al., 2015; Pedersen et al., 2011).

Here, we attempt to provide an account for the role of oxytocin in delay of gratification during intertemporal choice and value-based decision making. For this reason, in Chapter 2, consisting of the first paper in this dissertation, we tested the effect of intranasal oxytocin on non-social decision making, in delay of gratification and cognitive flexibility. The study was pre-registered and employed a placebo-controlled crossover design, where healthy participants performed decision making tasks on delay of gratification and reversal learning, in addition to inequity aversion and working memory that served as control tasks. We administered intranasal oxytocin or placebo in two separate sessions and hypothesized that oxytocin would result in enhanced delay of gratification and reversal learning compared to placebo.

1.5. Causal role of and oscillatory activity in dlPFC during self-control

Neuroimaging studies on self-control have clearly established a role of dlPFC in promoting patient decisions by modulating reward and value computations (Hare et al., 2009; Hare et al., 2011; Kable & Glimcher, 2010). Because neuroimaging evidence is typically correlational, neurostimulation studies over the past decade have taken up the challenge to elucidate the causal role of dlPFC in promoting self-control. With methods allowing to manipulate local neuronal excitability, thus disrupting or enhancing local brain function, evidence from neurostimulation studies has corroborated previous findings, revealing a causal role of dlPFC in intertemporal decision making (Cho et al., 2010; Essex, Clinton, Wonderley, & Zald, 2012; Figner et al., 2010; Hecht, Walsh, & Lavidor, 2013; Kekic et al., 2014).

Noninvasive brain stimulation has causally linked the dlPFC to various self-control behaviors. One of the first and most influential neurostimulation studies with respect to intertemporal decision making was that of Figner et al. (2010), providing for the first time clear causal evidence for the role of dlPFC in intertemporal choice. In this study, the authors applied low-frequency repetitive transcranial magnetic stimulation (rTMS) designed to disrupt local activity over the lPFC and showed that stimulation over the left and not right dlPFC led to increased choices of immediate rewards. Thus, disrupting left PFC activity impaired self-control processes (Figner et al., 2010). Moreover, a single session of high frequency rTMS on the left dlPFC has been shown to suppress cue-induced food cravings in healthy women (Uher et al., 2005; Van den Eynde et al., 2010). Similar to TMS, transcranial direct current stimulation (tDCS) has been shown to alter local neuronal excitability (Nitsche & Paulus, 2000; Stagg, Antal, & Nitsche, 2018), either enhancing it (anodal stimulation) or decreasing it (cathodal stimulation). Studies applying cathodal tDCS over the left dlPFC have reported more impulsive responding (Colombo, Iannello, Puglisi, & Antonietti, 2020) and fewer instances of successful self-control (Maier, Raja Beharelle, Polanía, Ruff, & Hare, 2020). Maier and colleagues further showed that tDCS particularly affected attribute weighting in the left dlPFC (Maier et al., 2020). With high definition tDCS (HD-tDCS) providing higher spatial specificity and ensuring the focality of stimulation effects, Shen and colleagues showed that anodal stimulation of the left dlPFC decreased impulsivity, while cathodal stimulation increased it, in line with previous findings. This modulation, however, was found to be dependent on baseline impulsivity (Shen et al., 2016). Finally, in agreement with previous findings, anodal HD-tDCS over the left dlPFC led to decreased discounting of future rewards (He et al., 2016).

Separate manipulations have shown similar effects of stimulation over the right PFC reducing impulsivity (Cho et al., 2010; Cho et al., 2012), drug (Camprodon, Martínez-Raga, Alonso-Alonso, Shih, & Pascual-Leone, 2007; Jansen et al., 2013), alcohol (Mishra, Nizamie, Das, & Praharaj, 2010) and food craving (Jansen et al., 2013; McClelland, Bozhilova, Campbell, & Schmidt, 2013), and bilateral frontal manipulations have shown to have beneficial effects in reducing impulsivity (Hecht et al., 2013) and suppressing food and drug cravings (Boggio et al., 2008; Fregni et al., 2008; Goldman et al., 2011; Kekic et al., 2014). However, bilateral stimulation paradigms cannot provide clear evidence on laterality of effects (results could be the case of inhibiting one area or enhancing activity in the other) and research (neuroimaging and neurostimulation) evidence is converging to a clear role of left dlPFC in promoting self-control.

A crucial aspect of the neurobiological antecedents of human behavior that is not addressed by the manipulations discussed above, is neuronal oscillatory activity (i.e., the rhythm of neuronal activity in the brain). Although MRI allows for localization of brain activity with good spatial resolution, it suffers with respect to temporal resolution and neurophysiological dynamics. Electroencephalograms (EEG), in turn, can provide a good account of temporal and oscillatory cortical dynamics. Research has shown that BOLD activity and connectivity across brain areas correlates with fluctuations in oscillatory power in the brain (Wang, Saalmann, Pinsk, Arcaro, & Kastner, 2012) and different wave oscillations have been linked to communication between cortical and subcortical areas (Fujisawa & Buzsáki, 2011; Schutter, Leitner, Kenemans, & van Honk, 2006; Siegel, Donner, & Engel, 2012) as well as several cognitive processes (Kahana, 2006; Sauseng & Klimesch, 2008; Ward, 2003). EEG research can therefore provide unique insights into the neurophysiological dynamics underlying decision making.

Through different EEG studies, several neural oscillation bands have been associated with various components of intertemporal decision making. In one of the first studies on the cortical dynamics of self-control, Hare and colleagues explored the role of PFC in dietary self-control. Measuring the changes in neural activity during exercising self-control, they found evidence for attentional filtering in the alpha band (10 Hz) in the early decision period, in line with previous research establishing a link between dynamic fluctuations in top-down attentional filtering by PFC during perceptual and working memory tasks (Lennert & Martinez-Trujillo, 2011; Suzuki & Gottlieb, 2013; Zanto & Gazzaley, 2009). Moreover, they showed that dlPFC was involved in

value modulation at a later decision stage, by increasing the weighting of stimulus value signals regarding the health attribute in vmPFC (Harris, Hare, & Rangel, 2013). In a more recent study, HajiHosseini and Hutcherson investigated the neurophysiological basis of value accumulation during self-control and reported that suppression of frontal and occipital alpha power was associated with the time course of evidence accumulation towards the decision and further tracked goal-relevant attributes. This effect is thought to have been regulated by early frontal and occipital activity in the theta band (5 Hz) (HajiHosseini & Hutcherson, 2021). Previous studies have shown that the temporal dynamics of evidence accumulation towards a decision have been associated with parietal and frontal theta (5 Hz) and alpha (10 Hz) (Hunt et al., 2012) and with both beta (20 Hz) and high gamma (> 40 Hz) oscillations (Polanía, Krajbich, Grueschow, & Ruff, 2014). Beta power has been more directly associated with impulsive decision making (Gianotti, Figner, Ebstein, & Knoch, 2012) and elevated reward processing as expressed with occipital alpha suppression, parietal beta and frontal theta activity, was correlated with a greater propensity to select the larger-later reward (Pornpattananangkul & Nusslock, 2016). Finally, with Electrocorticography (providing high spatial and temporal resolution), impulsive decisions were linked to frontal theta oscillations, whereas patient decisions were linked to beta oscillations pointing again to a top-down modulation of the reward system by lPFC (Gui, Yu, Hu, Yan, & Li, 2018).

There is therefore clear evidence for the involvement of different oscillatory patterns in the frontal cortex during intertemporal decision making. However, these findings, as with MRI, are correlational and do not provide a causal account for the involvement of this oscillatory activity in self-control. Research with noninvasive brain stimulation as outlined above is able to provide causal evidence on the involvement of certain brain areas in intertemporal choice and has provided crucial findings so far with respect to the neurocomputational role of different brain regions in decision making. The studies reviewed above, however, manipulated local cortical activity in a frequency-unspecific manner, either inhibiting or enhancing local function. Taking the two streams of research a step further, we tested here the causal effect of specific oscillatory rhythms in the left dlPFC. Specifically, we investigated the causal role of alpha and beta band oscillations in the dlPFC in the implementation of self-control. We did that by using transcranial alternating current stimulation (tACS), a neurostimulation method that can safely entrain oscillatory patterns in the brain (Antal & Paulus, 2013), allowing for a causal evaluation of the involvement of specific

oscillatory frequencies in self-control. In this, second study of the present dissertation presented in detail in Chapter 3, we stimulated the left dlPFC using tACS at the alpha (10 Hz), beta (20 Hz) and gamma (30 Hz) frequencies and expected altered responding in the delay discounting task under alpha and beta stimulation.

1.6. Neurocognitive aspects of self-control: The role of metacognition

At the process level, many cognitive functions and processes have been argued to play a role in self-control. Among the most reviewed ones are attention, reference dependence, time construal, situational factors, affect, episodic future thinking, working memory and perspective taking (Hinson, Jameson, & Whitney, 2003; Lempert & Phelps, 2016; Rung & Madden, 2018; Soutschek, Moisa, Ruff, & Tobler, 2020; Soutschek, Ruff, Strombach, Kalenscher, & Tobler, 2016; Wesley & Bickel, 2014). While it has been clear that people make decisions based on rules, habits and preferences, what is becoming increasingly clear over the past years is that they also deliberate over their options, thinking counterfactual outcomes and reflecting on their preferences (Bulley & Schacter, 2020). One relatively overlooked from an empirical perspective cognitive process, directly associated with successful decisions is metacognition. Metacognition refers to "cognition about cognition", or in other words our ability to assess, control and reflect on our thoughts, mental states, cognitive processes and actions (Flavell, 1979; Fleming, Dolan, & Frith, 2012). It has long been suggested that our decisions are not only dependent on the thought content itself, but rightfully so, also the metacognitive processes and experiences that accompany it. These experiences not only are equally informative as our thought contents, but they contribute significantly to forming and evaluating judgements and decisions across domains (De Martino, Fleming, Garrett, & Dolan, 2013; Deroy, Spence, & Noppeney, 2016; Schwarz, 2004; Soutschek & Tobler, 2020).

In relation to intertemporal decision-making metacognition is thought to enable controlling and evaluating prospection, our ability to think about the future, including the capacity to reflect on one's cognitive abilities' strengths and weaknesses in the future, together with evaluating alternative representations of future outcomes. In this sense, a decision maker may deliberate and compensate for anticipated changes of mind (Bulley & Schacter, 2020) and metacognitive insight

provides access to one's own future simulations allowing for their evaluation. Metacognition therefore allows decision makers to adjust their expectations or employ strategies in prospect of future failures (Bulley & Irish, 2018; Redshaw, Vandersee, Bulley, & Gilbert, 2018) and is necessary to consciously identify potential lapses of self-control (Soutschek & Tobler, 2020). Even considering future consequences (episodic foresight - a process enhancing self-control) is thought to stem from the ability to reflect on one's thoughts and behavior. Metacognition, finally, is thought to facilitate self-regulation by goal setting, enabling evaluation of whether the goals are reached and by adjusting behavior (Gifford, 2009).

An important contribution of empirical findings is that metacognitive abilities do not necessarily correspond to greater self-control, but rather better access to the noise and uncertainty in one's decision. Showing metacognitive insight, participants typically assign high confidence to decisions where the difference in subjective value between the two options is greater and the decision is in line with the individual's valuation, whereas less confidence in decisions is typically associated with changes of mind (Bulley, Lempert, Conwell, & Irish, 2021). With respect to intertemporal decision making, metacognition has further been associated with precommitment, a self-control strategy, through which one might restrict their future access to temptations via a binding choice for the long-term reward (Bryan, Karlan, & Nelson, 2010; O'Donoghue & Rabin, 1999; Soutschek & Tobler, 2020; Strotz, 1956; Thaler & Shefrin, 1981). Soutschek and Tobler recently provided evidence that metacognitive awareness of one's own susceptibility to future temptations was crucial for optimizing intertemporal decisions (Soutschek & Tobler, 2020).

Research on addiction has recently begun to take into account metacognitive processes. Metacognitive deficits have been characterized as a critical feature of the addiction phenotype, as there have been often reported a dissociation between self-report and actual behavior (low treatment compliance, relapse, lack of perception that treatment is needed). Especially the lack of perceived need for treatment is believed to stem from an impaired capacity to assess the severity of one's impairment or not even be aware that they have self-control problems (Ramey & Regier, 2019). Though most of the studies in the clinical field rely on self-report to assess metacognitive ability, and there is an apparent definitional heterogeneity, there has been a clear link between metacognitive deficits and addiction (Balconi, Finocchiaro, & Campanella, 2014; Hamonniere & Varescon, 2018; Wasmuth et al., 2015), where poor metacognitive abilities have been linked to

alcohol consumption, cigarette smoking (Spada, Nikčević, Moneta, & Wells, 2007; Spada & Wells, 2005), substance use disorder (Balconi et al., 2014) and gambling (Angioletti, Campanella, & Balconi, 2020; Brevers et al., 2013).

Research on the neural mechanisms of metacognitive ability has begun to elucidate this higher-level concept. De Martino and colleagues investigated how the valuation process interacts with subjective confidence in both brain and behavior. They showed that during value comparison, both the comparison process and the confidence in it are associated with vmPFC activation, while vmPFC-lPFC connectivity reflects metacognitive access to the accuracy of one's decision. Overall, they show that subjective confidence reveals systematic changes in the noise of the decision and that humans typically have access to this noise during value comparison, as shown by increased confidence associated with increased accuracy. It becomes apparent that not only confidence interacts with value, but it is really integral to how the brain represents value itself (De Martino et al., 2013). A number of further studies have localized metacognition across domains in the frontopolar cortex (FPC) (Fleming & Dolan, 2012; Qiu et al., 2018; Rouault, McWilliams, Allen, & Fleming, 2018; Vaccaro & Fleming, 2018), and neurostimulation research has supported the causal implication of FPC in metacognition (Rahnev, Nee, Riddle, Larson, & D'Esposito, 2016; Ryals, Rogers, Gross, Polnaszek, & Voss, 2016; Shekhar & Rahnev, 2018).

With respect to oscillatory activity, Wokke et al. showed that frontal theta oscillations were associated with metacognitive performance (Wokke, Cleeremans, & Ridderinkhof, 2017) and Soutschek et al. later provided support for a causal role of frontopolar theta oscillations in metacognition (Soutschek, Moisa, Ruff, & Tobler, 2021). In more detail, they found that enhancing frontopolar theta activity led to increased metacognitive accuracy in reporting subjective uncertainty during intertemporal decision making and strengthened the awareness of potential preference reversals. With causal evidence they showed that FPC does not passively represent confidence information but has an active, causal role in metacognitive reporting and evaluation via theta oscillations.

Though previous research has identified brain areas involved in metacognition, little is known about the neurocognitive mechanisms of metacognition at the network level. It is hypothesized that FPC might have a role in reading out signals from vmPFC or dlPFC via theta oscillations that would allow the FPC to access decision-related information (Soutschek et al.,

2021). Here, building on this previous research that established a causal role for frontopolar theta oscillations in metacognition, we address the precise neurocomputational trajectory adopted by the human brain at the network level in order to implement metacognition. As detailed in Chapter 4, consisting of the third paper of this dissertation, with a combined tACS-fMRI study we aimed to elucidate those mechanisms underlying tACS-induced effects on metacognitive ability and behavior. Participants performed a confidence accuracy task, consisting of the typical delay discounting task where they also had to indicate their confidence in their decisions in the MRI scanner. Simultaneously, they received HD-tACS over the FPC at the theta (5 Hz) and alpha (10 Hz) frequency. We expected theta stimulation to change metacognitive sensitivity in the task, expressed via altered connectivity between the FPC and areas encoding stimulus-related information (dlPFC, PPC, vmPFC).

In the following Chapters, the three studies comprising the present thesis are presented. As outlined throughout the Introduction, the separate papers investigate pharmacological, physiological and neurocognitive underpinnings of self-control. In the first study (Chapter 2) we investigate the role of oxytocin in delay of gratification and reversal learning. In the second study (Chapter 3) we explore the causal role of oscillatory frequencies in the dlPFC in implementing self-control, and in the third and final study of this thesis (Chapter 4) we investigate the neural networks underlying metacognition in intertemporal choice. In Chapter 5 I summarize the findings of each project and outline the theoretical and practical implications of the present work. Finally, in Chapter 6 I conclude this work and summarize its contributions.

2. The role of oxytocin in delay of gratification and flexibility in non-social decision making

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GEK, MAR, AJ, PNT, FP, and AS designed research; GEK, MAR, PC, and AS performed research; GEK and AS analyzed data; GEK and AS wrote first draft of manuscript; all authors approved manuscript

RESEARCH ARTICLE

The role of oxytocin in delay of gratification and flexibility in non-social decision making

Georgia Eleni Kapetaniou[1,2]*, Matthias A Reinhard[3], Patricia Christian[1,2], Andrea Jobst[3], Philippe N Tobler[4,5], Frank Padberg[3], Alexander Soutschek[1,2]

[1]Department of Psychology, Ludwig Maximilian University Munich, Munich, Germany; [2]Graduate School for Systemic Neurosciences, Department of Biology, Ludwig Maximilian University Munich, Munich, Germany; [3]Department of Psychiatry and Psychotherapy, University Hospital, Ludwig Maximilian University Munich, Munich, Germany; [4]Zurich Center for Neuroeconomics, Department of Economics, University of Zurich, Zurich, Switzerland; [5]Neuroscience Center Zurich, University of Zurich, Swiss Federal Institute of Technology Zurich, Zurich, Switzerland

Abstract Oxytocin is well-known for its impact on social cognition. This specificity for the social domain, however, has been challenged by findings suggesting a domain-general allostatic function for oxytocin by promoting future-oriented and flexible behavior. In this pre-registered study, we tested the hypothesized domain-general function of oxytocin by assessing the impact of intranasal oxytocin (24 IU) on core aspects of human social (inequity aversion) and non-social decision making (delay of gratification and cognitive flexibility) in 49 healthy volunteers (within-subject design). In intertemporal choice, patience was higher under oxytocin than under placebo, although this difference was evident only when restricting the analysis to the first experimental session (between-group comparison) due to carry-over effects. Further, oxytocin increased cognitive flexibility in reversal learning as well as generosity under conditions of advantageous but not disadvantageous inequity. Our findings show that oxytocin affects both social and non-social decision making, supporting theoretical accounts of domain-general functions of oxytocin.

***For correspondence:**
Georgia.Kapetaniou@psy.lmu.de

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Introduction

The neuropeptide oxytocin is well-known for its impact on social behavior, including maternal care, social recognition, or costly sharing (***Campbell, 2010***; ***Lee et al., 2009***; ***Macdonald and Macdonald, 2010***). Several theoretical accounts regarding the functional role of oxytocin for social cognition have been proposed. Two of the most prominent theories are the social salience hypothesis and the approach/withdrawal hypothesis. The social salience hypothesis ascribes oxytocin a crucial role for regulating attention to social cues (***Shamay-Tsoory and Abu-Akel, 2016***), whereas the social approach/withdrawal hypothesis posits that oxytocin facilitates approach-related and inhibits withdrawal-related social emotions (***Kemp and Guastella, 2011***). However, the specificity of oxytocin for the social domain is challenged by an increasing body of evidence for oxytocin effects on non-social cognition and behavior. For example, intranasal oxytocin was found to reduce craving in addiction (***Hansson et al., 2018***; ***McRae-Clark et al., 2013***; ***Miller et al., 2016***), reduce food intake in eating disorders (***Giel et al., 2018***), improve negative symptoms and working memory in schizophrenia (***Gibson et al., 2014***; ***Michalopoulou et al., 2015***; ***Pedersen et al., 2011***), and reduce avoidance of negatively valenced non-social stimuli (***Harari-Dahan and Bernstein, 2017***). From a mechanistic perspective, however, the role of oxytocin for non-social behavior remains poorly understood, given that the precise neuro-computational role of oxytocin is still a matter of controversy

(*Bethlehem et al., 2013*; *Chini et al., 2014*; *Veening and Olivier, 2013*). More recent accounts aim to reconcile the social and non-social effects of oxytocin by positing a domain-general role of oxytocin for allostasis (*Quintana and Guastella, 2020*) or for approach versus avoidance motivation (*Harari-Dahan and Bernstein, 2014*). According to the latter approach, oxytocin modulates approach-avoidance behavior by facilitating the processing of personally relevant and emotionally evocative cues. The allostatic theory of oxytocin claims that oxytocin enables maintaining stability in changing environments by facilitating the anticipation of future needs and flexible behavioral adaptations. The ability to delay gratification by resisting immediate temptation impulses is a hallmark of future-oriented behavior, whereas behavioral flexibility relies on the capacity to re-learn old, dysfunctional associations between environmental cues and outcomes (reversal learning). In fact, a role of oxytocin for delaying gratification and reversal learning could potentially explain several of the observed oxytocin effects on non-social behavior: beneficial oxytocin effects on addiction or over-eating may relate to improved delay of gratification, while deficits in re-learning of dysfunctional cue-outcome associations are a hallmark of the negative symptoms in schizophrenia (*Bowen and Neumann, 2017*; *Reddy et al., 2016*; *Waltz and Gold, 2007*). We therefore tested the impact of intranasal oxytocin on these two core aspects of non-social decision making, delay of gratification (reward impulsivity), and cognitive flexibility (reversal learning). By assessing also the impact of oxytocin on generosity (inequity aversion), we directly compare oxytocin effects on social and non-social decision making in humans and thereby bring two lines of research together that remained largely separate in the past. Thus, our study investigates the role of oxytocin beyond standard theoretical accounts focusing on its function for social cognition and behavior (*Kemp and Guastella, 2011*; *Shamay-Tsoory and Abu-Akel, 2016*).

For this purpose, we conducted a pre-registered randomized, placebo-controlled, within-subject study in which 49 healthy participants performed decision-making tasks measuring delay of gratification, reversal learning, and inequity aversion after intranasal administration of either oxytocin or placebo in two separate sessions. To explore whether the impact of oxytocin on decision making is mediated by effects on working memory capacity (WMC) (*Michalopoulou et al., 2015*), participants performed the digit span backward task as measure of WMC both before and after substance administration. Measuring WMC before substance administration allowed us to test whether the impact of oxytocin on behavior depends on baseline difference in cognitive performance, as has been observed for other pharmacological interventions particularly in the domain of reversal learning (*Cools et al., 2009*; *Kimberg et al., 1997*). We hypothesized that intranasal oxytocin (relative to placebo) increases the preference for delayed rewards in intertemporal choice, in line with previous findings from animal research and clinical studies suggesting reduced craving and impulsiveness under oxytocin (*Hansson et al., 2018*; *Hurlemann et al., 2019*; *Miller et al., 2016*). For reversal learning, we hypothesized that oxytocin improves cognitive flexibility, as suggested by animal findings (*Roberts et al., 2019*). Finally, we hypothesized that oxytocin increases advantageous inequity aversion (*Pornpattananangkul et al., 2017*).

Results

Oxytocin enhances delay of gratification

First, we tested the hypothesis that oxytocin improves delay of gratification (i.e., weakens the decline of the subjective value of delayed rewards with longer delays). In the intertemporal choice task, participants chose between smaller-sooner (SS; ranging from 0.5 to 4.5 euros received at the end of the experiment) and larger-later (LL; 5 euros received after a delay ranging from 1 to 180 days) reward options in 54 trials (*Figure 1A*). In a model-free analysis, we regressed choices (0 = SS option, 1 = LL option) on predictors for Substance, baseline WMC, Delay, SS reward, Order of substance administration, and all interactions. As to be expected, the analysis revealed a main effect of immediate reward, beta = −7.56, $z = -7.77$, $p < 0.001$, and a significant SS reward × Delay interaction, beta = −4.57, $z = -4.72$, $p < 0.001$. Moreover, the analysis suggested the presence of carry-over or task repetition effects, because order of substance administration modulated the main effect of oxytocin, beta = −2.13, $z = -2.68$, $p = 0.007$, as well as the impact of oxytocin on Delay, beta = −1.97, $z = -2.27$, $p = 0.022$. No other factors or interactions reached significance, all $p > 0.05$ (*Supplementary file 1a*). In order to control for the confounding effects of Order of

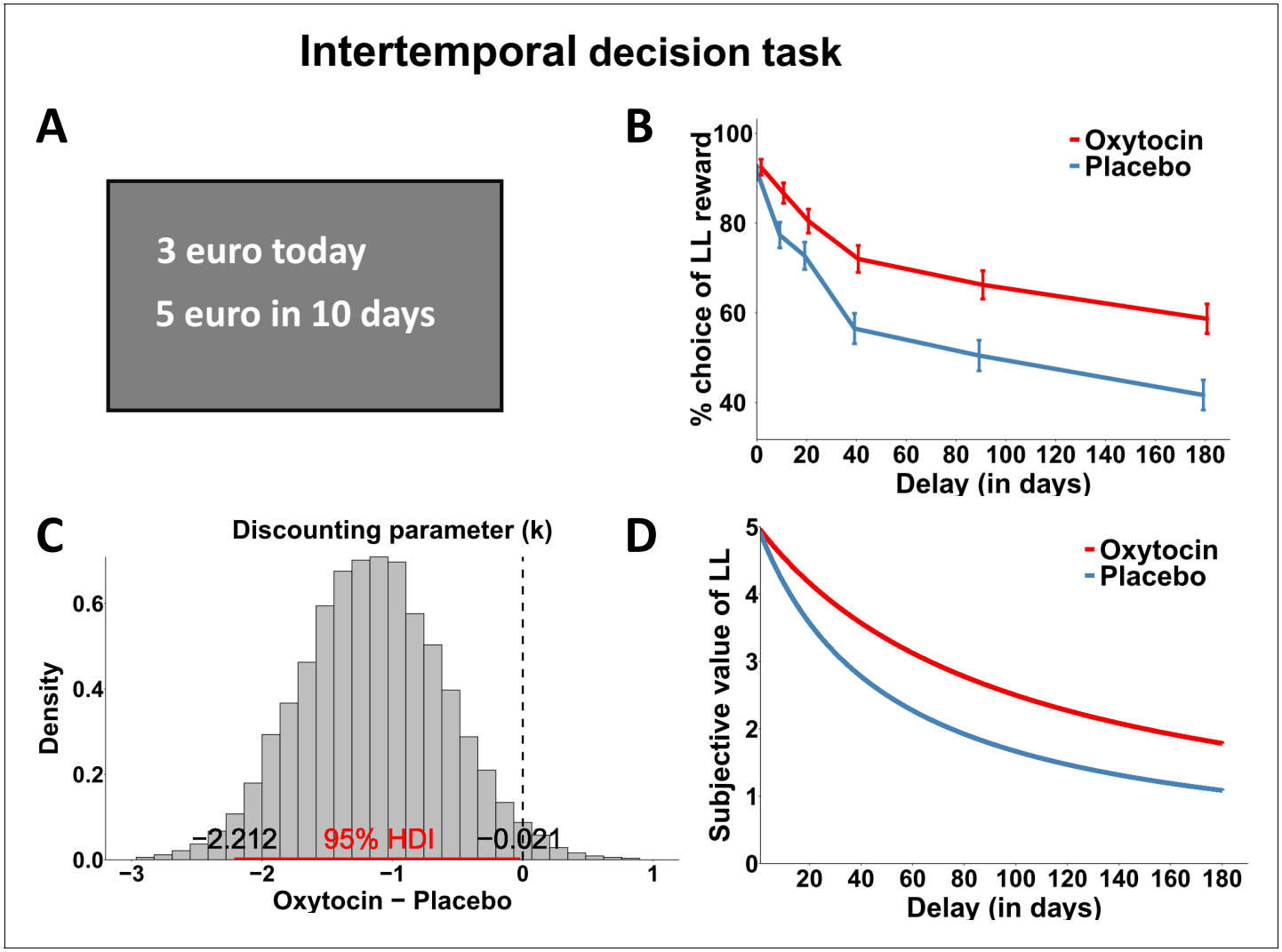

Figure 1. Intertemporal decision task design and results. (**A**) In the intertemporal choice task, participants decided between an immediate reward option (0.5–4.5 euros) and a larger-later reward option (5 euros) delivered after a delay of 1–180 days. (**B**) Model-free oxytocin effects on intertemporal choice. Under oxytocin, participants chose the delayed reward more frequently than under placebo (data from the first experimental session). Error bars represent standard error of the mean. (**C, D**) Model-based results of the intertemporal decision task. (**C**) Posterior distribution and 95% highest density interval (HDI) of the difference (Oxytocin – Placebo) for the discounting parameter (k). The HDI does not include 0, suggesting that the mean parameter estimates under oxytocin are lower than under placebo and that discounting of future rewards was reduced. (**D**) Subjective value of the delayed reward as a function of delay, based on group-level mean estimates. Participants under placebo showed overall steeper discounting of future rewards compared to oxytocin.

substance administration, we restricted our analysis on the first experimental session and re-computed the MGLM described above, leaving out predictors for Order and WMC. This procedure is recommended for crossover designs with significant carry-over effects, as the data from the first experimental session by definition are free from carry-over or task repetition effects (although at the cost of lowering the statistical power of the analyses) (***Armitage and Hills, 1982***). A sensitivity analysis indicated that our between-subject comparisons could detect effects of Cohen's $d = 0.81$ with a power of 80% (alpha = 5%). In this analysis, we found significant main effects of Delay, beta = −4.10, $z = -2.28$, p = 0.022, SS reward, beta = −5.99, $z = -6.27$, $p < 0.001$, and the Delay × SS reward interaction, beta = −3.50, $z = -4.19$, $p < 0.001$. Importantly, a significant Substance × Delay interaction, beta = 5.24, $z = 2.11$, p = 0.034, suggests that oxytocin reduced delay discounting, supporting our hypothesis (***Figure 1B***). We found no significant interaction between Substance and SS reward, beta = −1.50, $z = -1.15$, p = 0.248 (***Supplementary file 1b***). We note that there

was no evidence for baseline differences in WMC between oxytocin and placebo groups, $t(46) = 0.827$, $p = 0.412$, such that the oxytocin effects on delay discounting are unlikely to be explained by pre-existing group differences in baseline cognitive performance.

Our model-free findings are supported by model-based analyses. Using hierarchical Bayesian modeling, we estimated the group-level hyperbolic discount parameter k (***Laibson, 1997***) in the first experimental session (due to the carry-over effects in the model-free results), separately for the oxytocin and placebo groups. To assess group differences, we computed the highest density interval (HDI) of the difference between the posterior distributions of the log-transformed group-level estimates (oxytocin minus placebo). As the 95% HDI = [−2.21; −0.02] showed no overlap with zero, we can conclude with 95% confidence that the discount rate was lower under oxytocin than under placebo (***Figure 1C, D***). In contrast, there was no evidence for group differences in the noise parameter ('inverse temperature'), HDI = [−0.20; 0.34]. Thus, the model-free and model-based findings provide converging evidence that impulsivity in intertemporal choice is reduced in the oxytocin compared to the placebo group.

Oxytocin improves reversal learning as a function of baseline WMC

Next, we tested the hypothesis that oxytocin improves the flexible re-learning of stimulus-outcome associations. In the reversal learning task, participants were presented with two stimuli ('X' or 'O'), one of which was associated with reward (+1) and the other with loss (−1). In 120 trials, the participants were instructed to predict the outcome associated with each stimulus and use feedback to learn the correct associations, which were subject to be reversed across the task (***Figure 2A***). We regressed mean correct responses after reversal trials with predictors for Substance, Previous outcome (−1 = punishment, 1 = reward), Order, baseline WMC, and the interaction effects. While we found an interaction of Substance × Order, beta = 0.04, $t(134) = 2.49$, $p = 0.013$

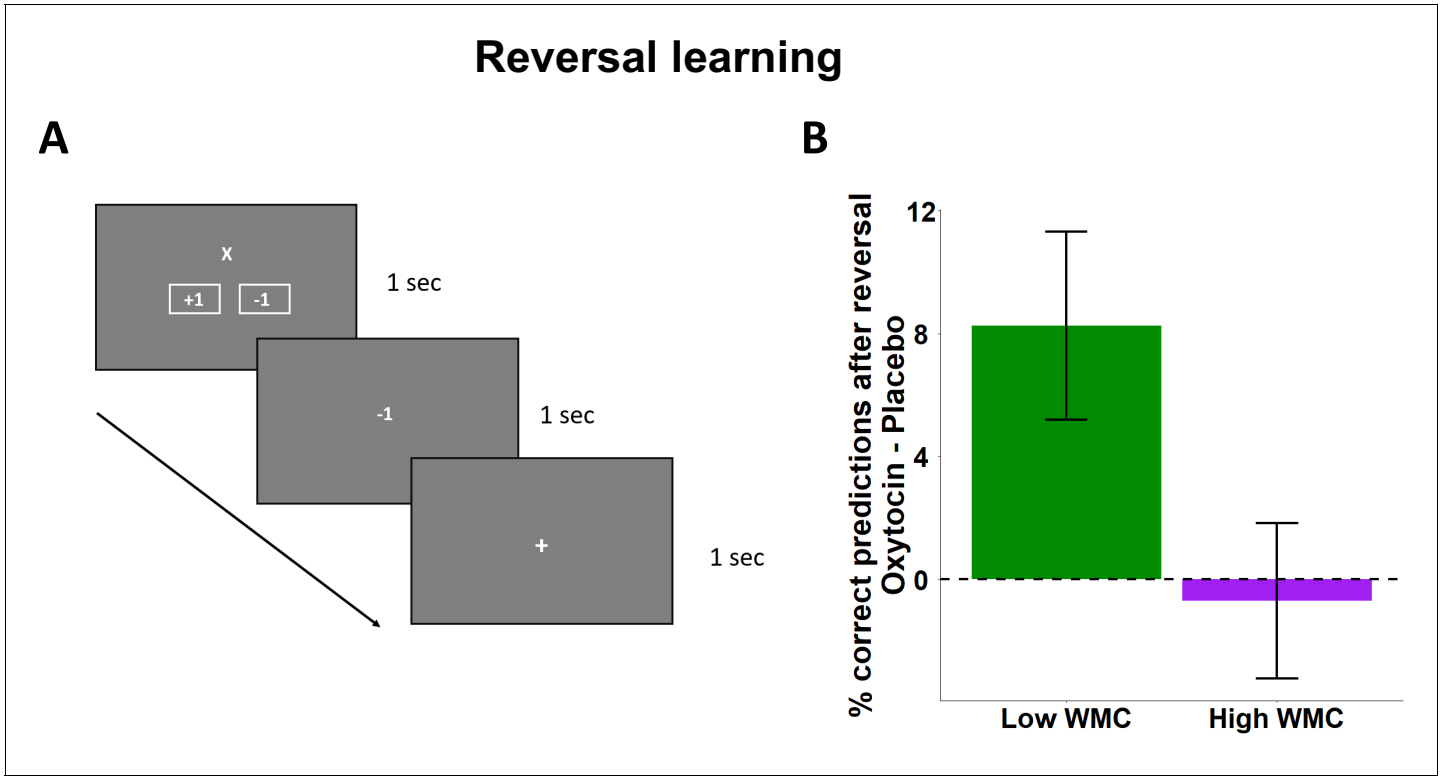

Figure 2. Reversal learning task design and results. (**A**) In the reversal learning task, participants were presented with one of two stimuli ('X' or 'O') and were asked to predict whether the stimulus was associated with reward (+1) or punishment (−1). Following the choice, participants viewed the outcome with which the stimulus was associated and were instructed to use this feedback to learn the correct associations. (**B**) Oxytocin increased the number of correct predictions following reversal trials relative to placebo. This effect was significant for individuals with low baseline working memory capacity. Error bars represent standard error of the mean.

(*Supplementary file 1c*), oxytocin tended to improve reversal learning relative to placebo independently of order effects, beta = 0.03, $t(134) = 1.90$, p = 0.058, and this effect was significantly modulated by baseline WMC, beta = −0.04, $t(134) = -2.26$, p = 0.025. No further effect was significant, all p > 0.05. To resolve this interaction effect, we performed separate analyses for the two WMC groups. While we found no significant oxytocin effects in the high WMC group, beta = −0.007, $t(68) = -0.27$, p = 0.782, we observed significant improvement of reversal learning under oxytocin, relative to placebo, in the low WMC group, beta = 0.08, $t(66) = 2.69$, p = 0.008 (*Figure 2B* and *Supplementary files 1d, e*). Variation in the data due to Order of substance administration in the low WMC group was accounted for by a Substance × Order interaction, beta = 0.069, $t(66) = 2.28$, p = 0.025. These findings are in line with previous animal findings (*Roberts et al., 2019*) and suggest that oxytocin improves reversal learning as a function of baseline WMC, consistent with the baseline-dependent impacts of other pharmacological interventions (including dopamine agonists and antagonists) on reversal learning (*Cools et al., 2009*; *Kandroodi et al., 2020*; *Kimberg et al., 1997*; *Soutschek et al., 2020b*; *van der Schaaf et al., 2014*).

Oxytocin increases advantageous but not disadvantageous inequity aversion

We further assessed whether oxytocin influences generosity under both advantageous and disadvantageous inequity. In the modified dictator game, participants chose between an equal and an unequal allocation of coins for themselves (M_{self}) and another randomly selected participant (M_{other}). The unequal allocations could be either advantageous ($M_{self} > M_{other}$) or disadvantageous ($M_{self} < M_{other}$) to the participant, allowing us to test whether oxytocin has dissociable effects on

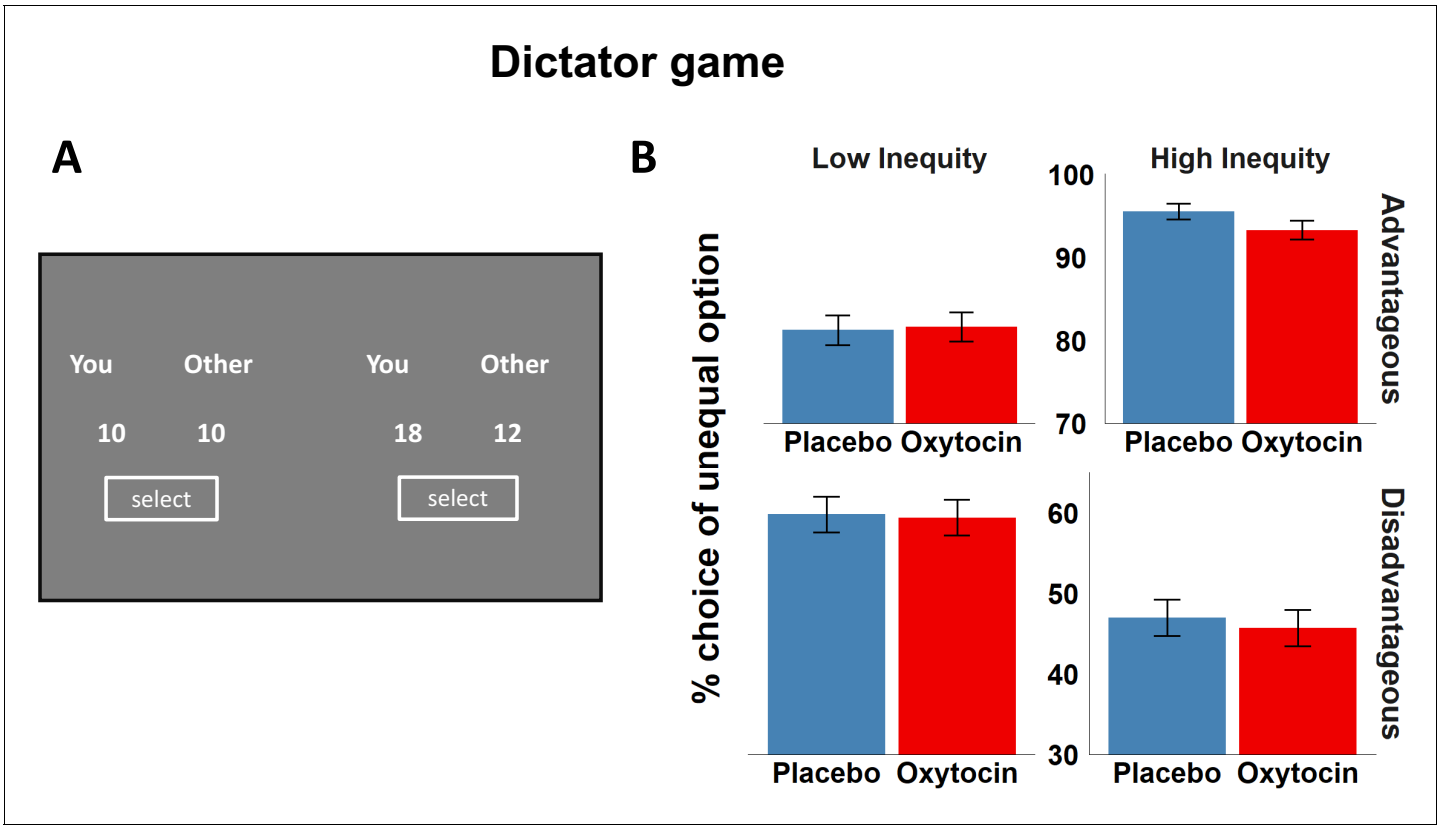

Figure 3. Dictator game task design and results. (**A**) In the modified dictator game, the participants made a choice between an equal allocation of money (You 10, Other 10) and an unequal allocation between themselves and another person. Half of the unequal allocations were advantageous for the participant (e.g., You 18, Other 12), the other half was disadvantageous (e.g., You 12, Other 18). (**B**) Oxytocin reduced choices of unequal reward options relative to placebo under conditions of high advantageous inequity, indicating increased aversion to being better off than others. The impact of oxytocin was significantly stronger on advantageous than on disadvantageous inequity aversion. For illustration purpose, we show oxytocin effects separately for low and high inequity trials. Error bars represent standard error of the mean.

advantageous and disadvantageous inequity aversion (***Figure 3A***). We regressed choices in the dictator game (0 = equal option, 1 = unequal option) on predictors for Substance, Order, baseline WMC, Inequity type (advantageous versus disadvantageous; the reference category was set to advantageous inequity), Inequity amount (absolute difference between M_{self} and M_{other}), and all interaction effects, controlling for Efficiency (sum of M_{self} and M_{other}). We observed significant effects of Inequity amount (beta = 5.32, z = 3.81, p < 0.001), Efficiency (beta = 20.97, z = 7.75, p < 0.001), Order × WMC (beta = 2.68, z = 2.08, p = 0.036), and Order × Inequity amount × WMC interactions (beta = 1.85, z = 2.13, p = 0.032) (***Supplementary file 1f***). Furthermore, participants chose the unequal option less often under conditions of disadvantageous relative to advantageous inequity (indicating stronger aversion to disadvantageous compared to advantageous inequity), main effect of Inequity type, beta = −23.09, z = −6.22, p < 0.001, with this effect being even more pronounced with increasing Inequity amount, beta = −14.05, z = −5.68, p < 0.001. As hypothesized, the preference for unequal over equal splits with increasing advantageous inequity was weaker under oxytocin compared with placebo, beta = −2.37, z = −1.93, p = 0.026, one-tailed (as pre-registered), replicating previous findings that oxytocin increases generosity (***Pornpattananangkul et al., 2017***; ***Strang et al., 2017***; ***Zak et al., 2007***). We note, though, that the impact of oxytocin on advantageous inequity aversion was weaker than the effects of other task-specific experimental manipulations (e.g., Inequity amount) and would have been only marginally significant (p = 0.052) with a two-tailed test. Interestingly, oxytocin more strongly affected advantageous relative to disadvantageous inequity aversion, beta = 3.15, z = 2.20, p = 0.027 (***Figure 3B***). No further effect was significant, all p > 0.05. Thus, oxytocin increases generosity, specifically in conditions of advantageous inequity, rather than inequity aversion per se.

A model-based analysis using the Fehr–Schmidt model for inequity aversion (***Fehr and Schmidt, 1999***) revealed no significant oxytocin effects, advantageous inequity aversion: 95% HDI = [−0.04; 0.04], disadvantageous inequity aversion: 95% HDI = [−0.18; 0.10]. We note, though, that the Fehr–Schmidt model may provide a poor fit of dictator game data (***Engelmann and Strobel, 2004***). Nevertheless, our model-free results replicate the finding that oxytocin increases generosity (***Pornpattananangkul et al., 2017***; ***Strang et al., 2017***; ***Zak et al., 2007***), extending previous findings by showing that oxytocin increases prosociality more strongly under advantageous than under disadvantageous inequity.

No evidence for effects of oxytocin on working memory performance

The observed impact of oxytocin on social and non-social decision making raises the question as to whether these effects are mediated by a common mechanism. We explored whether working memory, as measured with the digit span backward task, might constitute such a common process, based on previous reports of oxytocin effects on working memory in schizophrenia (***Michalopoulou et al., 2015***). However, there was no evidence for significant oxytocin effects on working memory, beta = −0.003, t(147) = −0.12, p = 0.902 (***Supplementary file 1g***). The results further revealed significant effects of Order, beta = 0.07, t(100) = 2.70, p = 0.008 and Substance × Order, beta = −0.101, t(147) = −4.186, p < 0.001, all further effects were p > 0.05. However, even when restricting our analysis to session 1, there was no evidence for a Substance × Assessment time interaction, beta = 0.007, t(49) = 0.132, p = 0.89, which would suggest that oxytocin changes post-test relative to pre-test WMC. When we computed a Bayes factor indicating how strongly the data favor the alternative over the null hypothesis using the brms package (four sampling chains with 2000 iterations including 1000 warm-up iterations and normal priors with mean = 0 and sd = 1) (***Bürkner, 2017***), the Bayes factor of 0.024 indicated strong evidence in favor of the null hypothesis.

Lastly, there was no evidence for oxytocin effects on future orientation, mood, or restlessness neither on a within-subject level (across both experimental sessions; future orientation: t(48) = 0.78, p = 0.437; mood: t(48) = 0.504, p = 0.617, restlessness: t(48) = 0, p = 1) or a between-subject level (restricting our analysis to the first experimental session; future orientation: t(46) = 0.39, p = 0.697; mood: t(46) = 0.34, p = 0.735; restlessness: t(46) = 0.157, p = 0.857). It is thus unlikely that the observed oxytocin effects on decision making were driven by effects on these measures.

Discussion

Oxytocin has been of major scientific interest for its influence on social behavior, but researchers are just beginning to explore its impact on non-social behavior (**Giel et al., 2018**; **Hansson et al., 2018**; **Miller et al., 2016**). Here, we show that intranasal oxytocin affects important components of non-social decision making, that is, delaying gratification and reversal learning.

Delay of gratification was increased under oxytocin compared with under placebo, as evidenced by both the model-based and model-free results. This result is consistent with previous evidence suggesting a link between oxytocin receptor genes and impulsiveness (**Yim et al., 2016**) as well as beneficial effects of oxytocin on impulsiveness in social anxiety disorder (although using a non-incentivized task with hypothetical rewards, hampering the validity of the measures) (**Hurlemann et al., 2019**). We speculate that oxytocin might have reduced impulsiveness via interactions with the dopaminergic system as delay of gratification has been related to dopaminergic activity (**Pine et al., 2010**; **Weber et al., 2016**), whereby blocking dopaminergic neurotransmission increases delay of gratification similar to our current findings.

Oxytocin facilitated also the re-learning of previously learned stimulus-outcome associations. This effect of oxytocin was more pronounced in individuals with low, compared with high, WMC, which mirrors the findings of dopaminergic manipulations on reversal learning (**Cools et al., 2009**; **Soutschek et al., 2020b**; **van der Schaaf et al., 2014**). Low working memory performance is associated with low dopamine baseline levels, and in fact the influence of oxytocin on learning has been hypothesized to be mediated by oxytocin-dopamine interactions (**Baracz and Cornish, 2013**). We therefore speculate that oxytocin might have improved reversal learning by strengthening valence-unspecific prediction error signals in the striatum, in analogy to previous findings for the dopamine antagonist sulpiride in a combined pharmacology-neuroimaging study (**van der Schaaf et al., 2014**). Alternatively, reversal learning also crucially depends on orbitofrontal cortex (**Schoenbaum et al., 2007**), which too is susceptible to oxytocin manipulations (**Preckel et al., 2015**). While the underlying neural mechanisms require further investigation, our results are in line with recent animal findings suggesting significant improvement in the probabilistic reversal learning task after oxytocin administration in rodents (**Roberts et al., 2019**) and provide first evidence in humans for a causal role of oxytocin for the flexible updating of cue-outcome associations. Furthermore, the result is in line with the allostatic theory (**Quintana and Guastella, 2020**) that predicts improved reversal learning under oxytocin.

Finally, we extend previous reports on the role of oxytocin for prosocial giving (**Pornpattananangkul et al., 2017**; **Strang et al., 2017**; **Zak et al., 2007**) by showing that oxytocin promotes generosity predominantly under conditions of advantageous, not under disadvantageous, inequity. Our findings therefore imply that rather than rendering behavior more altruistic or more equity-seeking in general, oxytocin strengthens the willingness to reduce self-serving inequity. Rephrased in psychological terms, our findings suggest that oxytocin reduces egocentricity when being better off than others but does not affect envy related to being worse off.

Our data raise the question as to whether common or dissociable mechanisms underlie the observed impact of oxytocin on non-social and social decision making. Oxytocin receptors are available in both prefrontal cortex and striatum (**Jurek and Neumann, 2018**), and decisions in all of the investigated domains depend on a balance between frontal and striatal networks (**Dalley et al., 2008**; **Peper et al., 2013**). It is worth noting that we found no impact of oxytocin on working memory functioning, which rather speaks against a mediating role of prefrontal activation for the observed oxytocin effects on decision making. It is thus tempting to speculate that oxytocin might have influenced decision making via oxytocin receptors expressed in striatal reward circuits, where oxytocin might mirror the effects of dopamine antagonists (**Love, 2014**). According to this view, a plausible interpretation of our findings might be that oxytocin could have increased prosocial giving and delay of gratification by lowering the subjective values of selfish and immediate rewards, respectively, whereas it may have facilitated reversal learning by enhancing neural prediction error signals. Alternatively, oxytocin might have affected decision making via interactions with the endocannabinoid system (**Pagotto et al., 2006**; **Wei et al., 2015**), which, similarly to dopamine, was linked to delay discounting and reward learning (**Boomhower and Rasmussen, 2014**; **Parsons and Hurd, 2015**).

Our findings are consistent with recent theoretical accounts ascribing oxytocin a domain-general role for both social and non-social behavior. Consistent with the predictions of the allostatic theory (**Quintana and Guastella, 2020**), oxytocin improved reversal learning and future-oriented behavior, which both may enhance an organism's survival. In this framework, aversion to advantageous inequity too may improve allostasis by strengthening social cohesion. Consistent with the neuropharmacological mechanism we proposed for our findings, optimizing behavior in changing environments relates to dopaminergic activity (**Le Heron et al., 2020**). The allostatic theory might account for the observed findings better than the approach-avoidance account (**Harari-Dahan and Bernstein, 2014**) as this account may have difficulties to explain why oxytocin reduced cost sensitivity in delay discounting instead of increasing the preference for immediate rewards (which is typically considered as approach behavior). Likewise, also the salience-based account of oxytocin would need to explain why delayed rewards and advantageous inequity are more salient than immediate rewards and disadvantageous inequity, respectively.

Alternatively, the results for delay discounting and inequity aversion might be explained by oxytocin's role for perspective taking (**Domes et al., 2007**; **Tomova et al., 2019**), given that perspective taking promotes both patient and prosocial choice (**Soutschek et al., 2016**). Perspective taking might be considered as a mechanism that enhances survival in terms of the allostatic theory, but this explanation could not explain the reversal learning results, such that the assumption that oxytocin modulates value processing appears more parsimonious. Oxytocin also reduces stress and anxiety (**Neumann and Slattery, 2016**); however, stress effects on delay discounting or reversal learning reported in the literature (**Haushofer et al., 2013**; **Joffe et al., 2019**) do not match the oxytocin effects observed in our study. On balance, oxytocin effects on the neural reward system, which on a psychological level may regulate allostatic processes, appear to be the most plausible and parsimonious explanation for the observed effects on decision making.

Our findings inform observations in clinical studies. Intranasal oxytocin has been shown to have beneficial effects on both social and non-social key symptoms of several psychiatric disorders. Regarding non-social symptoms, for example, oxytocin reduces drug craving in addiction (**Hansson et al., 2018**; **McRae-Clark et al., 2013**; **Miller et al., 2016**) and over-eating in eating disorders (**Giel et al., 2018**). Despite the evidence for such beneficial effects, a mechanistic understanding of them is limited. By providing insights into the domain-general role of oxytocin for decision making, our findings advance the field toward this direction. Given that deficits in delay of gratification contribute to the symptoms in addiction and obesity, the beneficial effects of oxytocin in these disorders might (at least partially) be caused by oxytocin-induced decreases in impulsivity. Likewise, impaired reversal learning has been associated with the negative symptoms in schizophrenia, which too may be ameliorated after oxytocin treatment (**Ota et al., 2018**). Our findings in healthy humans may thus corroborate and extend the effectiveness of oxytocin-based treatments of these disorders and suggest that it may arise at least partly through reduced delay discounting.

Some limitations are worth to be mentioned. First, we employed a systemic manipulation of oxytocin levels. As discussed above, while oxytocin effects on the dopaminergic reward system are a plausible candidate for a common neural mechanism, other mechanisms of oxytocin action with a different functional neuroanatomy (e.g., prefrontal cortex) need to be discussed as well. Furthermore, given possible carry-over effects in the delay of gratification task we followed the recommended approach of restricting our analysis to the data from the first session (**Armitage and Hills, 1982**). However, this procedure comes at a cost. First, it reduces the statistical power of our analysis due to lowering the sample size and due to relying on a between-subject instead of a within-subject comparison. Second, we cannot exclude the possibility that potential unassessed confounding variables might have driven the significant difference between the oxytocin and the placebo group. These issues could be addressed in future research by employing a parallel group design with higher statistical power or by increasing the time between the experimental sessions to lower the risk of task repetition effects. We can only speculate about the reasons for the repetition effects in the intertemporal choice task. The fact that choices were more patient in the second (mean = 73.4%) than in the first experimental session (70.6%) indicates potential anchoring effects, such that participants receiving placebo in the second session might have remembered their relatively more patient choices under oxytocin in the first session. In any case, we note that one should be cautious with ascribing oxytocin a causal role for delaying gratification due to the nature of the performed between-subject comparisons. A further limitation is that we restricted our sample to male

participants. Oxytocin may have dissociable effects on decision making and behavior in males and females (**Hoge et al., 2014**; **Kubzansky et al., 2012**), consistent with reports of gender differences in the reward system's sensitivity to the value of sharing (**Soutschek et al., 2017**). To the best of our knowledge, however, there is no evidence so far for gender differences in the neural basis of delay discounting and reversal learning, suggesting generalizability of these findings.

To conclude, our findings provide evidence for an impact of intranasal oxytocin on delay of gratification and reversal learning, demonstrating that oxytocin affects key components of both social and non-social decision making in humans. These findings contribute to the accumulating evidence challenging the specificity of oxytocin for social behavior and support recent accounts positing a domain-general role of oxytocin.

Materials and methods

Participants

Fifty healthy male volunteers were recruited through the participant pool of the Melessa lab at the Ludwig Maximilian University Munich, Germany. The sample size was based on a power analysis (power = 80%, alpha = 5%) assuming an effect size of Cohen's d = 0.38 as observed in a previous study on the impact of oxytocin on social decision making (**Pornpattananangkul et al., 2017**). One participant dropped out after the first experimental session, resulting in a final sample of 49 participants (mean age = 23.9 years, sd = 4.14, range 18–36). The study protocol was approved by the local Ethics Committee. All participants were screened for contraindications of intranasal oxytocin and gave written informed consent before the start of the experiment. For their participation, they received 40 euros and a bonus depending on their choices. The study was pre-registered on the Open Science Framework (https://osf.io/ykvd5).

Study design and procedures

The study followed a randomized, double-blind, placebo-controlled, crossover experimental design, spanning over two sessions timed 1 week apart. The participants were randomly allocated to two groups, one receiving oxytocin in the first and placebo in the second session, the other group receiving the substances in reversed order. Participants were assigned a subject code according to order of arrival at the lab and received the corresponding substance for that subject code in the given session. The random assignment of subject codes to drug condition was implemented by the pharmacy of the University Hospital Heidelberg and was unknown to the experimenters (double-blind design). At the beginning of the session, participants performed the digit span backward task as baseline measure of cognitive performance, followed by intranasal administration of either oxytocin or placebo. Following the standard guidelines for intranasal oxytocin administration in human participants (**Guastella et al., 2013**), the participants self-administered under supervision 24 IU (six hubs per nostril) of oxytocin (Syntocinon) or placebo, which contained the same ingredients except for the neuropeptide. Participants were unable to distinguish between oxytocin and placebo, $\chi^2(1) = 1.04$, p = 0.307.

After a waiting period of 45 min for oxytocin to reach peak levels (**Bethlehem et al., 2013**; **Spengler et al., 2017**), participants performed a task battery including the digit span backward task, reversal learning task, dictator game, and intertemporal decision task in counterbalanced order (total task performance lasted less than 30 min). At the end, participants filled out questionnaires on demographic information, potential side effects, future orientation, mood, and restlessness. As measure for future orientation, participants rated how well they could imagine (i.e., have a clear image of) their general life situation in 10 years on a 20-point Likert scale. Mood and restlessness were measured on a 7-point Likert scale ranging from 'very bad' to 'very good' and from 'very restless' to 'very calm', respectively.

Behavioral assessments

All tasks were programmed in zTree version 4.1.6 (**Fischbacher, 2007**).

Intertemporal decision task

In the intertemporal choice task, participants made choices between SS and LL rewards. The amount of the immediately available SS reward varied from 0.5 to 4.5 euros in 0.5 increments (e.g., 3 euros today), whereas the LL was fixed to 5 euros and delivered after a variable delay (e.g., 5 euros in 40 days; used delays: 1, 10, 20, 40, 90, and 180 days). Crossing nine immediate amounts with six delays resulted in a total of 54 trials (***Soutschek et al., 2020a***; ***Soutschek et al., 2016***). The SS and LL options were presented on the top and bottom of the screen (counterbalanced across trials), and participants made their choices by clicking with the mouse on the corresponding button (***Figure 1A***). Participants were informed in advance that one trial would be randomly selected at the end of the experiment and the chosen decision would be implemented. If a participant had chosen the SS option, the amount was paid out at the end of the experiment, whereas if he had chosen the LL option, the corresponding amount was sent to him after the corresponding delay via mail.

Reversal learning task

We adopted a version of the reversal learning task that allows dissociating between reward and punishment reversal learning (***Cools et al., 2009***; ***van der Schaaf et al., 2014***). In this task, the participants were presented with two stimuli: the letter 'X' or the letter 'O'. One of the stimuli was associated with reward, a +1 sign, and the other with a loss, a −1 sign. In a total of 120 trials, the participants were instructed to predict the outcome associated with the currently presented cue by clicking with the mouse on the corresponding button (***Figure 2A***). After the selection, the correct association appeared on the screen and the participants were instructed to use this feedback to learn the correct associations. They were instructed, however, that these associations may change within the task and they should again use the feedback to learn the new associations as quickly as possible. After such reversals, participants faced an unexpected punishment after selecting a stimulus previously associated with reward or unexpected reward after selecting a stimulus previously associated with punishment. Accuracy on the trials following reversals is thought to reflect the ability to update stimulus-outcome associations after unexpected outcomes (rewards or punishments).

Dictator game

In the modified dictator game (***Gao et al., 2018***), participants chose between allocations of coins for themselves and a randomly selected anonymous participant in the room ('other') in order to assess inequity aversion. Each trial included two options, one with an equal allocation of coins between the participant and the other (M_{self} = M_{other}, e.g., 'You 10 and Other 10'), the other option with an unequal allocation (***Figure 3A***). In half of the trials, the unequal allocation was advantageous for the participant (e.g., 'You 18 and Other 12') and in the other half disadvantageous (e.g., 'You 12 and Other 18'), allowing to dissociate between advantageous and disadvantageous inequity aversion. Generosity is indicated either by increased advantageous inequity aversion or lower disadvantageous inequity aversion. In a total of 42 trials, participants were presented with different combinations of M_{self} and M_{other}, with M_{self} and M_{other} ranging from 2 to 30 coins. The position of the two options on the screen was counterbalanced, and participants made their choice via mouse-click on the corresponding button. Experimental coins were translated to money at an exchange rate of 4 coins to 1 euro, and one randomly selected trial was paid out at the end of the experiment. Thus, each participant received the payoff selected for himself in the given trial and the amount another participant had selected for the other person.

Digit span backward task

Participants performed the digit span backward task before and after substance intake in both sessions. In this task, participants were presented with a series of numbers displayed separately on the screen and were asked to write the numbers in the reverse order. This task represents a widely used measure of WMC as it requires both the maintenance and active manipulation of items in working memory. The difficulty increased gradually from 3 to 10 digits. This task allowed to assess whether the effects of oxytocin on decision making are mediated by potential oxytocin effects on WMC, as reported in schizophrenia (***Michalopoulou et al., 2015***, but see ***Bradley et al., 2019***), and whether the strength of oxytocin effects on the decision making task varies as a function of baseline cognitive

performance, similar to other pharmacological manipulations of value-based choice (**Cools et al., 2008**; **Kimberg et al., 1997**; **Soutschek et al., 2020b**).

Data analysis

Model-free analyses

Statistical analyses were performed with R version 3.6.0 (**R Development Core Team, 2019**). The alpha threshold was set to 5% two-tailed for all analyses except for the dictator game where we used a one-tailed test (as pre-registered) to replicate previous findings that oxytocin increases generosity (**Pornpattananangkul et al., 2017**). Given these previous findings, we would consider both a too-weak effect in the expected direction and an effect in the unexpected direction as failed replication of previous reports that oxytocin increases advantageous inequity aversion. All data supporting the findings of this study are available on the Open Science Framework (https://osf.io/yg7ah/files/).

To assess whether oxytocin effects depend on baseline cognitive performance levels, we used WMC as a proxy of baseline cognitive performance. To calculate individual WMC scores, we summed the correct responses over the two pre-test assessments in the digit span backward task. This variable was normally distributed with mean = 8.69, median = 9, range = 4–14, and sd = 2.45. We used a binary WMC variable where participants with performance above and below the median were categorized as high and low WMC group, respectively. We used WMC as binary rather than continuous predictor to reduce the impact of outliers in WMC performance on statistical results (**Kimberg et al., 1997**; **Soutschek et al., 2020b**).

For all model-free analyses, we used the lme4 package in R for mixed generalized linear models (MGLMs) (**Bates et al., 2015**). All MGLMs included dummy-coded predictors for Substance (0 = placebo, 1 = oxytocin), WMC (−1 = low, 1 = high), and Order of substance administration (−1 = placebo in session 1 and oxytocin in session 2, 1 = oxytocin in session 1 and placebo in session 2). Substance × WMC interactions modeled potential baseline-dependent effects of oxytocin, whereas Substance × Order interactions allowed to statistically detect and control for potential order or carry-over effects of drug administration. All within-subject fixed effect predictors were also modeled as random slopes in addition to participant-specific random intercepts. Detailed results tables for all models are reported in **Supplementary file 1**.

Model-based analyses

For the intertemporal decision and the dictator game tasks, we also conducted model-based analyses. The benefit of model-based analyses is that they allow assessing how oxytocin affects latent psychological processes (e.g., that decision makers integrate rewards and delays to hyperbolically discounted subjective reward values) (**Forstmann et al., 2011**; **Konovalov et al., 2018**; **Soutschek et al., 2020a**). Model-free analyses, in contrast, assess the impact of experimental manipulations (e.g., reward magnitude and delay) on choice behavior without making any assumption regarding the underlying psychological processes.

We performed model-based analyses for the intertemporal decision task and the dictator game data using hierarchical Bayesian modeling with the hBayesDM package version 1.0.2 (**Ahn et al., 2017**) and Stan version 2.19.1 (**Carpenter et al., 2017**). While individual maximum likelihood parameter estimation often results in noisy parameter estimates, hierarchical Bayesian modeling estimates group-level hyperparameters in addition to individual estimates. This leads to more stable and reliable parameter estimates as it allows individual parameters to be informed by the group-level hyperparameters (**Ahn et al., 2017**). For parameter estimation, we used four Markov Chain Monte Carlo sampling chains with 5000 iterations (including 1000 warm-up iterations).

As parameter estimates from hierarchical Bayesian modeling violate the independence assumption of frequentist inference statistics, we assessed group differences (oxytocin versus placebo) with the HDI of the posterior distribution of the difference between group-level hyperparameters. The HDI corresponds to the range of the difference between the group-level posterior distributions that spans 95% of the distribution, thus the range that entails the difference in group-level hyperparameter with 95% probability. If the HDI does not overlap with zero, the parameter estimates are considered to differ between the groups (**Ahn et al., 2017**; **Ahn et al., 2014**; **Kruschke, 2013**). Note that this procedure is not equivalent to frequentist null hypothesis testing, but it can be interpreted in a similar way.

For the *intertemporal choice* data, we computed hyperbolic discounting functions indicating the discounted value of delayed rewards as a function of delay. In hyperbolic discounting, the subjective value of reward x delivered after delay D is given by the following function:

$$SV(x,D) = \frac{x}{1+kD}$$

where k corresponds to the individual discounting rate. Greater k indicates greater discounting of future rewards (**Laibson, 1997**). To estimate the individual and group-level parameters, we used the default options of the hBayesDM toolbox, that is, normal prior distributions with mean 0 and standard deviation of 1, parameter bounds for k between 0 and 1 and starting value at 0.1. For the inverse temperature parameter, the bounds were set to 0 (lower) and 5 (upper) and starting value at 1.

For the *dictator game* data, we used the Fehr–Schmidt model for inequity aversion (**Fehr and Schmidt, 1999**). This is a widely used model of social preferences that allows dissociating between advantageous and disadvantageous inequity aversion. According to the model, the subjective value of an option depends on both one's own payoff and the payoff of the other according to the following formula:

$$SV\left(M_{self}, M_{other}\right) = M_{self} - \alpha \max\left\{M_{other} - M_{self}, 0\right\} - \beta \max\left\{M_{self} - M_{other}, 0\right\}, \quad M_{self} \neq M_{other}$$

where M_{self} is the decision maker's own payoff and M_{other} is the other's payoff in a given trial. Parameters α and β reflect the weight given to disadvantageous and advantageous inequity, respectively. For the parameter estimation, we used normal prior distributions with mean 0 and standard deviation of 1 for all parameters. All parameters were unbounded with random starting values.

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Additional information

Competing interests

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Author contributions

Georgia Eleni Kapetaniou, Conceptualization, Data curation, Software, Formal analysis, Investigation, Visualization, Methodology, Writing - original draft, Project administration; Matthias A Reinhard, Conceptualization, Investigation, Methodology; Patricia Christian, Investigation, Methodology; Andrea Jobst, Philippe N Tobler, Frank Padberg, Conceptualization, Methodology; Alexander Soutschek, Conceptualization, Resources, Data curation, Software, Formal analysis, Supervision, Funding acquisition, Investigation, Visualization, Methodology, Writing - original draft, Project administration

Author ORCIDs

Georgia Eleni Kapetaniou https://orcid.org/0000-0002-0020-1158
Alexander Soutschek https://orcid.org/0000-0001-8438-7721

Ethics

Human subjects: All participants gave written informed consent before the start of their participation in the study. The study protocol was approved by the Ethics Committee of the Department of Psychology, LMU Munich.

Decision letter and Author response

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Additional files

Supplementary files

- Supplementary file 1. Full regression models output.
- Transparent reporting form

Data availability

All data generated and analyzed during this study are included in the manuscript. Source data files and code for the statistical analyses and graphs are available online, on the Open Science Framework (https://osf.io/yg7ah/).

The following dataset was generated:

Author(s)	Year	Dataset title	Dataset URL	Database and Identifier
Kapetaniou GE, Reinhard MA, Christian P, Jobst A, Tobler PN, Padberg F, Soutschek A	2020	Oxytocin improves delay of gratification and cognitive flexibility in non-social decision making	https://osf.io/yg7ah/files/	Open Science Framework, yg7ah

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3. Neural oscillations implementing self-control in intertemporal choice

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Neural oscillations implementing self-control in intertemporal choice

Georgia E. Kapetaniou[1,2], Marius Moisa[3], Christian C. Ruff[3], Philippe N. Tobler[3,4], Alexander Soutschek[1,2]

[1] Department of Psychology, Ludwig Maximilian University Munich, Munich, Germany

[2] Graduate School for Systemic Neurosciences, Department of Biology, Ludwig Maximilian University Munich, Munich, Germany

[3] Zurich Center for Neuroeconomics, Department of Economics, University of Zurich, Zurich, Switzerland

[4] Neuroscience Center Zurich, University of Zurich, Swiss Federal Institute of Technology Zurich, Zurich, Switzerland

Author contributions: GEK, MM, CCR, PNT and AS designed research; GEK performed research; GEK analyzed data; GEK and AS wrote first draft of manuscript

Correspondence should be addressed to:

Georgia E. Kapetaniou
Ludwig Maximilian University Munich
Department for Psychology
Leopoldstr. 13
80802 Munich, Germany
Email: Georgia.Kapetaniou@psy.lmu.de

Abstract

The dorsolateral prefrontal cortex (dlPFC) is suggested to be a core brain area for implementing self-control in intertemporal choice. Evidence, however, on the neural oscillations in the dlPFC that causally implement self-control is scarce. With the present study we tested the effects of alpha and beta band oscillations on intertemporal choice using noninvasive transcranial alternating current stimulation (tACS). Thirty-four healthy participants performed an intertemporal choice task, where they decided between smaller-sooner and larger-later monetary rewards, while receiving tACS stimulation over the left dlPFC. In a within-subjects design, participants received alpha (10Hz), beta (20Hz), gamma (30Hz – control frequency), and sham stimulation, while performing the task. In line with our hypothesis, we found that beta stimulation led to more patient choices, through dampening the effects of delay and immediate reward on choice. Additionally, alpha stimulation also reduced impulsivity compared to baseline, such that participants were more likely to select the larger-later reward option. Contrary to our expectations, gamma stimulation was found to have a facilitatory effect on self-control, via attenuating the effect of delay, but not of immediate reward on choice. Here, we show that alpha, beta and gamma oscillations in the dlPFC contribute differentially to the implementation of self-control in intertemporal choice, potentially pointing towards different underlying processes being involved in this ability.

Keywords: intertemporal choice; self-control; tACS; delay discounting; non-invasive brain stimulation

Introduction

Whether it is deciding to eat a salad instead of a chocolate cake or to save up instead of buying an expensive gadget, self-control, our ability to delay gratification for the sake of a greater long-term goal, is crucial for multiple everyday decisions. Successful self-control is a key ability facilitating the formation and maintenance of long-term goals and has been linked to several beneficial life outcomes (Mischel, Shoda, & Peake, 1988; Strömbäck, Lind, Skagerlund, Västfjäll, & Tinghög, 2017). Self-control deficits on the other hand, have been long associated with disorders such as obesity and addiction (Bickel et al., 2019; Bickel & Marsch, 2001). Therefore, investigating and understanding the underlying mechanisms of self-control can be of great benefit both for clinical and general purposes.

A brain area known to be key for the implementation of self-control is the dorsolateral prefrontal cortex (dlPFC). The left dlPFC in particular has been established to play a critical role in self-control, a view supported both by correlational (Hare, Camerer, & Rangel, 2009; McClure, Laibson, Loewenstein, & Cohen, 2004; Peters & Büchel, 2011) and causal findings (Figner et al., 2010; Shen et al., 2016). In one of the first studies to show a causal role of the left dlPFC for the implementation of self-control, Figner and colleagues (2010) stimulated the left dlPFC with repetitive transcranial magnetic stimulation (rTMS) and found that disrupting the function of the left lateral prefrontal cortex led to more impulsive decisions. In line with previous findings (Hare et al., 2009), they suggested that dlPFC function is crucial for successful self-control. More recent stimulation studies have reached similar conclusions, despite the vast methodological differences (He et al., 2016; Shen et al., 2016). In spite of these converging results, however, one characteristic of previous research is that the methods typically used were based on frequency-unspecific

approaches, designed to either inhibit or enhance local function, thus leaving open the question of the role of different oscillatory frequencies and dynamics in intertemporal decision making.

Previous EEG studies have shown the involvement of frontal alpha oscillations in self-control decisions with a putative role in early attentional filtering of goal-irrelevant information (Harris, Hare, & Rangel, 2013) or part of the evidence accumulation process (HajiHosseini & Hutcherson, 2021). In a dietary self-control task, Harris et al. 2013 found evidence for top-down attentional filtering early in the decision period (150-200 milliseconds post stimulus onset), a process suggested to be implemented via long-range synchronization of frontal and occipital regions in the alpha band (8-12 Hz). Their results further point to enhanced frontal-occipital synchrony that in the self-control context could reflect an early initial strategy for the successful maintenance of goals (Harris et al., 2013). In a subsequent study HajiHosseini and Hutcherson (2021) set out to extend these findings and elucidate the neurocomputational mechanisms underlying self-control in dietary decisions. Using a model-based approach they found that self-control might partially be driven by altered representation of attributes at the alpha band (in left frontal and right parietal-occipital cortical areas from 500 to 1000 milliseconds after food image presentation) and this process was in line with the simulated evidence accumulation time course rather than the attribute construction phase. Overall, alpha suppression correlated with taste when deciding naturally and with health when exercising self-control, thus suggested to reflect the processing of the goal-relevant attribute (HajiHosseini & Hutcherson, 2021). Though this correlational evidence clearly shows an involvement of alpha band oscillations in attribute weighting through attention reorientation, causal evidence on its role in the dlPFC in implementing self-control is still missing. Specifically, if increased activity in the alpha band is associated with increased attention through long-range synchronization with parietal and occipital areas, entraining

alpha oscillations in the dlPFC should enhance its contribution to self-control and thus render participants more patient, whereas if alpha suppression is responsible for tracking and integrating goal-relevant information, then stimulating the dlPFC entraining alpha oscillations should impair self-control, making participants more impulsive.

Although the evidence for the role of alpha oscillations in the dlPFC for self-control is not yet clear, there exist more direct associations between beta band oscillations and intertemporal decision making. Previous electrocorticography (ECoG) evidence has linked patience in intertemporal decisions to increased beta oscillatory activity in lPFC electrodes, whereas decreased beta activity was observed in the same brain areas during impulsive decisions (Gui, Yu, Hu, Yan, & Li, 2018), an activity pattern that could imply that lPFC implements self-control by inhibiting subcortical activity in the reward pathways via top-down neural control (Gui et al., 2018). In addition to evidence supporting a role of beta band oscillations in top-down processing (Engel, Fries, & Singer, 2001) and inhibition (Schutter & Van Honk, 2005), a clear association has been made between beta oscillations and impulsivity (Gianotti, Figner, Ebstein, & Knoch, 2012). More specifically, Gianotti and colleagues (2012), reported a negative correlation between beta band oscillatory activity and delay discounting, with a lower level of resting beta activity in the left dlPFC linked to steeper delay discounting (Gianotti et al., 2012). These findings point to a potential involvement of beta oscillations as a neural signature of self-control in the left dlPFC, but so far causal evidence of this association is missing. We predicted that beta band entrainment in the dlPFC would lead to an increase in delay of gratification in the intertemporal choice task.

With this study we investigate the causal role of alpha and beta band oscillations in the dlPFC for implementing self-control. By using transcranial alternating current stimulation (tACS), a technique widely known for safely inducing oscillatory patterns in the brain (Antal & Paulus,

2013), we were able to investigate the role of these frequencies for self-control using a causal manipulation and thus advancing previous findings on the topic. We stimulated the left dlPFC with alpha (10 Hz), beta (20 Hz), gamma (30 Hz – control frequency) and sham tACS. We expected alpha stimulation to provide evidence on the implication of alpha oscillations in self-control and beta stimulation to enhance responses favoring the long-term reward.

Methods

Participants

A total of 34 volunteers (mean age = 24.5, range = 19-37, sd = 4.1, 20 female) were recruited through the participant pool of the MELESSA lab at the Ludwig Maximilian University Munich, Germany. Data from one participant were dropped due to a technical problem resulting in a final sample size of 33 participants. All volunteers gave written informed consent before participating and were additionally screened prior to stimulation for adherence to the stimulation safety criteria. Participants received a fixed compensation of 12 euros for their participation in the experiment, plus an added bonus depending on the decisions they made in the task. The study was approved by the local ethics committee.

Stimuli and task design

Participants performed a monetary intertemporal choice task, programmed in Matlab (Matlab, Cogent toolbox). In each trial they had to decide between an immediately available reward (smaller-sooner reward; SS) ranging from 1 to 4.5 euro in steps of 0.5 euro that would be

delivered immediately at the end of the experiment, and a larger reward fixed at 5 euro (larger-later reward; LL), which would be delivered at a later date, after a delay of 5 to 240 days (the following delays were included: 5, 10, 20, 40, 60, 90, 120, 180, 240 days) (Figure 1A). We additionally included a set of easy, no-brainer trials as attention control, in which the SS reward was set to 0 euros and the LL reward at 5 euros, delivered after a delay, identical to the main experimental trials. The two options were randomly presented on the left or right side of the screen and participants made their choice by pressing the left or right arrow on a standard keyboard. Participants received visual feedback on their choice, such that after selecting one of the two options, the option turned red for the remaining time of the trial. The trial duration was set to 3 seconds, followed by an intertrial interval of 2 seconds.

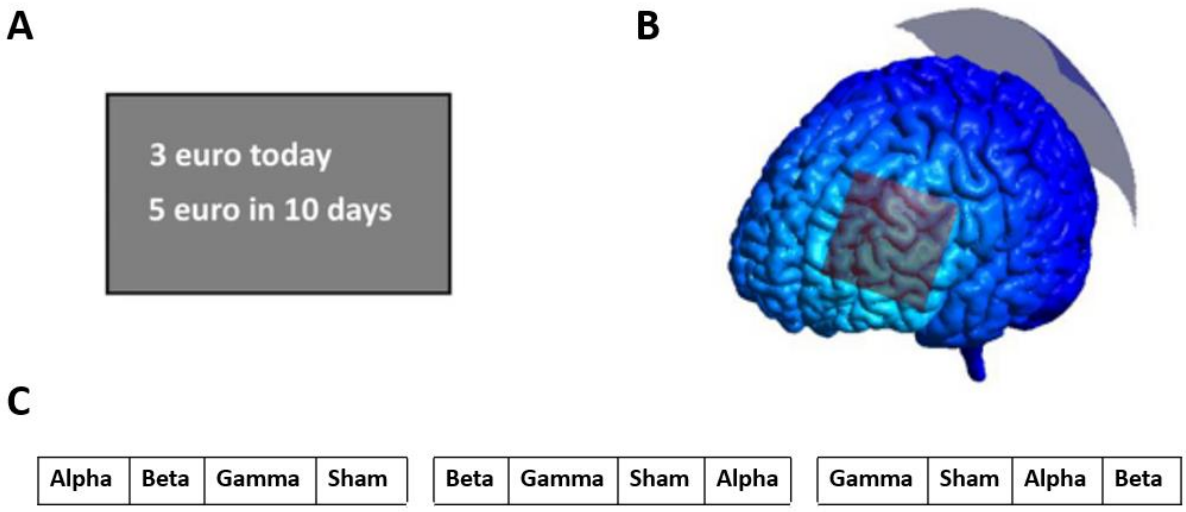

Figure 1. (A) In the intertemporal choice task participants made a series of choices between a smaller-sooner reward delivered at the end of the experiment (e.g., 3 euro today) and a larger-later reward delivered at a later date (e.g., 5 euro in 10 days). (B) During task performance participants were stimulated with alpha (10 Hz), beta (20 Hz), gamma (30 Hz) and sham tACS over the left dorsolateral prefrontal cortex with a 5x5 cm^2 electrode (position F3, 10-20 system). The reference electrode (10x10 cm^2) was positioned over

the inion. (C) Participants performed 12 miniblocks of the task. Stimulation lasted for 155 seconds for each miniblock, including 15 seconds of ramp-up and 5 seconds of ramp-down. For the sham blocks, stimulation lasted 10 seconds, in addition to the 15 seconds ramp-up and 5 seconds ramp-down. Between the blocks there was a 15-second stimulation-free break. tACS order was counterbalanced.

Procedure

The task included a total of 324 trials. The combination of all immediate reward values with all delays yielded a total of 81 trials per condition. Each 81-trial set was therefore repeated 4 times, one per tACS condition. Following a previously validated experimental design shown to minimize stimulation-induced after-effects (Soutschek, Moisa, Ruff, & Tobler, 2021) the task was divided in 12 miniblocks of 27 trials. Each of these miniblocks was paired with a different stimulation condition (alpha, beta, gamma, sham tACS) and the order of stimulation conditions was counterbalanced (Figure 1C).

Each miniblock started with a current ramp-up period of 15 seconds. The task and stimulation started immediately after ramp-up and lasted for 135 seconds, ending with 5 seconds of ramp-down. The total duration of stimulation for each miniblock was 155 seconds. In the sham condition, the current was ramped up for 15 seconds, followed by a 10-second stimulation period and 5 seconds of ramping down. Between the miniblocks there was a task-free break of 30 seconds, including a stimulation-free break of 15 seconds. At the end of each miniblock, participants were asked to indicate their perceived discomfort and flickering due to the stimulation on a rating scale from 0 (not at all) to 20 (very strongly). In order to control for the influence of perceived discomfort and flickering induced from tACS on task performance, we added these individual ratings as control variables to all statistical models.

At the end of the experiment participants filled in a short questionnaire providing demographic information and overall, no serious side effects were reported due to the stimulation. Finally, one trial of the task was randomly selected and paid out to the participant. If in that trial the participant had chosen the SS reward, the corresponding amount was paid out to them at the end of the experiment, whereas if they chose the LL reward, the LL amount was sent to the participant via mail after the corresponding delay.

tACS protocol

We applied tACS using a 4-channel tDCS stimulator (DC-Stimulator MC, neuroConn, Ilmenau, Germany). As our target area was the left dlPFC, we placed the smaller active electrode (5x5 cm^2) over position F3 and a larger (10x10 cm^2) reference electrode over position Pz (above the inion) according to the international 10-20 system (Figure 1B). We used a larger reference electrode in order to minimize the stimulation effect at the reference position following Soutschek et al. (2021). Before the experiment we also performed current modeling using the Simnibs 2.1 toolbox (Saturnino et al., 2019), which suggested that with this particular electrode set up we ensure that the strongest current density is in the dlPFC, while there were virtually no stimulation effects under the reference electrode. The rubber electrodes were placed inside sponges that were soaked in saline water and were fixed to the head of the participants using rubber straps. We stimulated participants in the alpha (10 Hz), beta (20 Hz) and gamma (30 Hz) band with a current strength of 1.5 mA (peak-to-peak).

Statistical analysis

Data were analyzed with generalized linear mixed models (GLMMs) in R (R Core Team, 2020) using the lme4 package (Bates, Mächler, Bolker, & Walker, 2014). We regressed choices (1 = LL reward, 0 = SS reward) on predictors for tACS condition, SS reward, Delay and their interaction terms. We additionally included predictors for previous stimulation condition (immediately preceding the current miniblock), discomfort and flickering to control for stimulation-related confounds. All models included random slopes for all predictors varying at the individual level in addition to participant-specific random intercepts. All models reported in this manuscript converged successfully.

Participants' discounting functions (i.e., calculating the discounted value of delayed rewards as a function of the individual discounting rate) were estimated with Bayesian modeling at the single subject level for each tACS condition, with the hyperbolic discounting model as implemented in the hBayesDM package (version 1.0.2; Ahn, Haines, & Zhang, 2017). According to the hyperbolic discounting model, the subjective value of a future reward r delivered after a delay of D units is given as follows:

$$SV(r, D) = \frac{r}{1+kD}$$

where k corresponds to the discounting rate of the individual and larger k values indicate greater discounting of future rewards (Laibson, 1997). For parameter estimation, we used the default options for the single-subject hyperbolic discounting model of the hBayesDM toolbox, which included normal prior distributions (mean = 0, sd = 1) and parameter bounds between 0 and 1 for k and 0 and 5 for beta (inverse temperature parameter). We estimated the model with 4 Markov Chain Monte Carlo sampling chains, with 4000 iterations and an additional 1000 warm-up iterations.

Results

Here, we tested our two hypotheses, investigating the effects of stimulation at the alpha and beta frequency over the left dlPFC in the intertemporal choice task. For the analysis we excluded data from 4 participants as they always selected the LL option resulting in no variation in their data. Thus, our final sample consisted of 29 subjects.

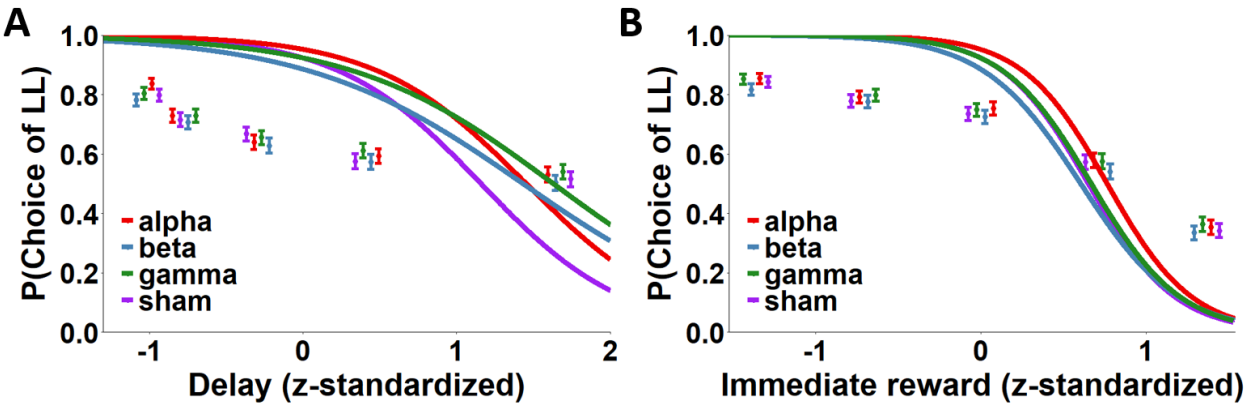

Figure 2. Probability of selecting the LL reward as a function of (A) delay and (B) immediate reward. Participants were more likely to select the LL option under the three frequencies compared to sham as indicated by a main effect of alpha stimulation on behavior, as well as interaction effects of beta with both attributes and gamma with delay. Regression lines are drawn from the group-level fixed effect parameter estimates from the regression models. Binned raw data are overlaid over regression lines for reference. Error bars represent standard error of the mean.

In line with previous findings, the analysis revealed a main effect of SS reward, beta = -3.82, z = -8.59, $p < 0.001$, and a main effect of Delay, beta = -2.14, z = -5.36, $p < 0.001$, indicating that participants selected the LL option less often with longer delays or larger SS reward amounts. A significant main effect of alpha tACS, beta = 0.50, z = 2.03, p = 0.041, suggested a causal effect

of alpha stimulation in enhancing self-control during intertemporal choice compared to sham. Additionally, we found a significant beta X Delay interaction, beta = 0.71, $z = 3.56$, $p < 0.001$, and a beta X SS reward interaction, beta = 0.43, $z = 2.21$, $p = 0.026$, suggesting a role of beta oscillations in enhancing self-control through attenuating both the effect of delay and of immediate reward on behavior. Our analysis further revealed a significant gamma X Delay interaction, beta = 0.62, $z = 2.96$, $p = 0.003$, along with a gamma X Delay X SS reward interaction, beta = -0.59, $z = -2.87$, $p = 0.003$, suggesting a possible role of gamma oscillations as well in facilitating patient choice by dampening the effect of delay but not in combination with the reward attribute as indicated by the negative beta (Table 1). Additional analyses revealed no significant difference between alpha and gamma or beta and gamma stimulation (all relevant comparisons $p > 0.05$) (Table 2). Overall, our model-free analysis showed a main effect of alpha in increasing patience but also revealed several interactions pointing to effects of both beta and gamma stimulation frequencies on behavior.

We further performed an analysis of model-based results as obtained by the hyperbolic discounting model. This analysis revealed no significant difference in (log transformed) discounting rate, $F(1, 28) = 1.04$, $p = 0.314$, or inverse temperature (an indication of decision noise), $F(1, 28) = 0.00$, $p = 0.997$, among the four tACS conditions. Taken together, our results suggest that the model-free findings were the result of stimulation frequencies altering the processing of the choice attributes, but not a change of the discounting parameter itself or of a stimulation-induced change in the decisional noise.

Table 1. Results of MGLM modeling choices in the intertemporal choice task. 1 = LL, 0 = SS, baseline tACS condition set to sham.

Predictors	***Beta weight***	***Std. Error***	***z***	***p***
Intercept	2.48	1.11	2.24	**0.025**
$tACS_{Alpha\text{-}Sham}$	0.50	0.24	2.03	**0.041**
$tACS_{Beta\text{-}Sham}$	-0.44	0.27	-1.63	0.103
$tACS_{Gamma\text{-}Sham}$	-0.00	0.24	-0.01	0.993
Delay	-2.14	0.40	-5.36	**<0.001**
SS Reward	-3.82	0.44	-8.59	**<0.001**
Previous tACS – Alpha	0.49	0.18	2.76	**0.005**
Previous tACS – Beta	0.34	0.20	1.66	0.095
Previous tACS – Gamma	0.47	0.24	1.93	0.052
Discomfort	0.08	0.19	0.46	0.645
Flickering	0.02	0.14	0.18	0.850
$tACS_{Alpha\text{-}Sham}$ X Delay	0.09	0.22	0.39	0.690
$tACS_{Beta\text{-}Sham}$ X Delay	0.71	0.20	3.56	**<0.001**
$tACS_{Gamma\text{-}Sham}$ X Delay	0.62	0.20	2.96	**0.003**
$tACS_{Alpha\text{-}Sham}$ X SS Reward	-0.08	0.17	-0.49	0.621
$tACS_{Beta\text{-}Sham}$ X SS Reward	0.43	0.19	2.21	**0.026**
$tACS_{Gamma\text{-}Sham}$ X SS Reward	0.10	0.23	0.42	0.671
Delay X SS Reward	-0.01	0.22	-0.02	0.978
$tACS_{Alpha\text{-}Sham}$ X Delay X SS Reward	-0.07	0.22	-0.31	0.753

$tACS_{Beta\text{-}Sham}$ X Delay X SS Reward	-0.39	0.21	-1.87	0.060
$tACS_{Gamma\text{-}Sham}$ X Delay X SS Reward	-0.59	0.20	-2.87	**0.003**

Table 2. Results of MGLM modeling choices in the intertemporal choice task. 1 = LL, 0 = SS, baseline tACS condition set to gamma.

Predictors	***Beta weight***	***Std. Error***	***z***	***p***
Intercept	2.50	1.08	2.31	**0.020**
$tACS_{Sham\text{-}Gamma}$	0.03	0.47	0.07	0.943
$tACS_{Alpha\text{-}Gamma}$	0.53	0.53	0.98	0.323
$tACS_{Beta\text{-}Gamma}$	-0.42	0.43	-0.96	0.332
Delay	-1.50	0.52	-2.85	**0.004**
SS Reward	-3.72	0.51	-7.23	**<0.001**
Previous tACS – Alpha	0.49	0.20	2.41	**0.015**
Previous tACS – Beta	0.33	0.23	1.45	0.145
Previous tACS – Gamma	0.45	0.25	1.77	0.075
Discomfort	0.10	0.28	0.36	0.711
Flickering	0.04	0.21	0.22	0.819
$tACS_{Sham\text{-}Gamma}$ X Delay	-0.62	0.39	-1.58	0.112
$tACS_{Alpha\text{-}Gamma}$ X Delay	-0.54	0.49	-1.10	0.270
$tACS_{Beta\text{-}Gamma}$ X Delay	0.10	0.36	0.30	0.763
$tACS_{Sham\text{-}Gamma}$ X SS Reward	-0.12	0.45	-0.27	0.784

$tACS_{Alpha\text{-}Gamma}$ X SS Reward	-0.20	0.47	-0.42	0.668
$tACS_{Beta\text{-}Gamma}$ X SS Reward	0.30	0.42	0.71	0.475
Delay X SS Reward	-0.62	0.30	-2.02	**0.042**
$tACS_{Sham\text{-}Gamma}$ X Delay X SS Reward	0.55	0.37	1.48	0.137
$tACS_{Alpha\text{-}Gamma}$ X Delay X SS Reward	0.55	0.37	1.46	0.142
$tACS_{Beta\text{-}Gamma}$ X Delay X SS Reward	0.18	0.37	0.48	0.624

Discussion

The left dlPFC is established as a brain area with a crucial role for self-control. While its precise neurocomputational role is still debated (Harris et al., 2013; Hutcherson & Tusche, 2021), a great amount of stimulation studies have provided extensive evidence and support on its causal involvement in self-control (Figner et al., 2010; He et al., 2016; Shen et al., 2016). These studies, however, have so far only employed an all-or-nothing approach using stimulation designed to either disrupt dlPFC activity or to enhance it irrespective of local oscillatory dynamics. Building on previous EEG studies that explored these precise oscillatory dynamics, we investigated the role of two oscillatory frequencies in the dlPFC previously linked to intertemporal decision making. By employing tACS, which allowed us to entrain specific oscillatory activity over the dlPFC, we reveal a causal role of alpha band oscillations in promoting patient decisions and additionally provide evidence for a role of beta and gamma band oscillations in self-control.

Self-control as reflected by patient decisions in our paradigm was increased under alpha stimulation compared to sham. This result is consistent with previous findings ascribing frontal alpha activity an important role in intertemporal choice (HajiHosseini & Hutcherson, 2021; Harris

et al., 2013). The precise role of alpha oscillations in the left dlPFC, however, is not clear. Our results showed a main effect of alpha stimulation on behavior, such that under alpha stimulation participants were more patient compared to sham. We found, however, no significant interactions of alpha tACS with the two main attributes of our options (i.e., delay and reward). These two results could suggest that alpha stimulation had a general effect on behavior and was not involved in attribute-specific modulations. This would be consistent with a general role of alpha oscillations in providing a "protective" strategy in favor of self-control through synchronizing with posterior brain regions in order to suppress goal-irrelevant information as suggested by Harris et al. (2013). Importantly, increased alpha activity has been associated with tasks requiring top-down control and access to memory (Klimesch, Freunberger, & Sauseng, 2010) and bilateral dlPFC alpha tACS has been previously shown to improve inhibitory control in a substance use disorder group (Daughters, Jennifer, Phillips, Carelli, & Fröhlich, 2020) and to reduce cravings and impulsive decisions in combination with an attention modification intervention in a tobacco use disorder sample (Mondino, Lenglos, Cinti, Renauld, & Fecteau, 2020). Taken together, we show in a healthy sample that alpha stimulation in the left dlPFC can enhance self-control in an attribute-unspecific manner, possibly through enhancing attentional processes.

In addition to the effect of alpha stimulation on behavior, our analyses revealed an effect of beta tACS, such that under beta stimulation, participants showed reduced sensitivity to longer delays and larger immediate rewards. Beta stimulation was found to improve patience through reducing the effect both of delay and immediate reward on behavior and this result is in line with previous research reporting higher beta activity in the left lateral PFC during patient choices (although with a limited, clinical sample) (Gui et al., 2018), as well as reports for a link between resting beta activity and delay discounting in the left PFC (Gianotti et al., 2012). Moreover, beta

oscillations have been associated with patience in a healthy sample (Guleken, Sutcubasi, & Metin, 2021) and additionally with reward processing (Doñamayor, Schoenfeld, & Münte, 2012), inhibition (Hofman & Schutter, 2012; Swann et al., 2009) and top-down modulation (Engel et al., 2001). It is therefore possible that beta oscillations facilitated self-control via top-down modulation of the impact of reward and delay on decisions.

In contrast to previous reports (Gui et al., 2018) and our expectations, gamma tACS was also found to have an effect on self-control in our task. Specifically, we found a positive effect of gamma stimulation on choice, such that it lowered the effect of delay and made participants more patient, though with a negative effect when both delay and reward were taken into account. This finding was relatively surprising as not many previous studies to our knowledge have reported the implication of gamma band in intertemporal choice. A possible interpretation for this result could be that gamma stimulation enhanced self-control through enhancing working memory processes in the dlPFC. A link between working memory and intertemporal decision making has been previously established (Bickel, Yi, Landes, Hill, & Baxter, 2011; Hinson, Jameson, & Whitney, 2003) and neural mechanisms of both processes have been found to overlap in the left dlPFC (Wesley & Bickel, 2014). Moreover, gamma tACS in the same region has been shown to improve working memory performance (Hoy et al., 2015). It is therefore possible that gamma enhanced patience through facilitating working memory processes, thus allowing the long-term goals to be kept in mind. Alternatively, it is also possible that gamma tACS increased beta activity locally similarly to what has been reported in prior research combining tACS with offline EEG (Kim, Kim, Jeong, Roh, & Kim, 2021), though our differential results of gamma and beta stimulation do not support this interpretation.

Taken together, our findings suggest a facilitatory role of alpha, beta and gamma oscillations in the left dlPFC for self-control and are in line with accounts ascribing an important role of both attention and working memory in intertemporal choice (Bickel et al., 2011; Lempert & Phelps, 2016; Wesley & Bickel, 2014). One important limitation of our findings, however, is the possibility that the effects of stimulation on behavior might be driven by frequency-unspecific effects in the brain. We note that these effects are unlikely to be the result of induced noise in the brain, as previous research has pointed towards differential effects of tACS and tRNS (random noise stimulation) on cognition (Santarnecchi et al., 2016). A further limitation of the present study is that despite the fact that we can ascribe a causal role to the three frequencies in implementing self-control, we can only speculate on whether these frequencies correspond to implementing the same or different processes in intertemporal choice. Future research can disentangle the potentially differential effects of the three frequencies in self-control and address their neurocomputational role in promoting patience with the use of control tasks, and/or methods allowing for a complete account of the effect such as combined tACS-fMRI.

Our findings can have clinical implications as tACS has been already introduced as a potential method for reducing psychiatric symptoms and has shown potential for the amelioration of substance use disorder symptoms, including craving and delay discounting (Daughters et al., 2020; Elyamany, Leicht, Herrmann, & Mulert, 2021; Mondino et al., 2020). The possibility to refine previously all-or-nothing methods with specific oscillatory activity involved in self-control could provide a new pathway for improved interventions.

Taken together, our findings provide evidence for a causal role of alpha, beta and gamma band oscillations in self-control during intertemporal choice, cueing the many cognitive processes involved in this multifaceted ability.

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Funding and competing interests

All authors declare to have no conflicts of interest.

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4. Brain mechanisms underlying metacognition in decision making

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Brain mechanisms underlying metacognition in decision-making

Georgia E. Kapetaniou[1,2 †], Marius Moisa[3 †], Christian C. Ruff[3], Philippe N. Tobler[3,4 *], Alexander Soutschek[1,2 *]

[1] Department of Psychology, Ludwig Maximilian University Munich, Munich, Germany

[2] Graduate School for Systemic Neurosciences, Department of Biology, Ludwig Maximilian University Munich, Munich, Germany

[3] Zurich Center for Neuroeconomics, Department of Economics, University of Zurich, Zurich, Switzerland

[4] Neuroscience Center Zurich, University of Zurich, Swiss Federal Institute of Technology Zurich, Zurich, Switzerland

Author contributions: GEK, MM, CCR, PNT and AS designed research; GEK and MM performed research; GEK analyzed data; GEK and AS wrote first draft of manuscript

† Shared first authorship

* Shared senior authorship

Correspondence should be addressed to:

Georgia E. Kapetaniou
Ludwig Maximilian University Munich
Department for Psychology
Leopoldstr. 13
80802 Munich, Germany
Email: Georgia.Kapetaniou@psy.lmu.de

Abstract

Metacognitive access to our preferences is known to facilitate rational decision making. A causal link has been previously established between metacognitive sensitivity in decision making and theta band oscillations in the frontopolar cortex (FPC) (Soutschek et al., 2021), little is known however, on how FPC manages to read-out performance-related information from other brain regions. Here we addressed this question with a combined HD-tACS concurrent functional MRI paradigm. In a within-subjects design, 41 healthy participants received high intensity theta (5Hz), alpha (10Hz; control frequency) or sham tACS stimulation with a 3x1 high-definition electrode set up over the FPC (AFz position) during task performance in the fMRI scanner. Participants performed a confidence accuracy task, where they selected between smaller-sooner and larger-later rewards, and subsequently indicated how confident they were in their decisions. Theta tACS was found to impair metacognitive accuracy in the reports of subjective uncertainty compared to sham. Additionally, theta stimulation led to altered functional connectivity between the FPC and bilateral lateral prefrontal cortex and right posterior parietal cortex. We additionally tested the effect of stimulation on mentalizing with a false belief task, as metacognition and mentalizing have been found to overlap and be expressed with theta oscillations in the FPC. We found no significant difference in mentalizing performance between the stimulation conditions. Taken together, our findings provide support for the causal role of theta FPC oscillations for metacognition and are consistent with an active role of FPC in metacognitively accessing decision-related information through modulating communication with relevant brain regions.

Keywords: metacognition; frontopolar cortex; transcranial alternating current stimulation (tACS); fMRI; mentalizing

Introduction

Awareness and evaluation of our preferences have been shown to complement our core decision making processes and contribute to our decisions almost as much as the preferences themselves (De Martino, Fleming, Garrett, & Dolan, 2013; Soutschek, Moisa, Ruff, & Tobler, 2021; Soutschek & Tobler, 2020). Metacognition, our ability to introspect, monitor and evaluate our thoughts and behavior, is deemed an important factor both in retrospective and prospective decisions (Fleming & Dolan, 2012; Soutschek et al., 2021). More specifically, in retrospective judgements metacognition reflects the accuracy of reported confidence in a choice, whereas in prospective judgements, taking place before the actual decision, it can reflect the ability of the individual to predict future decisions (Soutschek et al., 2021; Soutschek & Tobler, 2020). The connection between decision making and metacognitive access to our preferences has been successfully addressed by previous research not only theoretically, but also empirically, with findings showing that confidence in our decisions is integrated in the valuation process (De Martino et al., 2013) and awareness of our preferences can guide self-control and associated strategies (Soutschek et al., 2021; Soutschek & Tobler, 2020).

While several studies have investigated how metacognition is represented in the brain, little is known about how metacognition is implemented in the brain. Previous findings point to a central role of the frontopolar cortex (FPC) in instantiating the connection between metacognition and decision making (De Martino et al., 2013; Soutschek et al., 2021; Vaccaro & Fleming, 2018), while neurostimulation studies have revealed a central, causal role of this brain region in metacognition in various domains (Rahnev, Nee, Riddle, Larson, & D'Esposito, 2016; Ryals, Rogers, Gross, Polnaszek, & Voss, 2016; Shekhar & Rahnev, 2018). With respect to oscillatory activity, which is known to also reflect brain network interactions (Schnitzler & Gross, 2005; Thut, Miniussi, &

Gross, 2012; Varela, Lachaux, Rodriguez, & Martinerie, 2001), higher frontopolar activity at the theta band was associated with metacognitive judgements (Wokke, Cleeremans, & Ridderinkhof, 2017), as well as representation of choice difficulty and confidence in dorsolateral prefrontal cortex (dlPFC) and ventromedial prefrontal cortex (vmPFC) (Garrido, Barnes, Kumaran, Maguire, & Dolan, 2015; Lin, Saunders, Hutcherson, & Inzlicht, 2018), suggesting that theta oscillations could be a neural signature of metacognition, allowing the FPC to readout decision-related information from these areas.

Indeed, Soutschek et al. (2021), using transcranial alternating current stimulation (tACS), a method shown to safely modulate brain rhythms and induce frequency-specific changes (Antal & Paulus, 2013; Kuo & Nitsche, 2012), showed that enhancing theta oscillatory activity over the FPC improved metacognitive access to preferences and judgements in intertemporal decision making, further revealing a causal role of frontopolar theta oscillations for facilitating metacognitive access to our preferences and potential anticipated changes, in order to optimize decision making (Soutschek et al., 2021). With respect to retrospective confidence, in specific, Soutschek et al. (2021) showed that theta-band oscillations in the FPC led to improved metacognitive accuracy in retrospective judgements, establishing a causal role not only of FPC but also theta oscillations in metacognition during intertemporal decisions.

Although previous research has provided evidence on the involvement of FPC and theta oscillations in metacognitive evaluations, what still remains unknown is how the FPC interacts with other brain regions in order to metacognitively access and evaluate our preferences and decisions and how the observed stimulation-induced effects on metacognition correspond to relevant changes in brain activity. As Moisa and colleagues have highlighted before, such changes

could be driven by altered local activity of the stimulated area, altered activity at the network level or even network compensatory changes in activity (Moisa, Polania, Grueschow, & Ruff, 2016).

Therefore, whether the effects of frontopolar theta tACS on metacognition reflect solely local changes in activity or also the activity of other brain regions involved in decision making remains an open question. We addressed this question by combining high definition (3x1) tACS with functional magnetic resonance imaging (fMRI). With this method we entrained theta-band activity in the FPC while participants performed a confidence accuracy task involving intertemporal decisions in the scanner. This allowed us to observe the effect of stimulation not only on behavior (aiming to replicate previous findings), but also on brain activity at the local and network levels. With this study we aimed to determine the neural networks that underlie metacognitive accuracy in value-based choice and hypothesized that FPC theta tACS facilitates metacognition via increasing the functional connectivity between the FPC and dlPFC and/or vmPFC.

Additionally, we explored a possible link between metacognition and mentalizing as both processes have been found to overlap at the theoretical (C. D. Frith, 2012) and empirical level (Vaccaro & Fleming, 2018). Moreover, frontal theta activity has been reported in false belief tasks (Yuk, Anagnostou, & Taylor, 2020) and we therefore hypothesized that theta stimulation would also improve mentalizing in a false belief task, as frontopolar theta oscillations could be the common neural substrate between metacognition and mentalizing.

Methods

Participants

In the experiment participated 40 volunteers (mean age = 24.1, range = 18-32, sd = 3.7, 18 female, all right handed) recruited through the participant pool of the Laboratory for Social and Neural Systems Research at the University of Zurich, Switzerland. The sample size was determined with an a priori power analysis (a = 0.05, power = 80%) based on the effect of theta tACS on behavior in Soutschek et al., (2021) (Cohen's d = 0.54). The power analysis indicated a sample size of 30 participants, which we increased to 40 in order to increase the power of our design. All participants provided written informed consent prior to participating and had no history of neurological or psychiatric disorders. The study and all procedures were approved by the local Ethics Committee and all participants received a compensation of 120 Swiss francs plus a bonus depending on the decisions they made in the experiment.

Stimuli and task design

Participants performed two tasks in the scanner: a confidence accuracy task and a false-belief task. Both tasks were programmed in Matlab (Matlab, Cogent toolbox).

Confidence accuracy task. The task was a monetary intertemporal choice task, with confidence ratings (Soutschek et al., 2021). In each trial participants selected between two monetary rewards, a smaller, immediately available reward (smaller-sooner reward; SS) and a larger reward, delivered after a delay (larger-later reward; LL). The SS ranged from 3 to 9 CHF in steps of 1 CHF and the LL was fixed at 10 CHF, delivered after a delay ranging from 1 to 180 days (1, 2, 5, 10, 20, 40, 60, 90, 120, 180). The two options were presented randomly on the left or right side of the screen in the scanner and participants made their choices by pressing the respective button on an MRI-compatible response button box. Participants had 3 seconds to make their

choices and received visual feedback on their choice (chosen option turned red) for the remaining time of the 3 seconds if they responded earlier. Following each choice participants viewed the fixation cross for a mean of 0.5 seconds jittered with a Poisson distribution (mean = 0.5 seconds, range = 100 to 2000 milliseconds). After each choice, they were asked to indicate their confidence on having made the best choice on a rating scale ranging from 0 (not confident at all) to 7 (very confident) within 3 seconds (Figure 1A). They navigated the scale and confirmed their answer using the respective buttons on the response button box. The next trial started after a variable intertrial interval, whose duration was sampled from a Poisson distribution with a mean of 2 seconds and range of 800 to 3200 milliseconds. At the end of the experiment one trial was randomly selected and implemented such that if the participant had chosen an immediate reward it was added as a bonus to their compensation, whereas if they chose the delayed option, 10 CHF were sent to them by mail after the corresponding delay.

False-belief task. Participants also performed an adapted false belief task (Yuk et al., 2020), often used to assess mentalizing abilities (C. D. Frith & Frith, 2006; U. Frith & Frith, 2003). In this task, participants had to indicate the position of a ball, either from their own or from another agent's perspective. Each trial started with the presentation of two images. In the first image (500 milliseconds), Jack holds a ball over one of two hats, while Jill is watching. In the next image (500 milliseconds), he places the ball in one of the two hats while Jill is absent. The ball either changed position or was placed in the same hat as in the first picture, resulting in 4 conditions (Perspective X Change; Jill-switched, Jill-unswitched, Self-switched, Self-unswitched). After a jittered interval (mean = 0.5 seconds, range = 100 to 2000 milliseconds), where participants saw only the fixation cross, the decision screen appeared for 1.5 seconds. Thus, participants only knew the question in addition to whether Jill held a False Belief or not, after viewing both images. At the top of the

screen participants saw a cue indicating according to whose perspective they should respond (Figure 1A). In the Jill conditions, the word “Jill” appeared at the top of the screen and participants were asked to indicate “Which hat does Jill think the ball is in?”. They could respond “Left” or “Right” using the respective button at the button box. If the ball position was in the same hat, Jill held a True Belief, whereas if Jack switched the position, Jill held a False Belief on the position of the ball. In the Self (control) condition participants had to indicate whether there was a change in the position of the ball or not, responding with “Change” or “No Change”. After participants indicated their response, the chosen option turned red for the remainder of the 1.5 seconds. The trial concluded with an intertrial interval, with a duration sampled from a Poisson distribution with a mean of 2 seconds and range of 800 to 3200 milliseconds. All positions of the ball, agents and decision options were counterbalanced across trials.

Procedure

The confidence accuracy task included 180 trials, 60 for every tACS condition. The false-belief task included a total of 216 trials, 72 for every tACS condition (18 per task condition). Participants performed the tasks in an interleaved design, in 6 runs of approximately 9 minutes each (Figure 1A). Each run included 6 miniblocks of 11 trials, including 5 confidence accuracy trials and 6 false-belief trials. The order of the tasks as well as of the stimulation conditions was counterbalanced.

Each miniblock started with a 17.5-second period where only the fixation cross was presented on the screen and the participant was instructed to rest. Before the task started, the fixation cross changed color (counterbalanced across participants) indicating the task that comes

next. Participants performed the tasks for a total of 72.5 seconds per miniblock. At the end of each miniblock they had to rate their perceived discomfort and flickering due to the stimulation, each within 3 seconds, on a rating scale from 0 (not at all) to 7 (very much). The stimulation miniblocks were consecutive for each real stimulation condition, such that each stimulation block included two task miniblocks. The current was ramped-up for 1 second (ramp-up was on top of the sin wave), and ramped down for 1 second, while stimulation lasted for 189 seconds. For sham stimulation, the miniblocks were either presented together, or separately, resulting in three run types according to stimulation: (1) R – R – S – S – R – R, (2) R – R – S – R – R – S, (3) S – R – R – S – R – R, where R corresponds to real stimulation and S to sham (Figure 1B). During sham stimulation, each stimulation block lasted for 94 seconds and was composed of 2-second stimulation intervals (1 second ramp-up, 1 second ramp-down; either at theta or alpha frequency), followed by 25 seconds of no stimulation. This pattern was repeated throughout the miniblock, in order to make sure that the sensations match real stimulation and participants would not differentiate between the conditions. Between the miniblocks there was a task-free break of 8.5 seconds if the stimulation block following was of the same condition or 17.5 seconds otherwise. In line with Soutschek et al. (2021), we kept the stimulation duration of each miniblock rather short and additionally included a sham block between the two frequencies, ensuring that stimulation-induced aftereffects are eliminated.

Participants attended one experimental session and prior to the experiment day they filled in a screening questionnaire in order to assess that their time preferences were not extreme and went through further screening for stimulation and MRI safety criteria. Before the participant went into the scanner, we applied a local anesthetic paste (Emla Crème 5%, Aspen Pharma Schweiz) to

minimize local sensations under the electrodes. They waited for 45 minutes for the creme to take effect and we subsequently attached the rubber electrodes.

Participants practiced both tasks prior to entering the MRI scanner. They also filled in the short form of the Metacognitions Questionnaire (MCQ-30; Wells & Cartwright-Hatton, 2004) and the Interactive Mentalizing Questionnaire (Wu, Fung, & Mobbs, 2021). At the end of the experiment, they filled in a short demographics questionnaire where they also indicated potential side effects due to the stimulation. No serious side effects due to the stimulation were reported.

tACS protocol

We applied tACS using an 8-channel tDCS stimulator (DC-Stimulator MC, neuroConn, Ilmenau, Gemrany). As in Soutschek et al. (2021), the active electrode was placed at position AFz according to the international 10-20 system and the three reference electrodes were placed equidistantly (at 5 cm) to the central one forming a triangle (Figure 1C). We used round rubber electrodes with a 2 cm diameter. We attached the electrodes using the Ten20 conductive paste (Ten20 EEG Conductive Paste, Weaver and Company) and kept them steady throughout the session with fixation bandages. Prior to the experiment we conducted electric field simulations using the SimNIBS 2.1 toolbox (Saturnino et al., 2019) in order to calculate the predicted electric field distribution in the brain as a result of our electrode set up. The simulation supported that current density was stronger under our active electrode and localized at the FPC (Figure 1C). Finally, the tDCS stimulator was placed outside the scanner room, and was connected to the electrodes with MR-compatible cables and filter modules. We applied tACS at the theta frequency (5 Hz), alpha frequency (10 Hz - control) and sham at an intensity ranging from 2.4 mA to 4 mA

peak to peak (mean = 3.6 mA, sd = 0.54). The stimulation was synchronized with the tasks and fMRI acquisition using a custom-written software toolbox programmed in Matlab.

MRI protocol

The neuroimaging data were collected on a Philips Achieva 3-Tesla whole-body MR scanner equipped with a 32-channel standard MR head coil (Philips, Amsterdam, The Netherlands). During each experimental run we collected 258 volumes with the following parameters: voxel size 3x3x3 mm^3, slice gap 0.5 mm, acquisition matrix size 80x78, TR/TE = 2334/30 ms, flip angle 90°. Each volume consisted of 40 slices acquired in ascending order in order to cover the full brain. We additionally acquired T1-weighted multislice fast-field echo B0 scans, in order to correct for possible distortions, with the following parameters: voxel size 3x3x3 mm^3; slice gap 0 mm; acquisition matrix size 80x80; TR/TE1/TE2 = 1150/4.6/6.9 ms; flip angle 72°, 50 slices interleaved. Finally, for each participant we acquired a high resolution T1-weighted 3D fast field echo structural scan which we used during preprocessing for image registration with the following parameters: voxel size 1x1x1 mm^3, acquisition matrix size 256x256, 170 sagittal slices.

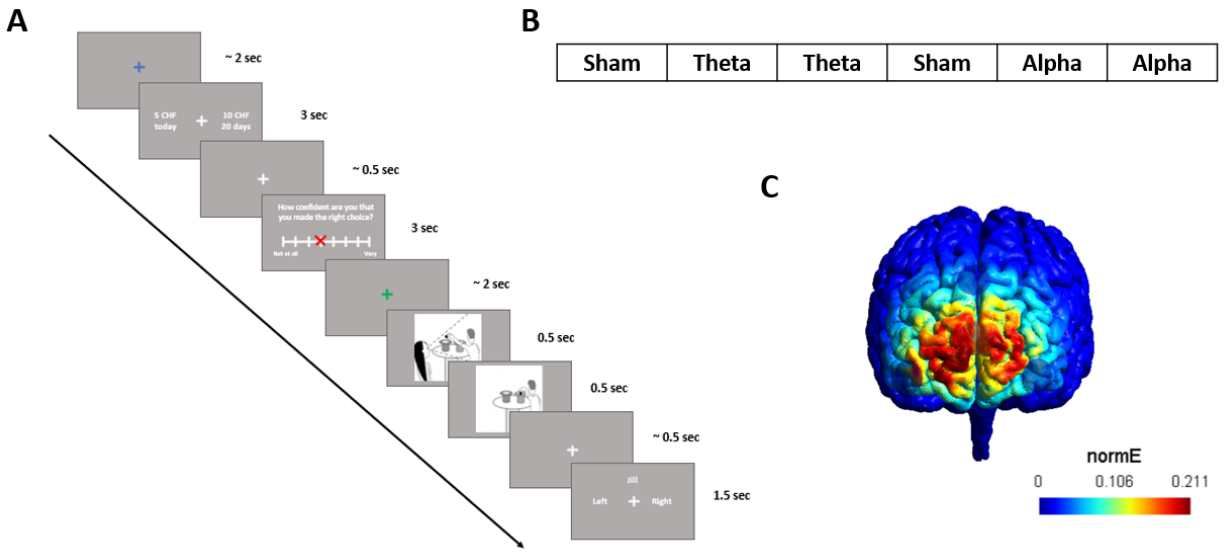

Figure 1. Task design and experimental paradigm. (A) Participants performed the two tasks in an interleaved way. In the confidence accuracy task, they selected between two rewards: a smaller-sooner reward delivered immediately (SS; e.g., 5 CHF today) and a larger reward delivered at a later date (LL; e.g., 20 CHF in 20 days). After each choice, they were asked to indicate their confidence in their decision on a scale from 0 to 7. In the false-belief task, participants viewed two consecutive images: In the first Jack was holding a ball above one of two hats, while Jill was watching. In the second, he placed the ball in one of the two hats, while Jill was absent. Participants had to indicate the position of the ball from their or Jill's perspective. Jill either held a True Belief (position did not change) or a False Belief (position changed). A colored cross (color counterbalanced across participants) indicated which task is next. (B) Example of stimulation blocks within a run. Participants performed the tasks in miniblocks of 11 trials (5 confidence accuracy trials and 6 false-belief). tACS for the real stimulation blocks (consisting of 2 miniblocks) lasted for 189 seconds, including 1 second of ramping-up and 1 second of ramping-down). For the sham blocks, which lasted 94 seconds, the current was switched on for 2 seconds every 25 seconds. Task order within the miniblocks and tACS order within the run were counterbalanced. (C) During performance of the tasks, participants received theta (5 Hz), alpha (10 Hz) or sham 3x1 HD-tACS over the frontopolar cortex. We

estimated the corresponding electric field density (normE = volts per meter, V/m) with Simnibs 2.1. Warmer colors indicate higher electric field density.

Statistical analyses

Behavioral data analysis

As in previous studies (Soutschek et al., 2021), we estimated each participant's discounting factor by fitting a hyperbolic discount function to their choices in the confidence accuracy task. We used Bayesian estimation with the hBayesDM package (Ahn, Haines, & Zhang, 2017) in R (R Core Team, 2020) and estimated the model parameters individually for each participant and tACS condition using the single-subject hyperbolic discounting model. Here, the subjective value (SV) of a future reward r, which is delivered after a delay D is given as follows:

$$\mathrm{SV}(r, D) = \frac{r}{1+kD}$$

where k describes the discounting rate of the individual indicating how strongly future rewards are discounted, i.e., a larger k value indicates steeper discounting of future rewards (Laibson, 1997). This subjective value of the reward was translated to choices, by subsequently fitting a standard softmax function to the individual's choices, describing the probability of selecting the LL reward, as a function of the difference in subjective value between the LL and SS rewards:

$$P(LL\ choice) = \frac{1}{1+e^{-\beta_{temp} \times (SV_{LL} - SV_{SS})}}$$

where the β parameter (inverse temperature) describes how strongly the individual relied on this difference to make their choice. For parameter estimation, the default options of the hBayesDM

toolbox were used, including normal prior distributions for both parameters (mean = 0, sd = 1), with parameter bounds between 0 and 1 for k and 0 and 5 for beta. The model was estimated with 4 Markov Chain Monte Carlo sampling chains with 5000 iterations (4000 plus 1000 warm-up iterations). In order to measure participants' metacognitive access to their decisions, we computed the difference in subjective value between the two options by subtracting the value of the SS reward from the subjective value of the LL reward as calculated for each trial using the hyperbolic discounting model and the parameter estimates derived before (SVL-SVS; as in Soutschek et al. 2021).

We analyzed the behavioral data with generalized mixed linear models (GLMMs) in R using the lme4 package (Bates et al., 2014). We regressed choices in the confidence accuracy task (1 = LL, 0 = SS) on fixed-effects predictors for tACS condition, subjective value difference and confidence ratings (both predictors z-standardized), and their interactions. We further included predictors for previous tACS, discomfort and flickering sensations as well as all predictors varying at the individual level as random slopes in addition to participant-specific random intercepts. As in previous studies (De Martino et al., 2013; Soutschek et al., 2021) we operationalize metacognitive sensitivity as the interaction between subjective value difference and confidence, reflecting participants' access to (i.e., the degree to which they are aware of) decision uncertainty during the choice process. For the mentalizing task, we regressed responses (1 = correct, 0 = wrong) on fixed-effects predictors for task condition (True Belief vs False Belief), tACS condition and their interaction term, in addition to predictors controlling for discomfort and flickering as well as previous tACS condition. All predictors were included as random slopes together with participant-specific random intercepts. All models reported in this manuscript converged successfully.

MRI data analysis

We analyzed the fMRI data using statistical parametric mapping (SPM 12; www.fil.ion.ucl.ac.uk/spm) in Matlab (MathWorks). Specifically, for each participant functional images were initially motion corrected and unwarped. The raw functional, structural and field map files were reconstructed into a single phase file, which was subsequently used to realign and unwarp the functional EPI images. We then performed slice-timing correction to the middle image and registered the structural images to the mean EPI images. Finally, we performed segmentation and normalization of the images into standard MNI space. Smoothing was performed with an 8 mm FWHM Gaussian kernel and data were further high pass filtered with a cutoff of 128 seconds.

For each participant statistical analysis was performed in two steps corresponding to two general linear models (GLMs). For the first-level analysis (GLM1) we computed for every participant a single subject fixed effects model. The GLM design matrix included 21 regressors, of which 6 modelled the events of the intertemporal choice task (with a combination of stimulation type and relevant regressors), 12 modelled the conditions of the mentalizing task (4 task conditions X 3 stimulation conditions) and 3 the block questions and missed trials.

For the intertemporal choice task, the regressors were modeled with a duration of 3 seconds corresponding to the trial duration. We had two types of regressors: the first modelled the absolute subjective value difference between the two choices and had a Value Difference parametric modulator and the other modelled confidence for each choice having two parametric modulators, i.e., Confidence rating and the Confidence X Value Difference interaction. Onsets of the two regressors were set to the corresponding screen appearance, i.e., the decision screen for the subjective value difference regressor and the confidence screen for the confidence regressor. No

modulator was orthogonalized. This set of regressors was repeated three times, one for each stimulation condition. Missed trials were modelled separately and all regressors included in the models were convolved with the canonical hemodynamic response function as implemented in SPM. Additionally, head movement parameters, derived individually for each participant, were modelled as regressors of no interest. For group-level analyses (GLM2) we performed second-level random-effects analyses. For each first-level contrast, the group contrasts at the second level were calculated with one-sample t-tests against zero. For significance we used a statistical threshold of $p = 0.05$, FWE corrected for multiple comparisons at the cluster level. To extract region of interest (ROI) activity parameters for visualization and further analyses we used the Marsbar toolbox (Brett, Anton, Valabregue, & Poline, 2002).

In order to identify brain regions that are functionally connected and assess changes with connectivity with the stimulated FPC (as a function of metacognition) during metacognitive evaluation of choice, we conducted a psychophysiological interaction analysis (PPI; Friston et al., 1997). With this analysis we sought to identify the brain regions showing altered functional coupling with FPC during the task and whether this connectivity changed as a function of stimulation. We extracted the physiological average time series in the FPC seed region corresponding to the psychological variable of metacognitive sensitivity as reflected by the Confidence X Value Difference interaction for each individual and run. For our seed region we selected a region in the FPC shown previously to reliably reflect metacognition across studies [28 50 26] (Vaccaro & Fleming, 2018) and built an 8 mm sphere around it. We separately modeled regressors for the same variables as in GLM1 for the theta-sham, theta-alpha and alpha-sham contrasts. The PPI regressors modeling the interaction between the FPC time course and metacognitive sensitivity were obtained by multiplying the psychological regressor (metacognitive

sensitivity) with the physiological regressor (time course of FPC). We again performed second level analysis in order to derive group-level inferences on FPC connectivity during metacognitive evaluation.

Results

Behavioral results

Data from three participants were dropped due to lack of variance in responses resulting in a final dataset of 37 participants. To ensure that stimulation did not affect directly choices or decision confidence per se we tested separately that neither decisions ($F(1, 36) = 0.18$, $p = 0.672$), nor confidence ratings ($F(1, 36) = 0.13$, $p = 0.714$) differed significantly between stimulation conditions. We further found no significant difference in (log transformed) discounting rate, $F(1, 36) = 0.06$, $p = 0.806$, or inverse temperature (decision noise), $F(1, 36) = 0.61$, $p = 0.437$, among the four tACS conditions.

To test our hypothesis that theta tACS would increase metacognitive awareness in the task (replicating Soutschek et al., 2021) we regressed choices (1= LL, 0 = SS) on predictors for tACS condition, subjective Value Difference, Confidence and their interaction, z-standardized to account for metacognitive bias at the individual level (Maniscalco & Lau, 2012), together with predictors for previous tACS, discomfort and flickering.

As expected, higher difference in subjective value in favor of the LL reward predicted a higher likelihood of selecting the LL reward, beta = 4.06, $z = 10.46$, $p < 0.001$. Moreover, higher retrospective confidence in the decision was associated with higher likelihood that the decision was the LL reward, beta = 1.26, $z = 3.95$, $p < 0.001$. Overall participants possessed metacognitive

access to the uncertainty in their decisions, as indicated by a significant Confidence X Value Difference interaction, beta = 2.39, z = 8.29, p < 0.001. Contrary to our hypothesis, the analysis revealed a negative effect of theta stimulation on metacognitive sensitivity compared to sham, beta = -0.63, z = -2.25, p = 0.024 (Figure 2). The difference in metacognitive sensitivity between alpha and sham was not significant, beta = -0.25, z = -0.86, p = 0.389, suggesting that as per our hypothesis the effect of stimulation on metacognitive sensitivity was specific to the theta frequency. In a separate MGLM we assessed the difference between theta and alpha stimulation as alpha frequency served as our control condition. There too, we found no difference between theta and alpha, beta = 0.37, z = 1.49, p = 0.136 (Figure 2). Our behavioral results show, contrary to our expectations and previous findings (Soutschek et al., 2021) that theta stimulation reduced metacognitive sensitivity in intertemporal choice compared to sham.

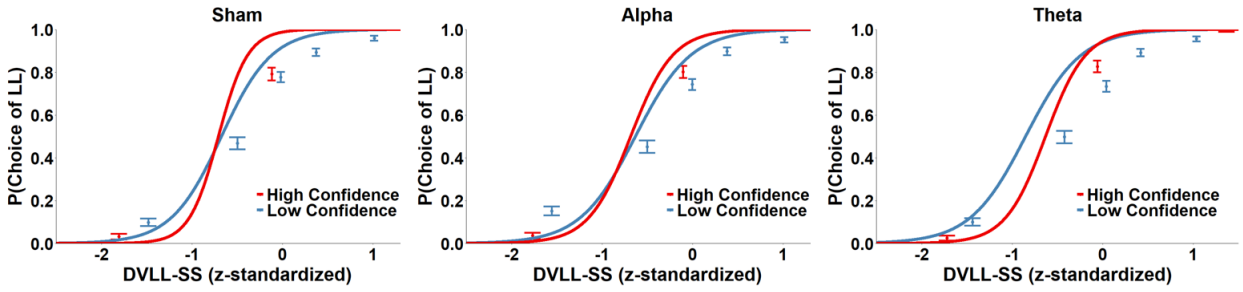

Figure 2. Stimulation effects on metacognitive sensitivity at the confidence accuracy task. Theta tACS significantly impaired metacognitive sensitivity compared with sham, as indicated by the larger slope difference between the logistic curves for decisions with low and high confidence. For illustration, we split the data into decisions with low and high confidence (median split). Regression lines are based on the group-level fixed effect parameter estimates from the regression models. Raw data are binned and overlaid over regression lines for reference. Error bars represent standard error of the mean.

As expected, in the mentalizing task participants made more mistakes in the False Belief (FB) compared to the True Belief (TB) conditions, as indicated by a significant main effect of condition type, beta = -1.39, z = -12.35, $p < 0.001$. The analyses for the mentalizing task revealed no significant effects of stimulation for the False Belief condition. More specifically, our analysis revealed a significant effect of theta stimulation on performance at the True Belief conditions, beta = -0.22, z = -2.49, p = 0.012, such that participants had fewer correct responses under theta compared to sham and although the results pointed to a "protective" effect of theta tACS on performance in the FB condition on a trend level, the theta X FB interaction did not reach significance, beta = 0.25, z = 1.83, p = 0.066. No other effects reached significance (all $p > 0.05$). Overall, we found no evidence that theta oscillations in the FPC are causally involved in mentalizing. Therefore, we did not pursue further analyses for this task.

fMRI results

To identify the brain regions involved in intertemporal choice and metacognition during the task, we investigated brain activity in the task averaged across all tACS conditions. As expected, value difference correlated positively with activation in the striatum, amygdala, bilateral posterior parietal cortex (PPC), insula (Table S1) and negatively with anterior cingulate cortex (ACC), hippocampus, left dlPFC, insula, left ventrolateral PFC, and right PPC (Table S2), $p < 0.05$ FWE corrected for multiple comparisons at the cluster level, in line with previously reported BOLD activation related to the representation of subjective value (Bartra, McGuire, & Kable, 2013; Peters & Büchel, 2011; Soutschek, Moisa, Ruff, & Tobler, 2020; Wesley & Bickel, 2014) validating that our task engaged the valuation system as would be expected during an intertemporal choice task. Additionally, decision confidence was correlated negatively with activation in the

dorsomedial PFC (dmPFC), bilateral dlPFC, right PPC and cerebellum (Table S3), $p < 0.05$ FWE corrected for multiple comparisons at the cluster level, again in line with previous findings on the role of these regions in cognitive control, conflict monitoring and confidence encoding (Chen, Feng, Shi, Liu, & Li, 2013; Huettel, Song, & McCarthy, 2005; Moritz, Gläscher, Sommer, Büchel, & Braus, 2006). We additionally tested whether these local representations of confidence and subjective value differed between theta and sham and found no significant clusters surviving correction for the theta>sham contrast. Finally, in order to assess local effects of the stimulation on the FPC, we extracted individual parameters reflecting BOLD activation in the stimulated area for each participant under the different conditions, with a sphere ROI of 8 mm. Although we did not find a significant difference for local activation between the stimulation conditions ($\chi^2_F(2)$: 2.12, $p = 0.347$), the mean activation parameters for each condition indicate that, if anything, theta tACS reduced local activation (mean beta = -0.001) compared to sham (0.033) as did alpha stimulation (-0.002) (Figure 3).

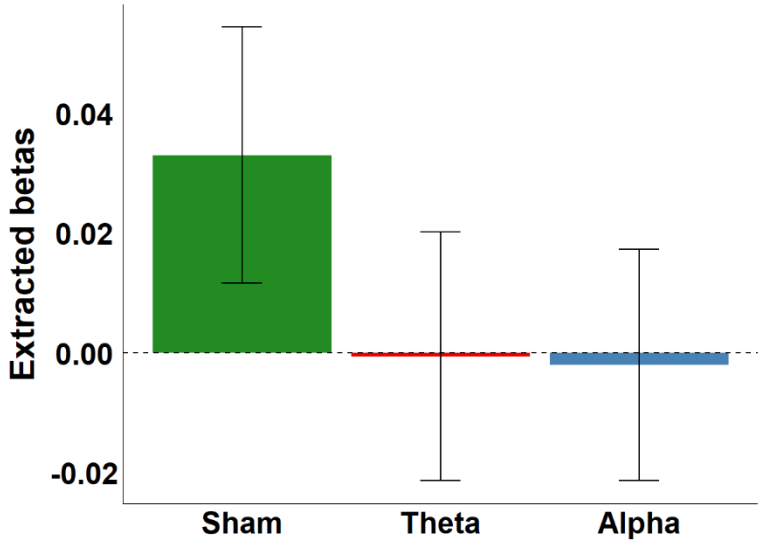

Figure 3. Stimulation effects on BOLD activation in the FPC. Extracted mean parameter estimates as obtained with an 8 mm sphere ROI in the FPC [28 50 26]. No significant stimulation effects were found for local activation. Error bars indicate standard error of the mean.

PPI analysis

Next, we investigated whether theta tACS modulation of the FPC is induced through functional interaction with other brain areas during the task. For this, we tested whether FPC altered its functional coupling with other areas in the brain during the task. A PPI analysis with seed region from a meta-analysis for metacognition (Vaccaro & Fleming, 2018) and subjective Value Difference X Confidence as the psychological term revealed a robust modulation of connectivity between FPC, lPFC and PPC (Figure 4). More specifically, during theta stimulation relative to sham the FPC showed reduced connectivity with bilateral lPFC and right PPC [peak coordinates (MNI): x = -54, y = 11, z = 26; k = 169; p = 0.001; left lPFC, x = 42, y = 23, z = 32; k = 86; p = 0.027; right lPFC, x = 42, y = -49, z = 44; k = 119; p = 0.007; right PPC], FWE corrected for multiple comparisons at the cluster level (Figure 4 & Table 1). No areas survived correction for theta-alpha and alpha-sham contrasts. Note that these results were also robust to using an anatomical mask of BA10 as seed region, [peak coordinates (MNI): x = -51, y = 29, z = 23; k = 58; p = 0.093; left lPFC, x = 42, y = 35, z = 23; k = 96; p = 0.018; right lPFC, x = 48, y = -64, z = 44; k = 57; p = 0.097; right PPC], FWE corrected for multiple comparisons at the cluster level.

We further tested whether the regions identified to show functional connectivity with FPC during metacognitive evaluation overlap with those found for the GLM1 for the difference in subjective value and confidence contrasts. For this, we extracted the clusters identified in the PPI analysis and created a binary mask, which we then used to apply small volume correction to the results for value difference and confidence in GLM1. Results showed to largely overlap with areas correlated negatively with Confidence [peak coordinates (MNI): x = 45, y = 20, z = 35; k = 84; p = 0.001; right lPFC, x = -51, y = 17, z = 26; k = 165; p < 0.001; left lPFC, x = 39, y = -43, z = 41; k = 89; p = 0.001; right PPC] and Value Difference [peak coordinates (MNI): x = - 45, y = 14, z =

32; k = 104; $p < 0.001$; left lPFC, x = 48, y = -43, z = 47; k = 68; $p = 0.002$; right PPC, x = 48, y = 23, z = 32; k = 58; $p = 0.003$; right lPFC], FWE corrected for multiple comparisons at the cluster level (reporting clusters with k > 20). Taken together, our results suggest that theta tACS impairs metacognition in decision making through reduced functional connectivity with lPFC and right PPC, via reading out choice related information such as choice difficulty and subjective confidence from these regions.

Table 1. Anatomical locations and MNI coordinates of the peak activations reflecting functional connectivity with FPC under theta compared to sham tACS in the PPI analysis. We report activations surviving whole-brain FWE correction at cluster level ($p < 0.05$). Hem = Hemisphere (L = left, R = right); BA = Brodmann area.

			MNI coordinates				
Region	Hem	BA	X	Y	Y	k	Z
Inferior frontal gyrus	L	44	-54	11	26	169	4.32
Supramarginal Gyrus	R	40	42	-49	44	119	4.16
Middle frontal gyrus	R	9	42	23	32	86	3.84

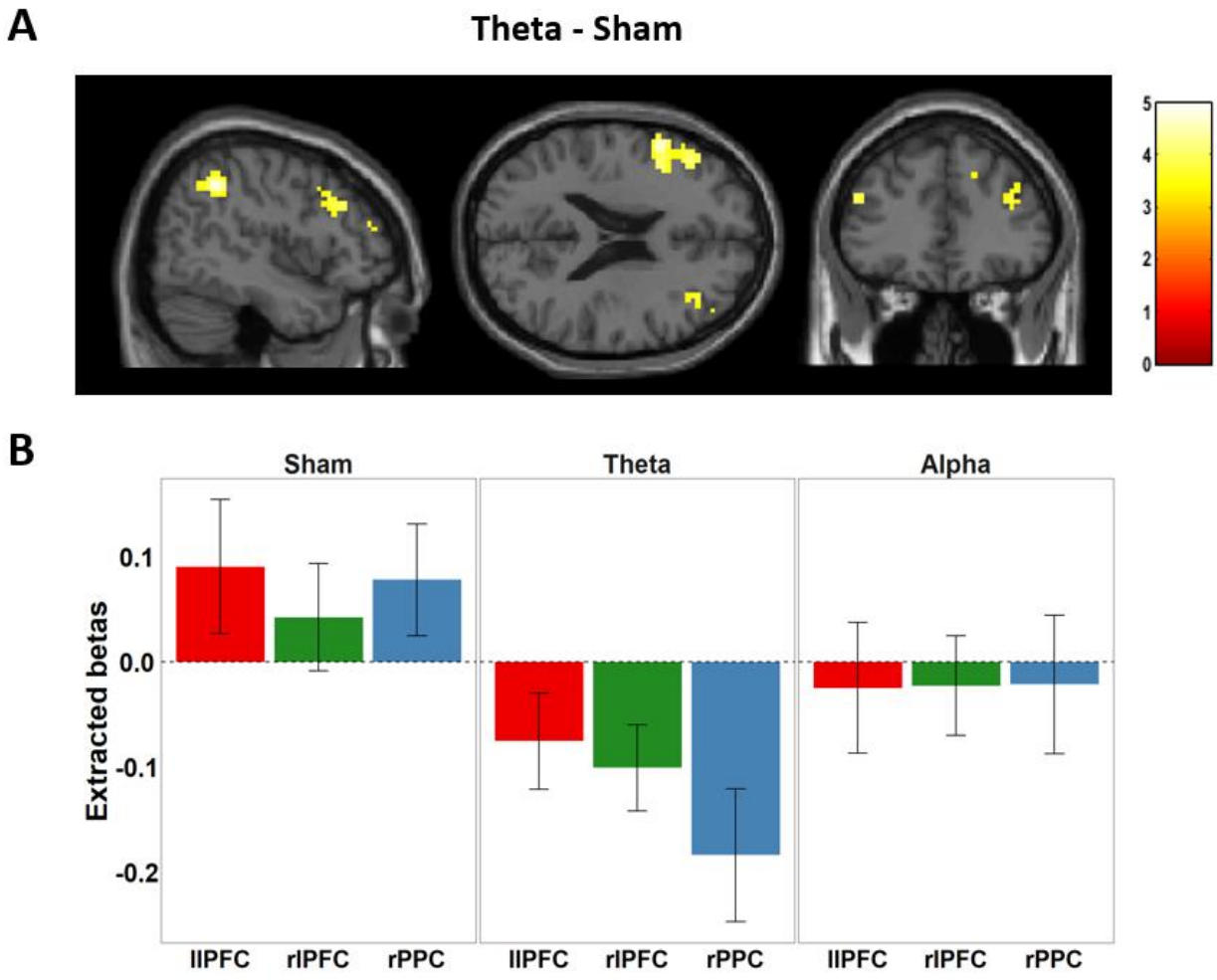

Figure 4. Effects of stimulation on connectivity with FPC. (A) Theta tACS over the FPC reduced functional connectivity between the FPC and bilateral lPFC and right PPC compared to sham (image FWE corrected at the cluster level, $p < 0.05$). (B) Extracted mean parameter estimates for right and left lPFC and right PPC as defined by the significant clusters in the PPI analyses for the metacognitive sensitivity term. Theta tACS significantly reduced connectivity between FPC, right PPC and bilateral lPFC. No voxels survived correction for the alpha – sham or theta – alpha contrasts. Error bars indicate standard error of the mean. llPFC, lateral prefrontal cortex; rlPFC, right lateral prefrontal cortex; rPPC, right posterior parietal cortex.

Discussion

In the present study we used a combination of online HD-tACS and fMRI to investigate the neural substrates of tACS-induced modulations of metacognitive sensitivity, shedding light on the link between brain activity, oscillatory patterns and metacognition. We investigated the neuronal signature of metacognition in intertemporal decisions (Soutschek et al., 2021) and extended previous findings by providing a neurophysiological account of the underlying brain mechanisms. More specifically, our findings converge with previous evidence for a causal involvement of the FPC in metacognitive sensitivity (Soutschek et al., 2021) and corroborated the finding that theta oscillations in the FPC are the neuronal signature of metacognition in decision making (Fleming, 2016; Murphy, Robertson, Harty, & O'Connell, 2015; Soutschek et al., 2021; Wokke et al., 2017). Further, we extended these previous results by showing that frontopolar theta stimulation impacted metacognition through altered connectivity with bilateral lPFC and right PPC. More specifically, reduced metacognitive sensitivity as a result of theta stimulation, was expressed through reduced functional connectivity between the FPC, bilateral PFC and right PPC. These areas were also found to encode subjective confidence and value difference information in the brain, thus showing that in order to metacognitively evaluate our decisions, the FPC modulates its connectivity with brain regions in order read out relevant decision-related information.

While establishing the causal link between FPC oscillations and metacognition, we provide support for previous findings on the role of FPC in reporting subjective confidence during value-based choice (De Martino et al., 2013; Soutschek et al., 2021), and for an active role of this region in performing and reporting metacognitive evaluations during decision making, rather than simply, passively representing confidence signals (De Martino et al., 2013; Soutschek et al., 2021; Vaccaro & Fleming, 2018; Wokke et al., 2017). Our findings support the hypothesized role of the FPC in

processing a readout of confidence signals from regions encoding relevant decision information (Bartra et al., 2013; Lebreton, Abitbol, Daunizeau, & Pessiglione, 2015) and further speak to the domain-generality of this resource for metacognition, in convergence with evidence linking the anterior PFC to metacognitive assessment of individual decision making and performance (Baird, Smallwood, Gorgolewski, & Margulies, 2013; Fleming, Huijgen, & Dolan, 2012; Fleming, Weil, Nagy, Dolan, & Rees, 2010).

The way that confidence information is read out and communicated has been a central question over the past years in the literature on metacognition. Our analysis revealed that impaired metacognitive ability was reflected in the brain by reduced connectivity of the FPC with bilateral PFC and right PPC, regions involved in confidence and value difference reflecting choice difficulty and confidence encoding as shown by our analysis and previous findings (Chen et al., 2013; Hoffman, et al., 2008; Huettel et al., 2005; Moritz et al., 2006; Van den Bos & McClure, 2013). These findings can shed light on existing neural models of metacognition as they indicate that FPC processes neural signals in communication with other regions in the brain and are in line with a hypothesized role of theta oscillations as the neural substrate facilitating the synchronization of FPC with these regions, thus accessing metacognitively decision-related information encoded in the theta frequency. Our findings are in line with previous accounts for a two-layer neural architecture (De Martino et al., 2013; Fleming & Dolan, 2012; Pasquali, Timmermans, & Cleeremans, 2010) where the first-order network encodes decision and performance information which is then communicated to the second-order network for metacognitive report of confidence. Indeed, we show that regions in which activity correlated with confidence and value difference in the brain, showed reduced connectivity with FPC under theta stimulation compared to sham,

implying that deactivating the FPC impaired the communication of relevant information and subsequently metacognitive ability.

One important finding of this present study is the negative effect of enhancing frontopolar theta band activity on metacognition. In contrast to Soutschek et al., 2021 we found that theta entrainment over the FPC impairs, rather than improves metacognitive sensitivity. In order to understand this seemingly conflicting result, we need to take into account a few methodological differences between the two studies. First of all, we used a high definition tACS set up, resulting in a different electric field distribution in the stimulated area. One could speculate that the different stimulation focality could underlie these differential effects. However, in Soutschek et al. (2021) as in the present paper, stimulation was shown to not directly affect decision variables that would reflect possible modulation of neighboring to the FPC areas such as dlPFC or vmPFC. A second important difference in our experimental set up is the higher stimulation intensity (mean intensity of 3.6 mA instead of 2 mA). Previous research has shown that higher stimulation intensities may result in unexpected effects of stimulation compared to lower intensities and the transcranial electrical stimulation dose-response relationship is still debated (Batsikadze, Moliadze, Paulus, Kuo, & Nitsche, 2013; Esmaeilpour et al., 2018; Moliadze, Atalay, Antal, & Paulus, 2012). A plausible explanation, therefore, in line with the observed reduced activation in the stimulated area in our study, is that our stimulation possibly deactivated the FPC instead of enhancing its activity.

Another question that arises in this case, is whether deactivating FPC with our paradigm should result in increased metacognitive ability as shown in previous studies (Rahnev et al., 2016; Ryals et al., 2016; Shekhar & Rahnev, 2018). However, these studies had smaller samples, variable stimulation target areas and similar results have been previously intensely debated (Bor, Schwartzman, Barrett, & Seth, 2017; Rounis, Maniscalco, Rothwell, Passingham, & Lau, 2010;

Ruby, Maniscalco, & Peters, 2018). Finally, and most importantly, the precise neurophysiological effects of stimulation methods are still not clear (Rafiei & Rahnev, 2021) and we cannot know the impact of stimulation in these studies on local cortical activity. In contrast, in our study we were able to measure local activity in the stimulated area and found that tACS, if anything, reduced rather than increased FPC activity. By combining tACS with fMRI we provide a neurocomputational account of metacognitive evaluation during decision making and show the associated oscillatory and spatial dynamics.

Finally, we did not find a significant effect of theta stimulation on mentalizing. The reasons for this lack of significant results in our paradigm can be manifold. Our findings could point to the conclusion that FPC is not part of the mentalizing network and metacognition and mentalizing may overlap only in other regions like vmPFC, dorsal anterior cingulate cortex (dACC) and dmPFC (Denny, Kober, Wager, & Ochsner, 2012; Vaccaro & Fleming, 2018; Van Overwalle & Baetens, 2009). Moreover, our findings could point to different underlying mechanisms between metacognition and mentalizing, or rather that frontopolar theta is specific for metacognition, which could further inform a clear theoretical dissociation of the two constructs. Future research can address these possibilities in more detail.

It is important that our findings can have clinical significance and implications, as metacognitive deficits have been implicated in poor self-control behaviors in addiction and other disorders (Goldstein et al., 2009; Moeller et al., 2016). In line with previous theoretical (Bulley & Schacter, 2020) and empirical findings (De Martino et al., 2013; Soutschek et al., 2021; Soutschek & Tobler, 2020) we show once again that humans possess metacognitive access to the noise in their valuation process during intertemporal decisions, which is not equated with self-control per se in disagreement with accounts associating deliberation with selecting the long-term “rational”

option (Bulley & Schacter, 2020), and where high accuracy is associated with high subjective confidence and vice versa. This ability can be crucial for revisiting past decisions, communicating certainty (De Martino et al., 2013) or strategizing for successful self-control (Soutschek et al., 2021; Soutschek & Tobler, 2020). Here we showed that the relationship between confidence and difference in value can be associated with decision making in the intertemporal decision-making task, simultaneously providing a neurobiological account of this link. Thus, our findings can provide novel insights into potential stimulation-based treatment solutions as tACS has been proposed as a viable, promising method for therapeutic interventions (Elyamany, Leicht, Herrmann, & Mulert, 2021).

In this paper we showed that high intensity theta tACS over the FPC impairs metacognitive ability in value-based decision making and this effect results from reduced connectivity between the FPC and areas encoding decision-related information. Taken together, our findings elucidate the neurophysiological basis of metacognition in decision making, shedding light on the combined underlying role of spatial and oscillatory dynamics in the brain.

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All authors declare to have no conflicts of interest.

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Supplementary material

Table S1. Anatomical locations and MNI coordinates of the peak activations correlating positively with difference in subjective value in GLM1. We report activations surviving whole-brain FWE correction at cluster level ($p < 0.05$). Hem = Hemisphere (L = left, R = right); BA = Brodmann area.

			MNI coordinates				
Region	Hem	BA	X	Y	Z	k	Z
Striatum	R		21	17	20	424	5.35
Insula	R	6	57	2	8	875	4.91
Supramarginal Gyrus	L	40	-51	-37	26	176	4.73
Amygdala	L		-24	-4	-16	106	4.72
Occipital pole	R	18	12	-94	23	121	4.61
Superior parietal lobule	R	7	18	-46	62	145	4.39
Superior Temporal Gyrus	L	22	-63	-25	2	111	3.89

Table S2. Anatomical locations and MNI coordinates of the peak activations correlating negatively with difference in subjective value in GLM1. We report activations surviving whole-brain FWE correction at cluster level ($p < 0.05$). Hem = Hemisphere (L = left, R = right); BA = Brodmann area.

			MNI coordinates				
Region	Hem	BA	X	Y	Z	k	Z
dmPFC	R	8	6	26	38	1086	5.99
Insula	R	13	39	20	-7	700	5.15
Orbitofrontal cortex	L	47	-33	26	-4	227	4.94
Middle frontal gyrus	L	8	-45	14	32	252	4.67
Hippocampus	R		24	-37	2	364	4.66
Supramarginal Gyrus	R	40	48	-43	50	188	4.63

Table S3. Anatomical locations and MNI coordinates of the peak activations correlating negatively with confidence in GLM1. We report activations surviving whole-brain FWE correction at cluster level ($p < 0.05$). Hem = Hemisphere (L = left, R = right); BA = Brodmann area.

Region	Hem	BA	MNI coordinates			k	Z
			X	Y	Z		
Frontal superior medial gyrus (extending to left and right dlPFC as well as dmPFC)	L	8	-3	23	44	7031	6.80
Cerebellum	L		-30	-64	-28	783	5.81
Superior parietal lobule	R	7	18	-67	62	3272	5.62
Cerebellum	R		30	-64	-31	363	5.22

5. General discussion

The goal of this dissertation was to investigate the neurobiological and neurocognitive basis of self-control in intertemporal choice. By taking a systemic approach in search of causal evidence, I explored pharmacological, neurophysiological and neurocognitive aspects of this valuable capacity, providing interdisciplinary empirical evidence on the mechanisms underlying impulsivity and intertemporal decisions. Below, I highlight and summarize the main findings and conclusions of the projects presented in this dissertation. Following that, I discuss theoretical and practical implications of the findings.

5.1. Summary of findings

5.1.1. Evidence for a positive effect of oxytocin on delay of gratification

In the first project of this thesis, we investigated the role of oxytocin in delay of gratification and cognitive flexibility. In a healthy group of participants, we administered intranasal oxytocin, with a double-blind crossover design, and revealed a clear role of this neuromodulator in non-social decision making. Oxytocin has traditionally been thought of as a social hormone with multiple theories attempting to account for its hypothesized role in social behaviors (Kemp & Guastella, 2011; Shamay-Tsoory & Abu-Akel, 2016). Here, we replicated previous findings on oxytocin improving generosity but further extended them to show that this result holds predominantly under advantageous inequity conditions. Intranasal oxytocin increased delay of gratification compared to placebo, a result that was supported both by model-free and model-based results, consistent with findings of a link between impulsiveness and oxytocin in clinical samples (Hurlemann et al., 2019; McRae-Clark et al., 2013). This effect of oxytocin might reflect modulation of choice attributes in the striatum, and it could further potentially reflect interactions with the dopaminergic system.

We further showed that oxytocin improved cognitive flexibility in the reversal learning task, albeit in individuals with low working memory capacity (WMC), in line with similar

pharmacological manipulations (Soutschek, Kozak, et al., 2020; Van der Schaaf et al., 2014). Interestingly, the results on delay of gratification were not dependent on baseline WMC. Though we speculate performance in both tasks may be underlied by the same mechanism, it is possible that baseline WMC might be more important for reversal learning were participants need to continuously update the relevant information in mind, in contrast to self-control, where working memory may be primarily associated with maintaining the relevant goals in mind (Hofmann, Schmeichel, & Baddeley, 2012). Again oxytocin-dopamine interactions have been suggested to play a role in working memory performance and is possible that this improvement was the result of strengthening prediction error signals in the striatum. Importantly, we found no effect of oxytocin on working memory, suggesting that the observed effects are more plausibly the result of oxytocin effects on striatal rather than prefrontal networks. It is therefore possible that oxytocin acted like a dopamine antagonist in striatal reward circuits, possibly by lowering the subjective values of immediate rewards and enhancing prediction error signals. Our findings are also in line with the novel, allostatic theory for oxytocin positing a role of the neuromodulator in regulating allostatic functions including future oriented behavior (Quintana & Guastella, 2020).

Future research should address the precise mechanisms underlying this effect as we employed a systemic manipulation, and we cannot fully disentangle the precise effects of oxytocin at the neural level. Overall, this first study linked for the first time in healthy humans, oxytocin with non-social behavior, in particular with impulsivity and delay of gratification, revealing its beneficial effects for these processes, and putting previous clinical and animal findings on firm ground and able to inform clinical interventions.

5.1.2. Oscillatory frequencies in the dlPFC show differential contributions to self-control

In the second study of this dissertation, we used transcranial alternating current stimulation (tACS) over the left dlPFC in order to investigate the causal involvement of specific neural oscillations in self-control. We stimulated the left dlPFC with alpha (10 Hz), beta (20 Hz), and gamma (30 Hz) frequency in order to clarify and disentangle previous findings in the EEG literature, pointing to a role of alpha and beta oscillations in implementing self-control (Gianotti et al., 2012; Gui et al., 2018; HajiHosseini & Hutcherson, 2021; Harris et al., 2013). While the

causal role of the left dlPFC in intertemporal decisions has been established with methods designed to inhibit or enhance its function, evidence on the neurophysiological signature of this involvement is scarce. Using the three frequencies, allowed us to investigate separate accounts of oscillatory activity in intertemporal choice and test the causal contribution of these oscillations in promoting patience.

Consistent with the causal implication of dlPFC in intertemporal choice, the results showed an effect of stimulation on behavior. Alpha tACS improved self-control, such that under alpha stimulation participants were more likely to select the larger-later reward compared to sham. This result points to the possibility that alpha effects reflect the modulation of relevant attentional processes in suppressing goal-irrelevant information as suggested previously (Harris et al., 2013). In addition to the effects of alpha stimulation, we found an effect of beta tACS such that beta entrainment appeared to promote self-control through attenuating the effect of delay and immediate reward on behavior. Supporting our hypothesis, it is possible that beta stimulation directly impacted attribute weighting during intertemporal choice, in line with previous research drawing a link between beta oscillations and self-control (Gianotti et al., 2012; Gui et al., 2018). Finally, we found an unexpected effect of gamma stimulation on decision making in the task. Gamma stimulation was shown to facilitate patient responding through reducing the effect of delay on choice. It is possible that gamma stimulation over the dlPFC enhanced working memory processes, thus enhancing patience through enabling participants to keep long term goals in mind.

Here, we showed that alpha, beta and gamma oscillations in the left dlPFC are causally involved in self-control, possibly by differentially enhancing separate cognitive processes involved in intertemporal choice. Future research could extend these findings by disentangling these sub-processes potentially affected by our stimulation conditions, with further studies employing control tasks and a combination of stimulation, neuroimaging and computational methods that would allow for a more detailed overview of the effects. Overall, our present findings reveal a causal role of dlPFC oscillatory activity in self-control and show that self-control can be enhanced via frequency-specific stimulation of the dlPFC.

5.1.3. Metacognition is implemented through functional FPC – lPFC/PPC connectivity

In the third and final study of this thesis, we investigated an important neurocognitive mechanism linked to intertemporal choice, that is metacognition. Using concurrent tACS and fMRI, participants were stimulated with high definition tACS at the theta (5 Hz), alpha (10 Hz) frequency or sham, while performing an intertemporal choice task with confidence ratings in the MRI scanner. This method allowed us not only to assess previous causal evidence of the link between FPC and metacognition, but also to pinpoint the underlying brain mechanisms facilitating behavioral change as a factor of stimulation. With this method, we are able to provide a mechanistic account of stimulation effects on metacognition, together with the neuronal signature of this process, theta oscillations.

Our behavioral results, as expected, revealed that participants overall possessed metacognitive access to the accuracy of and noise in their decisions in line with previous research (De Martino et al., 2013; Soutschek et al., 2021; Soutschek & Tobler, 2020). Here, we also provide additional evidence on the causal involvement of the FPC in metacognitive evaluation during decision making (Soutschek et al., 2021). Theta tACS was found to impair this ability, by reducing metacognitive sensitivity compared to sham stimulation. Our results provide support for a crucial role of FPC for metacognition, expressed with theta oscillatory activity, and its role in actively processing the related information signals from other brain regions into a metacognitive evaluation that the individual can access and report. Performing a connectivity analysis, we found that the FPC showed reduced connectivity with bilateral PFC and right PPC during metacognitive evaluation under theta stimulation compared to sham. It is possible that deactivating the FPC, reduced its connectivity, thus inhibiting communication with areas encoding decision information related to subjective confidence and value difference. These findings are further in line with theoretical models of metacognition suggesting a second-level role for FPC, drawing information from first-level processing areas and performing metacognitive evaluations (Fleming & Dolan, 2012; Pasquali, Timmermans, & Cleeremans, 2010).

The high intensity of stimulation was a novel aspect of our design, implemented to maximize stimulation effects. It is possible, however, that tACS in low intensity enhances local activity but rather inhibits it in higher intensities. Previous research has highlighted this possibility, speculating that neurostimulation effects may be non-linear, much like pharmacological manipulations (inverted U-shaped dose-response relationship) (Nitsche & Bikson, 2017), possibly

due to the involvement of deeper brain structures (though our data do not support this speculation). Prolonged stimulation time has shown similar effects in reversed directionality, a result ascribed potentially to a neuronal homeostatic system preventing over-excitation, by facilitating the activation of hyperpolarizing potassium channels because the effects of tDCS stimulation on cortical excitability are calcium-dependent (Batsikadze, Moliadze, Paulus, Kuo, & Nitsche, 2013; Monte-Silva et al., 2013). Indeed, the data pointed to reduced BOLD activity in the FPC during stimulation compared to sham. This finding is very interesting from a methodological point of view, highlighting the need for future research to clarify tACS effects dependent on current intensity. Closing, our method allowed us to provide a precise mechanistic account of metacognitive evaluation during intertemporal decision making and to investigate the critical link between metacognition, brain networks and cortical oscillations.

5.2. Theoretical contributions

With the three projects included in this dissertation, we investigated different aspects of intertemporal decision making, reflected in separate networks in the brain, which are typically involved in self-control. The first study causally affected the reward system (though we cannot fully exclude the possibility of frontal cortex involvement), the second study targeted the control system of intertemporal choice and the third study the second-level metacognitive/evaluative system. In addition to the empirical evidence introduced, our findings have several theoretical implications.

Although past research has predominantly focused on the role of neurotransmitters in self-control, we provided evidence showing that also hormones are meaningfully implicated in intertemporal decision making. Oxytocin was shown for the first time to improve delay of gratification in a healthy sample. This comes in contrast with previous theories, ascribing oxytocin a uniquely social role (Kemp & Guastella, 2011; Shamay-Tsoory & Abu-Akel, 2016). For many years oxytocin was known for its social effects and studied as such. Only recently, Quintana and Guastella put forth their allostasis theory for oxytocin, suggesting that oxytocin is much more than a social hormone but rather supports the organism with allostatic functions (Quintana & Guastella, 2020). Indeed, our findings provide support for this theory, since we had beneficial effects of

oxytocin both on delay of gratification and on reversal learning (flexibility). Our findings could not be explained by previous theories of oxytocin, thus providing clear evidence in favor of the allostasis hypothesis and further providing a steppingstone for reconceptualizing oxytocin's role in research and clinical environments. Further, showing that oxytocin could potentially affect reward processing, may yield fruitful insights into research examining both dopaminergic-oxytocinergic interactions and oxytocin effects on other types of individual decision making (e.g., risky decisions).

Our second study provided causal evidence for the role of alpha, beta and gamma oscillations in promoting self-control in intertemporal choice. With this evidence, we corroborate the role of the left dlPFC as the center of the control network in intertemporal choice and show that self-control can be facilitated by contributions of different frequencies in the dlPFC. Though we can only speculate on the nature of our stimulation-specific effects, they could potentially point to different processes being involved in self-control, in line with recent accounts conceptualizing self-control as more than just effortful inhibition but acknowledging the contribution of several cognitive processes (Lempert & Phelps, 2016). Recent accounts have suggested crucial roles of cognitive processes like attention and memory in self-control, each of which, with a different contribution in promoting patience in intertemporal choice. Our findings could provide further support towards these accounts and towards the multifaceted contribution of dlPFC in decision making (MacDonald, Cohen, Stenger, & Carter, 2000; E. K. Miller & Cohen, 2001).

Our third study allowed us to look at the mechanisms underlying metacognition in decision making. Our findings are in line with previous research showing a crucial role of metacognition in intertemporal choice, such that this ability helps in evaluating and potentially optimizing self-control decisions. Though we assessed metacognition with retrospective confidence ratings, this metacognitive access to our past decisions can be as helpful for the next decision, similarly to prospective confidence, since humans more often than not learn from their past experiences. At the theoretical level we show that metacognition is indeed not synonymous to self-control but allows accessing noisy or uncertain decisions (Bulley & Schacter, 2020; Soutschek et al., 2021; Soutschek & Tobler, 2020). We further show that metacognition is a second-order process that not only depends on FPC, but crucially also on other brain areas, which forward the necessary information to FPC. Activation in lPFC and PPC correlated with value difference and confidence,

suggesting that these areas are involved in representing those variables. We show that possibly these areas encode the relevant information at the first level, which is then metacognitively accessed by FPC to turn into an evaluation of the decision. This is in line with theoretical accounts for the role of FPC as an active region at the top of the neural hierarchy for metacognition, rather than a region passively representing confidence (Fleming & Dolan, 2012).

Overall, we provide crucial evidence on the neurobiological basis of self-control, by shedding light on different networks involved in intertemporal decision making. We show that self-control is reliant on multiple networks and processes, providing support to accounts positing that self-control is more than effortful inhibition. Here, we extend the dominant neural model of delay discounting by showing that in addition to brain activity and neurotransmitter function, hormones, oscillations and metacognition play a crucial role in self-control. Though developing a unified model of self-control can be challenging, the present findings can inform theory in this direction in order to provide an overall model of intertemporal choice taking into account the multitude of cognitive (Lempert & Phelps, 2016) and neurobiological (J. Peters & Büchel, 2011) processes involved.

It has been previously suggested that failures of self-control can be the result of frontostriatal imbalance causing either bottom up or top down failures (Heatherton & Wagner, 2011). Here, we show that three separate systems, which hitherto received little attention in the literature, contribute causally to intertemporal decision making. Thus, the observed self-control impairments may stem from the dysregulation of any of these systems, with the proposed frontostriatal imbalance being the end result of pharmacological (oxytocinergic), oscillatory or neurocognitive (metacognitive) changes. Bringing these systems together and understanding their computational and mechanistic roles, as well as their complex interactions, can provide unique insights into psychopathology (Lempert & Phelps, 2016), while a better understanding of underlying modulatory factors can significantly aid our understanding of cognitive and neural processes involved in self-control (J. Peters & Büchel, 2011). Moving away from dual systems operationalizations, recent accounts have called for a unified model of self-control, critically defined at the multiple levels involved and reflecting the intricate interrelations among them (Berkman et al., 2017; Lempert & Phelps, 2016; J. Peters & Büchel, 2011). This thesis can be a step towards this direction.

Future research can further investigate the effects of oxytocin on decision making with more fine-grained methods in order to determine its precise mechanistic involvement in self-control and the possible interactions with the dopaminergic system, while further stimulation studies in combination with fMRI could shed light on the precise neurocomputational role of the dlPFC in intertemporal choice and provide an account of its contributions to self-control and value modulation. Building on the order effect observed in our first study, it may be possible that the effect was evident with a session structure of one week apart, where memories of the participants' choices may have been consolidated for long-term use and later retrieved (perhaps with the knowledge that they would perform the task again), whereas in the second and third studies, the paradigm only allowed previous choices to be held in working memory and thus anchoring effects were not observed. Future research can take into account these possibilities with similar experimental settings. Further studies can additionally elucidate the system interactions between the different first- and second-level (metacognitive) systems and their differential contributions to the sub processes involved in successful self-control, as well as directly assess the impact and effects of frontopolar theta stimulation in clinical populations. Importantly, the results presented in this thesis may have limited generalizability, as participants in all three experiments were healthy, young adults. It would therefore be interesting to investigate whether and how these findings generalize to different age groups and clinical populations. Finally, theory and practice should move towards providing a unified account of self-control, taking the multilevel cognitive and neurobiological contributions to intertemporal choice into account.

5.3. Practical implications

The present thesis' findings can further our understanding on the neurobiological bases of self-control and value-based decision making. This can have not only theoretical implications, but direct, practical ones. Delay discounting has been closely linked to several psychiatric disorders and understanding the mechanisms behind it can inform clinical research on improving self-control deficits in psychiatric disorders, as well as point towards new therapeutic interventions. While previous clinical interventions targeting delay discounting have conventionally focused on altering excitability on the prefrontal control system or improving neurotransmitter function at the value

system, our findings suggest three novel intervention approaches: hormones, oscillations and metacognition. Similarly to providing a cognitive "toolbox" approach for behavioral interventions (Fujita, Orvell, & Kross, 2020), here we provide a multilevel approach to neural interventions.

In specific, the finding that oxytocin is involved in delay of gratification and reversal learning, revealed a novel characteristic of the neuropeptide, which had been previously overlooked. Intranasal oxytocin has been shown to improve key symptoms of social and non-social nature in psychiatric disorders (Giel et al., 2018; McRae-Clark et al., 2013; Michalopoulou et al., 2015; M. A. Miller et al., 2016; Pedersen et al., 2011), but so far a mechanistic understanding of those effects has been limited. Here, we provide insights on the domain-general role of oxytocin and give a basis for further advancement of the field. Addiction and obesity are two key examples where deficits in delay of gratification are thought to contribute to the symptoms (Amlung et al., 2017; Bickel et al., 2019; Bickel & Marsch, 2001). Therefore, previously reported beneficial effects of oxytocin, may arise through a reduction of impulsivity. Our findings can extend the knowledge on oxytocin effects on psychiatric disorders and point towards novel oxytocin-based treatments.

With the results of our second study, we add to a growing literature on beneficial effects of dlPFC stimulation on addiction and eating disorders (Camprodon et al., 2007; McClelland et al., 2013; Mishra et al., 2010). Previous research has shown a clear benefit of stimulation techniques in improving craving and other symptoms common in these disorders. Though most evidence is coming from frequency-unspecific methods (TMS, tDCS), here we show that oscillatory activity plays an important role in intertemporal decision making and that tACS methods can improve patience, by targeting specific oscillations that have been shown to be dysregulated in psychiatric disorders (Elyamany, Leicht, Herrmann, & Mulert, 2021). tACS therefore can serve as a targeted method for the reduction of symptoms of these disorders or even a long-term therapeutic intervention, as repeated stimulation might lead to longer lasting changes in the brain.

Our final study sheds light on second order processes involved in delay discounting and their underlying neurophysiological mechanisms. Similar to our second study, a clear link between frontopolar theta oscillations and metacognition was established, shedding simultaneously light on the functional connections between brain regions implementing metacognition and providing an

insight into the neurophysiological changes underlying this effect. Clinical research has only recently started to focus on the importance of metacognition as a symptom of various disorders and as a way to targeted improvement. The general ability of metacognition is increasingly recognized to play a role in disorders such as addiction (Balconi et al., 2014; Brevers et al., 2013; Spada et al., 2007), and even cognitive behavioral treatments have developed around it in order to improve metacognitive skills, predicting better efficacy of complementary therapeutic interventions (Caselli, Martino, Spada, & Wells, 2018; Wells, 2013). It could therefore be the case that improving metacognitive access to individuals' decisions through FPC stimulation, could prevent future relapses in addiction.

Taken together, our findings can inform clinical interventions in three novel directions, paving the way to oxytocin-based, oscillation-based or metacognition-based therapeutic tools in aid of clinical populations with self-control deficits.

6. Conclusion

In this dissertation, I attempted to provide novel insights into the neurobiological basis of self-control. With three different projects and a highly interdisciplinary methodological approach, I provide causal evidence for the mechanisms underlying self-control in relation to the different systems involved in this complex type of decisions. Overall, we provided evidence for a beneficial effect of oxytocin on delay of gratification, showing a non-social role of the hormone in value-based decision making. We further showed that stimulation over the dlPFC at the alpha, beta and gamma frequencies led to beneficial effects of self-control, each with a differential impact on attribute consideration and choice. Finally, we provided causal evidence for the role of frontopolar theta oscillations in metacognitive ability and further elucidated the network interactions that implement metacognition in the brain during decision making. By showing that these three different systems are causally involved in self-control, the present findings shed light on neurobiological, oscillatory and neurocognitive dynamics of self-control in intertemporal choice. Advancing the field of self-control research in these directions, we inform theoretical accounts in the respective fields, but also provide evidence towards a unified model of self-control in intertemporal choice. Beyond theoretical implications, the present findings provide novel insights into the underlying mechanisms of intertemporal decision making and pave the way towards novel therapeutic interventions in the clinical domain. Taken together, we empirically show that self-control is more than a “passion versus reason” dilemma, but rather a complex neurocognitive process with multiple interlinked neurobiological facets.

7. References of General Introduction and Discussion

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Affidavit

Eidesstattliche Versicherung/Affidavit

Georgia Eleni Kapetaniou

(Studierende / Student)

Hiermit versichere ich an Eides statt, dass ich die vorliegende Dissertation „The neural basis of self-control: Pharmacological, physiological and neurocognitive perspectives“ selbstständig angefertigt habe, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

I hereby confirm that the dissertation „The neural basis of self-control: Pharmacological, physiological and neurocognitive perspectives“ is the result of my own work and that I have only used sources or materials listed and specified in the dissertation.

München / Munich

24 June 2022

(Datum / Date)

Georgia Eleni Kapetaniou

(Unterschrift / Signature)

Author contributions

Chapter 2. The role of oxytocin in delay of gratification and flexibility in non-social decision making

The author of this dissertation contributed to research design, programmed the tasks, collected the data, performed data analysis, interpreted the results, created plots and wrote the manuscript.

Matthias A. Reinhard contributed to research design, assisted with data collection and provided comments on the manuscript.

Patricia Christian assisted with data collection and provided comments on the manuscript.

Andrea Jobst contributed to research design and provided comments on the manuscript.

Philippe N. Tobler contributed to research design and provided comments on the manuscript.

Frank Padberg contributed to research design and provided comments on the manuscript.

Alexander Soutschek contributed to research design, assisted with data collection and data analysis, contributed to the interpretation of results, supervised the experiment, and wrote the manuscript.

Chapter 3. Neural oscillations implementing self-control in intertemporal choice

The author of this dissertation contributed to research design, assisted in programming the experiment, collected and analyzed the data, interpreted the results, created plots and wrote the manuscript.

Marius Moisa contributed to research design.

Christian C. Ruff contributed to research design.

Philippe N. Tobler contributed to research design.

Alexander Soutschek contributed to research design, programmed the experiment, assisted in interpreting the results, supervised the experiment, commented on and critically revised the manuscript.

Chapter 4. Brain mechanisms underlying metacognition in decision making

The author of this dissertation contributed to research design, programmed the experiment, collected the data, performed data analysis, interpreted the results, created the plots and wrote the manuscript.

Marius Moisa contributed to research design, programmed stimulation sequences and performed safety and quality analyses, collected the data, contributed to the interpretation of results. Marius Moisa shares first authorship with Georgia Eleni Kapetaniou.

Christian C. Ruff contributed to research design and assisted in interpreting the results.

Philippe N. Tobler contributed to research design and assisted in interpreting the results. Philippe N. Tobler shares senior authorship with Alexander Soutschek.

Alexander Soutschek contributed to research design, assisted with data analysis and in interpreting the results, commented on and critically revised the manuscript.

Munich, 24.06.2022

Dr. Marius Moisa

Georgia Eleni Kapetaniou Dr. Alexander Soutschek