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JAAN TULVISTE

Modulation of decision-making by transcranial magnetic stimulation

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Institute of Psychology, University of Tartu, Estonia.

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The author of this thesis contributed to the publications as follows:

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In **Study III**, set the aims and formulated the research hypotheses, designed the experiment, participated in collecting the data, analyzed the data and wrote the manuscript as the main author.

1. INTRODUCTION

Human behaviour is regulated by a set of higher-order cognitive processes referred to as the executive functions of the brain and mind (Diamond, 2013; Miyake & Friedman, 2012). These general-purpose control mechanisms regulate human cognition and action, enabling the practice of self-control and self-regulation with broad and significant implications for everyday lives. Executive functions are manifested in goal-directed behaviour, resulting from a complex interplay of processes involving planning, organized search, and impulse control (Welsh, Pennington, & Groisser, 1991). The planning of actions involves consideration of possible outcomes of alternative options and guiding the focus of attention. It also involves rejection of disadvantageous options and impulse control to inhibit unwanted behaviours and experiences–resisting temptations, controlling for impulsive drives, and deliberately not attending to an object or event.

One of the central roles in the planning and practice of executive functions belongs to decision-making. Psychologists define decision-making as the ability to make the most advantageous choice, having carefully considered a selection of possible behaviours (Bechara, Tranel, & Damasio, 2000) and accounted for various risks and benefits relevant to the context (Knoch, Pascual-Leone, Meyer, Treyer, & Fehr, 2006a).

In scientific experiments, as in everyday life, a decision tends to be evaluated by its outcome: good or bad. To be able to accurately evaluate if "the most advantageous choice" was selected (Bechara, Tranel, & Damasio, 2000), the decision-making situation needs to be structured and unambiguous. However, compared to experimental settings, real-life decision-making scenarios do not always offer a correct or incorrect "verifiable" option, but may be essentially unstructured; the good and bad choice may also depend on the person making the decision as well as on various subjective circumstances of the situation.

The scientific study of decision-making is still mainly focused on right or wrong answer, veridical decision-making paradigms, although more than 40 years have passed since Tversky & Kahneman (1974) convincingly challenged the idea that human beings are merely rational actors. They showed this by demonstrating the role of heuristics and intuition in human decision-making. In clinical neuropsychology, the "gold standard" tests used for functional assessment of the frontal lobes–the Wisconsin Card Sorting Test (Grant & Berg, 1948), Stroop Test etc–are all veridical in nature (Goldberg, Funk, & Podell, 2012). The prevalence of veridical paradigms may be explained by the difficulty in producing valid and reliable non-veridical test batteries, or by the practical utility of correct vs. wrong answer tests, which are easy to implement and score.

The limits of veridical neuropsychological tests are reflected in Mesulam's (1986) observation–coined as "Mesulam's Mystery" by Burgess and colleagues (2009)–that some patients with frontal lobe damage show no cognitive impair-

ment according to traditional office-based assessment procedures, but nevertheless show marked cognitive handicap in everyday life. Some would argue that the mismatch between neuropsychological assessment scores and the actual ability of the person to independently perform activities of daily living reflects a generally low ecological validity of executive function tests (Dawson & Marcotte, 2017). Thus, developing novel executive functioning evaluation paradigms to better predict the everyday behaviour of the subject outside the testing facility, represents an ongoing challenge for researchers and clinicians.

As novel research methods and non-invasive neuromodulation techniques have become available, this thesis sets out to revisit the concept of non-veridical decision-making. The veridical vs. non-veridical model of decision-making was originally proposed in the 1990s (Goldberg, Podell, & Lovell, 1994a) based on findings from lesion studies. This thesis aims to test the hypothesis that the dorsolateral prefrontal cortex (DLPFC) as a region actively involved in cognitive control is functionally specialised also for non-veridical decision-making. Going beyond neuropsychological lesion studies and behavioural observations, the present work applies non-invasive manipulation of DLPFC function in healthy subjects. By observing the effects of non-invasive modulation of neural activity in the prefrontal cortex, the thesis aims to revisit the functional role and contribution of the DLPFC to decision-making processes and highlight the potential difference between veridical and non-veridical cognition. As the DLPFC is known to participate in risky human behaviour (e.g., Bembich et al., 2014; Boggio et al., 2010; Clark, Manes, Antoun, Sahakian, & Robbins, 2003; Fecteau et al., 2007; Guo, Zhang, Da, Sheng, & Zhang, 2018; Knoch et al., 2006b; Luo, Ye, Zheng, Chen, & Huang, 2017; Minati, Campanhã, Critchley, & Boggio, 2012), the thesis also engages a non-veridical task involving risk. Finally, the work addresses the role of genetic predispositions in non-veridical cognition. This is carried out by evaluating potential effects of the BDNF Val66Met genotype–known to be expressed in neurobiological endophenotypes involved in executive functions–on non-veridical cognition.

1.1. Executive functions and decision-making

Executive functions are “those capacities that enable a person to engage successfully in independent, purposive, self-serving behaviour” (Lezak, 1995) and can be thought of as a series of abilities needed to achieve a goal (Damasio, 1995; Fuster, 2017; Stuss et al., 2005). Specific executive functions include task initiation, planning, purposive action, self-monitoring, self-regulation, volition, inhibition, cognitive flexibility, information updating and monitoring, and decision-making (Stuss 2011; Miyake & Friedman, 2000). Dividing executive function into smaller parts or sub-functions is a complex task and can be performed from the perspective of structure, function, or dysfunction, without clear consensus among scientists (Hunter & Sparrow, 2012). Acknowledging the complexity of goal-directed behaviour, Stuss (2011) emphasises that executive

functions represent only one functional category within the frontal lobes: to fully understand the mechanisms of complex goal-directed behaviour, we need to look at connected non-frontal brain regions as well as various emotional and motivational processes that are integrated with executive functions. Several other researchers agree with this complex, multifaceted view of human goal-directed cognition (Badre & Nee, 2018; Zelazo & Cunningham, 2007).

Neurobiological mechanisms of human decision-making as the principal enabler of successful goal-directed behaviour, essentially depend on the function of the frontal lobes (Gazzaniga, 2004; Luria, 1966). The crucial role of decision-making processes in executive functioning is revealed in neurodegenerative disorders and brain injury: impairment of decision-making relates to loss of control over cognitive processes and goal-directed behaviour (Luria, 1966; Chan, Shum, Toulopoulou, & Chen, 2008). Treating the frontal lobes as a superstructure, Luria (1966) established that damage to the frontal lobes–particularly the prefrontal cortex–disrupts human goal-directed thought and regulation of behavioural outcomes. Pribram (1973) noted that "the frontal cortex appears critically involved in implementing executive programs when these are necessary to maintain brain organization in the face of insufficient redundancy in input processing and in the outcomes of behaviour", suggesting that the purpose of decision-making is to implement executive programs. These executive actions allow the person to pursue rewards and avoid/minimise loss or harm. As long as executive functions are intact, a person with significant cognitive impairment in other mental faculties can still be able to lead an independent, productive life (Lezak, Howieson, Loring, & Fischer, 2004). Impairment of executive functions, however, has a global effect on control and regulation of behaviour, whereby the person becomes unable to function well in everyday life, even if specific cognitive abilities have been preserved (Damasio, 1994; Miyake et al., 2000). Therefore, expanding our understanding of brain mechanisms subserving executive functions bears significant value for the society.

The organizational structure of the frontal lobes and their functional circuitry still remains largely unknown. Meanwhile, as pointed out above, researchers are increasingly challenged by academia and clinicians, as well as the society and industry, to explain how goal-directed behaviour in humans works–or doesn't work. The incentives for understanding goal-directed behaviour have several obvious explanations: (1) apt decision-making is a prerequisite for adapting to environments and solving practical tasks; (2) resilience to mentally stressful conditions largely depends on effective decision-making mechanisms; (3) revealing the individual patterns of goal-setting and decision-making is key to measuring personality and predicting individual behaviour; (4) successful therapeutic and rehabilitation practices considerably depend on relevant knowledge of decision-making mechanisms and ways in which to manipulate them; (5) as malfunction of cognitive control mechanisms is one of the main reasons behind risky behaviour and criminal conduct, sufficient knowledge about cognitive control and decision-making mechanisms can improve crime prevention, criminal investigation and rehabilitation practices; (6) advancements in techno-

logies related to artificial intelligence and autonomous robots can substantially benefit from knowing the mechanisms of executive processing in the brain.

Some would argue that executive functions are domain- and process-general, influencing lower-level cognitive processes actively across a wide variety of tasks to guide goal-directed behaviour (Fedorenko, Duncan, & Kanwisher, 2013). Others would argue that executive functions are diverse, separable, and poorly intercorrelated (Miyake et al., 2000). Friedman and Miyake (2017) suggest that executive functions follow a pattern of "unity and diversity", showing a general pattern of shared but distinct functions. Attempting to establish a general functional model, executive functions of the PFC have been divided into cognitive ("cold") and affective/reward-related ("hot") processes (Hongwanishkul, Happaney, Lee, & Zelazo, 2005; Nejati, Salehinejad, & Nitsche, 2018; Zelazo & Cunningham, 2007): the former relate considerably to the DLPFC and the latter to the orbitofrontal cortex (OFC).

One avenue to exploring the mechanisms of goal-directed behaviour is to focus directly on complex decision-making, instead of probing individual executive functions or cognitive processes. Decision-making can be considered a part of executive functions that allows the human to exercise cognitive control over behaviour while pursuing a goal (Fellows, 2013).

The act of making a decision can be broken down into three temporally and partially functionally distinct sets of processes (Ernst & Paulus, 2005): 1) evaluating possible options and forming preferences; 2) selecting and executing actions; 3) experiencing or evaluating the outcomes. Emphasizing that goals are steered by the value system, Fellows (2013) defines decision-making as processes involved in making non-arbitrary choices based on their perceived value. While the value-based approach to decision-making incorporates several aspects of traditional executive functions (i.e. planning and reasoning), it also accounts for motivational and emotional aspects relevant for understanding decision-making processes. Accordingly, part of the decision relates to extrinsically (objectively) correct solutions (a decision can lead either to correct solution or incorrect solution), while another part relates to the agent-centered, non-veridical solutions for which there are no objective criteria of correctness. A more detailed account of the typology of decisions will be drawn in Section 1.2.

1.2. Types of decisions

To define the cognitive and neural mechanisms that guide individual choice, one needs to consider the type and content of the decision to be made and extract the "decision variables" involved (Smith & Huettel, 2010). Depending on the nature of the decision and the corresponding decision variables, a "task force" of cortical and interconnected regions is mobilized, determined as fit by the cognitive control center handling the task.

In order to specify the neural substrates of various types of decisions, multiple classification systems have been proposed. By classifying decisions

according to their shared and non-shared characteristics, scholars attempt to create a model of the human decision-making system which would accurately predict decision outcomes from a given set of variables. The variables and characteristics of a decision that can determine the cortical response include contextual uncertainty, level of risk, emotional load, and reward immediacy (Bechara, Damasio, Tranel, & Damasio, 2005; Verdejo-Garcia, Pérez-García, & Bechara, 2006b).

1.2.1. Decisions involving uncertainty

When the full extent of potential outcomes and probabilities is unknown or will emerge only retrospectively, the decision is made under conditions involving uncertainty. Furthermore, decisions made under uncertain conditions can be divided into "decisions involving risk" and "decisions involving ambiguity" (Bechara, Damasio, Tranel, & Damasio, 2005). This division may not lead to mutually exclusive concepts as the factors determining the probabilities of gains and losses may not be known with absolute precision and the resulting decision-making challenge may involve a mix of risk and ambiguity.

Decisions involving risk

Risk is a widely recognized variable according to which decisions are classified: a decision is risky if the outcomes are uncertain, if there is a low probability of gain or a high probability of loss, or if the outcome of the decision or reward comes with a long delay. A decision made in a situation where the probability of a desired outcome is knowingly low, is considered a "risky decision". Although the probability of the desired outcome is low, the possible alternatives, consequences, and probabilities relevant for the decision are known (Volz & Gigerenzer, 2012). The riskiness embedded in risky decision-making is triggered by the need of the participant to decide between a safe choice and a risky choice, while knowing that the reward for the (low probability) risky choice is relatively more valuable (Bechara, Damasio, Tranel, & Damasio, 2005). Risky decision-making behaviour closely resembles what is described in the prospect theory (Kahneman & Tversky, 1979; Tversky & Kahneman, 1992), which states that while choosing between probabilistic alternative choices that involve risk, people base decisions on the potential value of gains and losses rather than on the value of the final outcome. Furthermore, people tend to underweight outcomes that are merely probable compared to outcomes that are perceived as certain. A commonly used task for risky decision-making is the Iowa Gambling Task (the IGT, Bechara, Damasio, Damasio, & Anderson, 1994), a card game involving probabilistic learning by monetary rewards and punishments. Other experimental tasks purporting to model risk-involving behaviour include the Balloon Analogue Risk Task (Lejuez et al., 2002) and the ball-throwing game of skill (Otsa, Paaver, Harro, & Bachmann, 2016).

Decisions involving ambiguity

Ambiguity of choices occurs in situations where there are conflicting options or where the likelihood of error is high (Rosenbloom, Schmahmann, & Price, 2012). In ambiguous conditions–unlike in risky decision-making–the alternative outcomes, consequences, and probabilities related to the potential outcomes of the decision are not known. As the probabilities of outcomes are unknown and unknowable, the probabilities of outcomes cannot be expressed with mathematical precision in frequencies nor in propensities (Volz & Gigerenzer, 2012).

Despite the rational explanation of differences and commonalities between risky and ambiguous decision-making offered by Bechara and colleagues (2005), a factor analysis comparing various decision-making tasks reveals that three commonly used decision-making tasks–the IGT, the Balloon Analogue Task, and the Columbia Card Task (CCT)–all measure unique, non-overlapping decision-making processes (Buelow & Blaine, 2015). Thus, the risky-to-ambiguous continuum model of decision-making and various widely used experimental tasks do not fully cover the range of decision-making processes and circuitry within the brain. In their review of ambiguous and risky decision-making neuroanatomy, Brand and colleagues (2006) conclude that the evidence is inconclusive, as "the IGT measures different types of decisions: decisions under ambiguity in the first parts of the task and decisions under risk or certainty when those rules have been figured out". Therefore, during the decision-making process, there must be a point at which the subject realizes the rules of the game, recognising the explicit terms for wins and losses; the ambiguous decision becomes a risky decision. Nevertheless, both for risky and ambiguous decisions, the rules and win/lose terms have been externally defined and the goal of the subject is to uncover the externally defined conditions of successful decision-making.

1.2.2. Decisions classified by veridicality of outcome: veridical vs. non-veridical

As the risky vs. ambiguous classification of decisions failed to explain the full variety of decision-making behaviours demonstrated by healthy subjects and impairments observed in patients, a more sophisticated model for human decision-making was required. An alternative approach to modeling human decision-making processes was proposed by Goldberg and colleagues (1994a): decisions can be categorized according to the veridicality of outcomes. Although involving uncertainty, for both risky and ambiguous decisions, it is still possible to establish whether the decision outcome is correct or incorrect according to unambiguous, externally verifiable, objective criteria. Thus, the nature of both, risky and ambiguous decisions, is "veridical". However, there are also decisions with outcomes for which there are no unambiguous, externally qualified criteria to objectively assess their correctness. Free choice or personal preference based, deliberately chosen options are all "correct" from the

agent-centered (or actor-centered) perspective, as their veridicality is subjective and depends on the preferences, taste, or feeling of "what is best for me" established by the actor (Goldberg, Funk, & Podell, 2012). Unlike in veridical decision-making, the latter kind of "non-veridical" decisions are not about delivering objectively correct solutions to problems; in non-veridical cognition, the correct solution is not inherent in the task, but depends on the person–the "agent"–making the decision. Thus, the "correct-incorrect" metric does not apply; a subject is free to choose what (s)he likes and each choice is in a sense correct, because it expresses a momentary disposition of the "free will" and subjective preference. In consequence, from the perspective of ethics, society, or practical utility the subjective choice may even seem "wrong" to an outsider, despite selected as the best by the person who made the decision. Moreover, in tasks requiring the subject to pursue a self-generated strategy balancing risk and rewards best suited from the actor's perspective, the non-veridicality of the cognitive challenge is unavoidable. Goldberg and colleagues (1994b) developed an experimental paradigm–the Cognitive Bias Task (CBT)–which quantifies decision-making preferences made in a cognitive task devoid of intrinsically correct or intrinsically false choice. In the CBT, each trial involves a presentation of a card with a simple geometric form (target card) and a subsequent presentation of two more cards (choice cards) vertically aligned below the target card. The participant is asked to look at the single target card presented on the screen first and then to pick one of the selection cards appearing below it, following the principle "Choose the one you like the best" (see Figure 1).

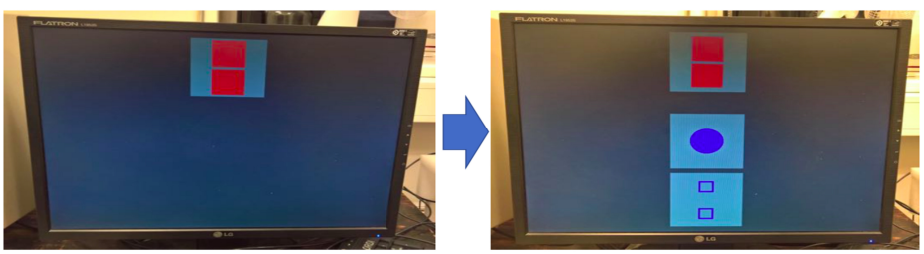

Figure 1. An example from the Cognitive Bias Task (CBT; Goldberg, Harner, Lovell, Podell, & Riggio, 1994)–a measure of non-veridical, agent-centered decision making. The (top) target card is presented alone for two seconds, followed by the presentation of two selection cards below the target card. From the bottom two selection cards, the subject has to pick the one "you like best". The score is derived by summing up the similarity index between the cards chosen by the subject and the target card (range: 0–5) for all trials, quantifying the impact of cognitive context on response selection. (Photo by J. Tulviste)

In support of the veridical vs. non-veridical dichotomy, real-life cognition and behaviour appear to be dominated by non-veridical choice situations, seeking a "what is best for me" answer (Podell, Funk, & Goldberg, 2012), ranging from trivial (e.g., which shirt to wear or which main course to have for dinner) to life-shaping (e.g., which career to pursue or which journal to publish in) choices. At the same time, research on PFC executive functions has so far been heavily dominated by methods employing veridical decision-making tasks, whereas PFC involvement in non-veridical decision-making has been rarely studied.

The non-veridical paradigm may appear to be closely related to ambiguous decision-making. However, unlike an ambiguous decision, a non-veridical decision does not represent a transition from an implicit to explicit state (Brand, Labudda, & Markowitsch, 2006) during which the subject discovers the implicit rules of the game. Specifically, the agent-centered principle is explicit from the beginning of the task: the correct solution depends on the preferences of the subject and is not defined by external rules specifying wins or losses for scoring purposes. Non-veridical decisions utilize divergent thinking to "disambiguate" the unstructured situation and select the best choice for the decision-maker, based on internal goals, past experiences, and expectations for the future (Goldberg & Podell, 2000; Verdejo-García, Vilar-López, Pérez-García, Podell, & Goldberg, 2006a).

1.2.3. Explicit vs. implicit decisions

The risky vs. ambiguous and the veridical vs. non-veridical dichotomies share several characteristics and both contribute to explaining specific decisions. Moreover, risky decision-making situations, where a subject deliberately chooses a suitable level of riskiness without external guidance, is not purely non-veridical in nature, but–depending on the task–may also involve veridical components, such as value calculations and utility calculations. In case of ambiguous decisions, initially appearing to be non-veridical, the subject is expected to figure out externally defined, "hidden" rules, in order to successfully solve the task. For example, to successfully solve the IGT (Bechara, Damasio, Damasio, & Anderson, 1994), the subject is expected to figure out which two out of the four card decks are advantageous, by trial and error. Unlike in a risky task, in ambiguous situations, the rules are initially implicit, not being revealed to the subject.

More generally, the explicit vs. implicit dimension of decisions can be applied to both the veridical vs. non-veridical as well as the risky vs. ambiguous models of decision-making. In non-veridical decisions, the rules are explicit from the start: "Choose the one you like the best!". Thus, the agent-centered approach whereby the decision depends on the preferences and subjective choice of the person making the decision, is explicitly revealed from the very beginning. Completing ambiguous decision-making tasks, however, is known to involve multiple stages: the initial ambiguity surrounding the implicit rules for

gains and losses is being resolved during the process of decision-making (Brand, Labudda, & Markowitsch, 2006). Specifically, in case of the ambiguous IGT concept, the ambiguity is dissolved at the point where the subject figures out the implicit rules for gains and losses. Thus, the IGT is veridical: the goal of the player is to uncover hidden, implicit rules; success is defined by the ability to make the hidden rules explicit. In non-veridical decisions, on the other hand, the lack of an externally defined, hidden correct or incorrect solution is explicit from the start, potentially establishing a different cognitive and neurobiological challenge for the subject compared to ambiguous decision processes concerned with making implicit rules explicit. Therefore, the cognitive and neural demands of veridical vs. non-veridical and explicit vs. implicit decision-making types appear to differ: the explicit rules embedded in the latter–although initially implicit–are still externally-defined and verifiable independently of the actor, not depending on the subjective preferences of the person making the decision.

1.3. Neural mechanisms of decision-making and TMS effects

The neurobiology of decision-making relies on a distributed network of cortical regions including the OFC, anterior cingulate cortex (ACC), DLPFC, thalamus, parietal cortices, and caudate (Ernst & Paulus, 2005).

Research findings on healthy subjects as well as on patients suggests that the key to explaining goal-directed behaviour including cognitive control lies within the prefrontal cortex (PFC) (Badre & Nee, 2018; Carlén, 2017; Fuster, 2015, 2017; Miller & Cohen, 2001). The main PFC areas involved in cognitive control are DLPFC, ventrolateral prefrontal cortex, and the orbitofrontal/ventromedial region of the PFC (Carlén, 2017; Fuster, 2015). The majority of decision-making structures–within, but also beyond the PFC–are lateralized. Accordingly, the contribution of the right and left DLPFC–a region famous for being a "usual suspect" in various cognitive tasks involving delayed response, online information processing, value calculations–is differentiated, suggesting advanced functional specialization within the DLPFC (Fuster, 2015, 2017; for illustration see Figure 2). However, the extent of functional specialization within the prefrontal regions also largely remains a mystery. The PFC has reciprocal connections with a wide range of cortical and subcortical structures, establishing its role as a high-level orchestrator of a wide range of cognitive and affective neural functions (Selemon & Goldman-Rakic, 1988; Szczepanski & Knight, 2014).

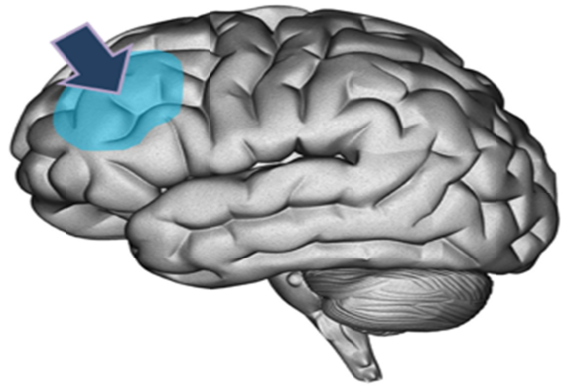

Figure 2. Localization of the left dorsolateral prefrontal cortex (DLPFC). The DLPFC covers an area of a few cm^2. Source image by Brainclinics (http://www.brainclinics.com/rtms).

While clinical studies have established that patients with damage to ventral and medial areas in the prefrontal cortex areas demonstrate impairments in social and personal decision-making without sacrificing intellectual abilities (Damasio, Tranel, & Damasio, 1991), the specific differentiation and boundaries of veridical vs. non-veridical cortical networks are still largely unknown. Research with neurotypical subjects whose PFC functionality is experimentally manipulated by non-invasive methods could add valuable insights to our knowledge on PFC involvement in non-veridical and veridical decision-making. Furthermore, in patients the PFC lesions vary to large degree in terms of location, type, and size, whereas in healthy subjects, brain stimulation can be targeted precisely and reliably by using neuronavigated anatomical or functional techniques.

Transcranial magnetic stimulation (TMS) is a non-invasive neuromodulation method, used to influence the neurophysiological processes and states of the brain. By applying magnetic pulses over the scalp of a subject, electrical currents are triggered in the neurons of the underlying cortex, inducing changes in the stimulated cortical region and associated neural circuits transiently. TMS principles were first applied in controlled laboratory settings by Barker and colleagues (1985), who demonstrated that the TMS impulse can be used to trigger a peripheral motor evoked potential (MEP) in the hand muscle. Prior to that, Merton and Morton (1980) had already demonstrated that running electrical currents through the scalp can activate the cortex and influence observable behaviours related to the underlying cortical areas. By modulating neural activity, TMS can be used to study the functional contribution of targeted regions to cognitive and perceptual processing or executive control (Pascual-Leone, Valls-Solé, Wassermann, & Hallett, 1994; Railo, Andersson, Kaasinen, Laine, & Koivisto, 2014; Ruff, Driver, & Bestmann, 2009; Valero-Cabré, Amengual, Stengel, Pascual-Leone, & Coubard, 2017).

For a theoretical as well as practical standpoint related to neuropsychological and clinical applications of TMS, it is important to acknowledge that cortically localised TMS produces a temporary, so-called virtual lesion (Pascual-Leone, Walsh, & Rothwell, 2000), with behavioural and cognitive effects similar to the real effects of lesions in patients. However, locally targeted TMS not only changes functionality of neural circuits directly beneath the TMS coil, but can also trigger cognitive and behavioural effects in the larger functional system, evoking activity in distant interconnected neural regions (Ilmoniemi et al., 1997). For example, single pulse TMS targeted at the left DLPFC has been shown to elevate the BOLD signal in the anatomically interconnected ACC, the caudate, and thalamus (Dowdle, Brown, George, & Hanlon, 2018). Likewise, Strafella and colleagues (2001) have shown that high-frequency repetitive TMS (rTMS) of the DLPFC triggers the release of dopamine in ipsilateral caudate nucleus.

Results of TMS research with neurotypical subjects can therefore serve as useful input to clinicians working with neuromodulation techniques in actual clinical settings to help develop the corresponding clinical practices. On the other hand, comparing data from experimental studies with healthy subjects to clinical data from patients, can point to limitations of TMS applications and methodology. Accordingly, promising future directions for advancing TMS based treatment methods and diagnostic tools may be discovered. For example, Pachalska and colleagues (2011) applied TMS to a frontal syndrome patient after severe traumatic brain injury and long-term coma in order to activate hypofunctioning areas in the frontal lobe. The rTMS intervention produced clinically significant improvements in executive dysfunction and behaviour, as well as physiological changes in EEG event-related potentials.

TMS can be applied in single pulses (single pulse TMS) or repeatedly (rTMS). RTMS can be used to induce sustained changes in cortical excitability outlasting the stimulation period. The specific neural effect of rTMS depends on the frequency and intensity of stimulation as well as on the cortical state of the subject at the time of the procedure (Kähkönen, Komssi, Wilenius, & Ilmoniemi, 2005; Silvanto & Pascual-Leone 2008). Low-frequency continuous stimulation results in depression of excitability at the target region, while high-frequency stimulation increases excitability of the region (Pascual-Leone, Valls-Solé, Wassermann, & Hallett, 1994). For example, 600 pulses delivered by continuous theta-burst stimulation (cTBS), a widely used rTMS protocol, has been shown to reduce the excitability of the cortical target site for more than 20 min (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005).

TMS studies illustrate the lateralization of DLPFC functions, proposing differential roles of the right and left DLPFC in decision-making. Disruption of the right DLPFC is reported to result in increased risk taking, willingness to accept unfair offers (van't Wout, Kahn, Sanfey, & Aleman, 2005) and higher acceptance of immediate personal rewards despite preserved awareness of value (Knoch, Pascual-Leone, Meyer, Treyer, & Fehr, 2006a). Srovnalova and colleagues (2012) have demonstrated that high-frequency stimulation of the right

DLPFC triggers significant improvements on the Tower of London task (Culbertson, Moberg, Duda, Stern, & Weintraub, 2004) in patients with mild to moderate Parkinson's disease, suggesting the causal role of the right DLPFC in strategic planning tasks. Thus, the role of the right DLPFC in decision-making is to exercise executive control over selfish impulses, while aligning behaviour with social norms and rules (Zelazo & Cunningham, 2007). Prior studies with TMS have confirmed the contribution of DLPFC to risky decision-making processes related to value judgements (e.g., Camus et al., 2009), fairness-related decisions (e.g., van't Wout, Kahn, Sanfey, & Aleman, 2005; Knoch, Pascual-Leone, Meyer, Treyer, & Fehr, 2006a), and deceptive behaviour (Karton & Bachmann, 2011; Karton, Palu, Jõks, & Bachmann, 2014).

As right DLPFC disruption impaired decision-making, but not the perception of underlying value and fairness (Knoch, Pascual-Leone, Meyer, Treyer, & Fehr, 2006a; Ruff, Ugazio, & Fehr, 2013), the right DLPFC appears to be relatively more responsible for action and execution of a decision, whereas the left DLPFC is committed to accumulation of evidence (Heekeren, Marrett, Ruff, Bandettini, & Ungerleider, 2006), value calculations, and manipulating verbal and spatial information in working memory (Barbey, Koenigs, & Grafman, 2013). MRI studies on value-based selection processes in the brain have also suggested that the fronto-parietal network is involved, whereby the DLPFC integrates values signals computed in the ventromedial PFC, and then activates the parietal cortex to read out the choice outcome (Domenech, Redouté, Koechlin, & Dreher, 2017).

1.4. Aims of the thesis

The general aim of the dissertation was to explore if non-veridical decision-making can be modulated by transcranial magnetic stimulation (TMS), in order to evaluate the theoretical basis of the non-veridical vs. veridical dichotomy. Throughout the studies featured in the current thesis, neural activity within the DLPFC is modulated by TMS in order to evaluate potential effects on performance across various cognitive tasks, including non-veridical tasks representing agent-centered cognition where correct solutions are not predetermined.

The DLPFC was chosen as the target of TMS stimulation due to its well established, although not fully known and explained role in decision-making processes. The specific aim of Study I was to selectively modulate non-veridical cognition without affecting veridical performance, by selecting multiple experimental tasks and combining various stimulation frequencies (low vs. high-frequency stimulation) and target sites (left vs. right DLPFC). The expectation of Study I was to identify target regions that specifically relate to non-veridical decision-making by manipulating activity in the underlying cortical areas. As Study I did not fully resolve the contributions of left and right DLPFC to non-veridical decision-making, Study II set out to test the effects of modulation on a risky non-veridical task. The aim of Study II was to identify the effects of TMS

inhibition of the right DLPFC on non-veridical decisions involving risk. Following up on Study I and Study II, Study III aimed to explore the role of genetic variability in determining non-veridical cognition and individual susceptibility to TMS influence. Specifically, Study III investigated the association of brain-derived neurotrophic factor (BDNF) Val66Met genotype to non-veridical task performance. The more detailed rationale for these studies will be presented in Sections 2, 3, and 4 of this dissertation.

The research questions addressed within the thesis are:

1. Can performance on non-veridical vs. veridical decision-making tasks be selectively modulated by applying rTMS stimulation to the right or left DLPFC?
2. How does rTMS stimulation of the right or left DLPFC affect performance on the non-veridical CBT task compared to baseline performance?
3. Does the right DLPFC play a role in risky non-veridical behaviour?
4. How does rTMS modulation targeted at the right DLPFC affect performance and preferences on the risky non-veridical task Game of Skill?
5. Does the BDNF Val66Met genotype affect non-veridical baseline performance and rTMS-induced changes on the CBT task?

2. SELECTIVE MODULATION OF NON-VERIDICAL VS. VERIDICAL DECISION-MAKING

2.1. Non-veridical vs. veridical decisions

Based on clinical observations in patients with frontal lobe lesions, an alternative model for decision-making was proposed by Goldberg and colleagues (1994a), suggesting a veridical vs. non-veridical division of cognition, including decision-making.

Veridical tasks are about finding an objectively correct answer, which is inherent in the task, and exists independently of the person handling the problem (Goldberg, Funk, & Podell, 2012). The correct response is intrinsic to the external situation and is actor-independent (Goldberg & Podell, 1999). Veridical questions can be about objectively measurable properties such as size ("Which is bigger–A or B?"), color ("Pick the red ball!") or time ("What year was it 5 years ago?") and the correctness of answer does not depend on the preferences or will of the person delivering the answer. A is bigger than B even if the person being asked does not like it that way.

Non-veridical decision-making, on the contrary, is an adaptive skill: the response is actor-centered, guided by the actor's priorities (Goldberg, Funk, & Podell, 2012). In non-veridical tasks, multiple alternatives exist in solution to a problem and several choices can appear as potentially advantageous, leaving room for the individual priorities and preferences of the agent (Goldberg, Podell, & Lovell, 1994a; Bechara, Damasio, Damasio, & Anderson, 1994).

Successful veridical decisions lead to an "unequivocally correct, albeit not always obvious answer" (Goldberg, Podell, & Lovell, 1994a), whereas failure is associated with picking a wrong answer or making a mistake. In non-veridical decision-making, however, there can be good or bad choices, but instead of being defined by the external situation, they depend on the preferences and priorities of the person making the decision. Making a non-veridical choice–such as which shirt or painting is "the best"–is an adaptive process that depends on the strategic self-regulation of behaviour by ranking and scaling the organism's priorities in relation to the characteristics of the given situation (Goldberg & Podell, 1999; Levine, Dawson, Boutet, Schwartz, & Stuss, 2000).

In the healthy brain, decision-making involves both, veridical and non-veridical processes, depending on the nature of the task; impairments selectively affecting veridical or non-veridical cognition are revealed in subjects with specific lesions, executive dysfunction, or cognitive impairments. Supporting the veridical vs. non-veridical distinction, Verdejo-Garcia and colleagues (2006a) observed abnormal non-veridical decision-making performance in substance abusers, who displayed normal performance on veridical tasks (the IGT).

In regard to how executive functions differ from cognitive functions (Lezak, Howieson, Loring, & Fischer, 2004), non-veridical decisions can be considered as executive rather than cognitive, addressing "How or whether a person goes

about doing something?" or "What is best for me?" (Goldberg, Funk, & Podell, 2012) instead of focusing on "What or how much?". By studying the preferences and priorities of the agent, non-veridical decision-making recognizes motivational and emotional factors involved in a decision. Thus, non-veridical decision-making attempts to explain not just "what" or "how", but "why" a certain behaviour was performed (Lezak, Howieson, Loring, & Fischer, 2004), contributing to the goal of value-based decision-making proponents to pay attention to motivational and emotional factors in flexible behaviour (Fellows & Farah, 2007). Importantly, a considerable share of a patient's maladaptation and executive dysfunction may be due to non-veridical decision-making impairment, despite displaying an adequate level of veridical decision-making. Therefore, expanding knowledge about the mechanisms and expressions of non-veridical decision-making as well as the effects of corresponding neurostimulation treatments represents both, scientific and practical significance.

2.2. Study I: Effects of repetitive transcranial magnetic stimulation on non-veridical decision-making

The aim of Study I was to explore if modulating prefrontal activity by applying TMS to the DLPFC would differentially influence veridical vs. non-veridical decision-making. The goal was to confirm previous evidence suggesting a veridical vs. non-veridical neurobiological divide witnessed in studies on lesions, addiction behaviour in substance abusers (Verdejo-Garcia et al., 2006a), and relevant neurostimulation research involving TMS (e.g., van't Wout, Kahn, Sanfey, & Aleman, 2005; Hadland, Rushworth, Passingham, Jahanshahi, & Rothwell, 2001) and transcranial direct current stimulation (tDCS) (e.g., Ye et al., 2016; Nejati, Salehinejad, & Nitsche, 2018). As previous studies were performed mainly in the framework of risky decision-making, loss aversion, or specific executive functions, to the author's knowledge there are no specifically veridical vs. non-veridical neurostimulation studies available.

Previous findings have established that the right and left DLPFC both contribute to decision-making performance (e.g., Knoch, Pascual-Leone, Meyer, Treyer, & Fehr, 2006a), whereas low and high frequency TMS protocols result in different effects on the underlying cortex (e.g., Romero, Anschel, Sparing, Gangitano, & Pascual-Leone, 2002; Kozyrev, Eysel, & Jancke, 2014) as well as different changes in behaviour (e.g., Pascual-Leone, Valls-Solé, Wassermann, & Hallett, 1994). Therefore, Study I explored stimulation effects by combining multiple rTMS target sites (left vs. right DLPFC) and stimulation conditions (low- vs. high-frequency). Several studies have also suggested that instead of causing lesion-like behavioural impairment effects, certain TMS protocols may trigger facilitation of cognitive performance (e.g., Cappa, Sandrini, Rossini, Sosta, & Miniussi, 2002). Neuromodulation of a target area may also result in compensatory activity changes in the contralateral cortical area, which forms the basis of using TMS stimulation in stroke rehabilitation whereby excitability

of the intact cortical region is reduced by low-frequency TMS in order to purposefully induce the participation of the damaged ipsilateral region (e.g., Johansen-Berg et al., 2002). Therefore, Study I included low-frequency (1-Hz) and high-frequency (intermittent 10-Hz) stimulation of both, left and right DLPFC, using both real TMS as well as Sham-stimulation.

The results of Study I partially supported the hypothesis that veridical and non-veridical decision-making would respond differently to DLPFC stimulation. All stimulation protocols triggered changes in non-veridical performance, whereas only low-frequency (1-Hz) stimulation of the right DLPFC also modified veridical behaviour.

The experiment revealed differences between hemispheres: non-veridical and veridical decisions both rely on the right DLPFC, whereas the left DLPFC is more specifically committed to non-veridical cognition. The attempt to replicate lesion study evidence resulted in findings contradicting the prediction: following TMS stimulation, the decision bias shifted notably towards context independent, less stimulus-driven choices. The observed shift in choice strategy is considered characteristic of posterior lesions rather than frontal lesions (Goldberg, Harner, Lovell, Podell, & Riggio, 1994b). Thus, findings of the present thesis emphasise non-focal, distal effects of focally applied TMS treatment, especially when applied to particularly richly interconnected cortical regions, such as DLPFC. As the CBT, the non-veridical task used in the current study, is not specifically a risky decision-making task, a follow-up study using a risky task concept would allow to further explain the role and hemispheric lateralization of decision-making within the DLPFC.

3. NON-VERIDICAL DECISIONS INVOLVING RISK

Knoch and colleagues (2006a) have demonstrated that suppression of the right, not left PFC using rTMS leads to overly risky decision-making while reducing consideration for the negative consequences of risky actions. Although risky decision-making is not exclusively associated with either veridical or non-veridical cognition, it may–depending on the task–involve both non-veridical, preference-based strategic considerations and also veridical components, such as value and utility calculations. As the results of Study I indicated that non-veridical and veridical decisions both rely more on the right DLPFC, whereas the left DLPFC may be more specifically committed to non-veridical cognition, we hypothesized that the role of the right DLPFC may be more prominently expressed in non-veridical decisions involving an added layer of risk. Reviewing the neurobiological basis of risky vs. ambiguous cognitive tasks, Brand and colleagues (2006) proposed that risky, but not ambiguous decisions, are accompanied by an active involvement of the fronto-striatal loop. In case of tasks in which the rules become explicit during repeated decision-making processes, whereby an initially ambiguous task becomes a risky task (See section 1.2.3), the fronto-striatal loop activates at the moment when the ambiguity becomes dissolved (Brand, Labudda, & Markowitsch, 2006). As in non-veridical decisions the agent-centeredness of the task–instructing the person to "Choose the one you like the best!" (see Section 1.2.2.)–is made explicit from the start, we can expect the activation of the right DLPFC and the fronto-striatal loop to be uniform throughout the course of the task.

3.1. Neural mechanisms of risky decision-making

Risky decision-making has been shown to be related to executive mechanisms of the DLPFC and related circuits (Bembich et al., 2014; Boggio et al., 2010; Clark, Manes, Antoun, Sahakian, & Robbins, 2003; Fecteau et al., 2007; Guo, Zhang, Da, Sheng, & Zhang, 2018; Knoch et al., 2006b; Luo, Ye, Zheng, Chen, & Huang, 2017; Minati, Campanhã, Critchley, & Boggio, 2012). However, risky decision-making has been associated also with activity in the OFC, the rostral areas of the ACC, and the parietal cortex (e.g., superior parietal cortex) (Ernst & Paulus, 2005; Krain, Wilson, Arbuckle, Castellanos, & Milham, 2006; Vorobyev, Kwon, Moe, Parkkola, & Hämäläinen, 2015). Studies have shown that value calculations and uncertainty processing as components of risky decision-making, are performed in distinct structures of the brain. Coding of reward magnitude, probability, and expected value engages the striatum and dorsolateral part of the frontal cortex, while reward uncertainty processing relies on recruitment of the OFC (Tobler, O'Doherty, Dolan, & Schultz, 2007). Engagement of neural substrates also depends on the stage of decision-making: forming preferences activates a different neural pattern than executing actions (Ernst & Paulus, 2005). Furthermore, magnetoencephalography studies have

shown that expected value calculation and predicted reward variability encoding processes recruit different regions of the brain and occur at different time points. Representations of mean reward are delivered by parietal and visual areas, followed up by activation of frontal regions including the OFC. Encoding of reward variability, on the other hand, occurs with a delay, after the mean reward coding has already engaged the OFC (Bach, Symmonds, Barnes, & Dolan, 2017).

Compared to risky decision-making, an ambiguous decision context does not provide sufficient information about the probabilities of outcomes and the value of alternative choices. The definition provided by Fellows (2013)–"decision-making is the processes involved in making a non-arbitrary choice based on value"–appears compatible with ambiguous decisions, as the person can assign value to secondary variables inherent in the context or decide based on personal preferences.

Zelazo and Müller (2002) propose that the neural substrates of risky and ambiguous decision-making–as well as of other executive functions–can be divided into "hot" and "cool" subtypes. The relatively hot affective aspects of executive functions are associated with ventral and medial regions of the PFC including the ACC, whereas the cool aspect is associated with the DLPFC. The cool executive functions are relatively likely to be triggered by abstract, de-contextualised problems, while the hot respond to problems requiring regulation of affect and motivation, including social understanding, and regulation of limbic system functions (Zelazo, Qu, Müller, & Schneider, 2005).

Theoretically, non-veridical decisions may relate to both, the hot and cool subtypes of executive functions, depending on the structure and gameplay of the specific task. However, as the current thesis is focused on goal-directed behaviour and the neural mechanisms subserving application of own preferences and free choice to solving cognitive tasks without an immediate affective component, the studies are more concerned with the cool subtype and the DLPFC.

3.2. Study II: Diminished risk aversion after right DLPFC stimulation: effects of rTMS on a risky ball throwing task

Study I demonstrated the role of the DLPFC in non-veridical decision-making by revealing a general effect of TMS stimulation on CBT task performance, triggering a shift in free choice preferences of the individual towards more internal representations driven, context independent selection style. However, to further explore the role of the DLPFC in non-veridical decision, the involvement of a risk factor appeared feasible. Numerous previous studies have specifically emphasized the role of DLPFC in active value-related tasks in win/loss situations, during which adaptive strategy execution is practiced by the subject (e.g., Camus et al., 2009; Manes et al., 2002). As prior research had also established the relevance of the PFC for planning and executing motor behaviour (e.g., Fuster, 2001; Goldman-Rakic, Bates, & Chafee, 1992), Study II

aimed to involve a risky decision-making task with a motor response. By selecting a motor response task, we attempted to achieve a more realistic and dynamic risk scenario for the subject, but also address the PFC as an area inherently dedicated for the planning and execution of motor behaviours as emphasized by Fuster (1997). From a practical perspective, the consequences of risky decisions and motor actions performed in a risky ball game are clearly and immediately conveyed to the participants, whereby the rewards and penalties following execution of a motor response appear sufficiently realistic and alert to create a sense of riskiness. Based on multiple previous studies (Knoch, Pascual-Leone, Meyer, Treyer, & Fehr, 2006a; Gable, Neal, & Threadgill, 2018), we decided to modulate the right DLPFC with a low-frequency TMS protocol, aiming to validate the critical role of the right DLPFC in guiding non-veridical decision-making in risky situations, where the subject has liberty to select a risk-taking or risk averse, loss avoiding strategy.

The chosen experimental task Game of Skill "Minimum-TB" (Otsa, Paaver, Harro, & Bachmann, 2016)–a ballgame combining fine motor action with an element of risk–encourages the player to obtain a high score by balancing wins and losses. To achieve a high score, the player needs to throw a tennis ball as close to the ceiling as possible, but has to avoid touching the ceiling by the ball in order to avoid penalties (see Figure 3). The player is free to decide on how much risk to take as there are no recommended strategies or "correct" choices for risk taking or loss aversion. Importantly, the experimental conditions also involved a TMS and Sham condition to test for the influence of right DLPFC functionality modulation on game performance. The game was played at two levels of risk: low and high. This experimental design was necessary in order to examine the impact of perceived riskiness on choice of strategy, level of game performance, and for relating the TMS effects to the level of risk.

The results of Study II revealed that rTMS stimulation of the right DLPFC changed subjects' risk-related behaviour on the non-veridical task involving execution of motor responses on which successful task performance depended. After TMS, the subjects became significantly more focused on immediate gains and less sensitive towards potential losses, leading to an overall immediately counterproductive strategy: the frequency of ceiling hits increased. Right DLPFC disruption–known to decrease inhibitory control–caused subjects to choose and execute riskier actions leading to unsuccessful immediate behavioural outcomes. To conclude, Study II suggests that the right DLPFC plays a role in execution and monitoring of risk-related behaviours in non-veridical tasks with a motor response.

Figure 3. Control panel view and experimental setup of the Game of Skill: Minimum-TB (for a detailed specification, see Otsa, Paaver, Harro, & Bachmann, 2016). The participant is instructed to throw a tennis ball as close to the ceiling as possible, but has to avoid touching the ceiling by the ball in order to prevent loss of game points. The player is free to decide on how much risk to take. The game is played at two levels of risk: low (a ceiling hit will result in loss of some of the points) and high (a ceiling hit will reset the score in game to zero). (Photo by J. Tulviste)

4. ROLE OF BDNF IN NON-VERIDICAL DECISION-MAKING AND IN RESPONDING TO TMS

Findings from previous studies included in the thesis suggested that prefrontal rTMS targeting the left DLPFC could selectively influence non-veridical, but not veridical decision-making (Study I) and that right DLPFC stimulation can influence the subject's risk seeking preferences and risk strategy selection in strategic goal-directed tasks involving a strong non-veridical component (Study II). To further explore the effects of neuromodulation on non-veridical decision-making, the role of executive functions associated neurotransmitters and neuromodulators could be considered. People demonstrate considerable inter-individual variation in decision-making strategies, likely being influenced by traits predisposing them to certain types of decisions. At the same time, heritable individual differences likely to determining the effects of TMS on non-veridical decision-making have not been studied. If TMS effects depend on individual endophenotypes, the design of treatment procedures must be adapted to account for this individual variability. Likewise, the majority of brain functions are expressed under influences of genetic factors and some specific instances of common genetic variability have been shown to significantly impact brain functioning, including the functions corresponding to decision-making (e.g., Bowirrat et al., 2012; Carpenter, Garcie, & Lum, 2011; Parasuraman & Jiang, 2012). Among the variety of genes expressed within prefrontal brain neurobiology, the brain-derived neurotrophic factor (*BDNF*) gene can be outlined as the one closely related to executive functions (e.g., Alfimova, Korovaitseva, Lezheiko, & Golimbet, 2012; Sun, 2018).

A functional polymorphism rs6265 resulting in the amino acid substitution of valine (Val) with methionine (Met) in the proBDNF protein at codon 66 (Val66Met) alters activity-dependent secretion of BDNF in the prefrontal cortex, affecting memory and executive functions (Egan et al., 2003; Bath & Lee, 2006). Compared to BDNF Met-carriers, Val homozygotes have been shown to respond differently to brief rTMS treatment of depression symptomatology (Bocchio-Chiavetto et al., 2008). Therefore, for the present study, the BDNF Val66Met genotype was selected to attempt to link common genetic variability, PFC, and the TMS intervention.

4.1. Genetic factors in non-veridical cognition and TMS-effects

Prior studies have established that in healthy subjects, the BDNF Val66Met genotype relates to changes in episodic memory performance (Egan et al., 2003), possibly mediated by reduced size of the hippocampus (Miyajima et al., 2008). In certain veridical types of visual discrimination tasks, common genetic variants of BDNF Val66Met interact with the level of performance (e.g.,

Maksimov, Vaht, Harro, & Bachmann, 2013). Performance on the IGT veridical decision-making tasks was shown to be influenced by *BDNF* genetic variants (Da Rocha, Malloy-Diniz, Lage, & Correa, 2011). However, to the author's knowledge, there are no studies available that have specifically addressed the relationship between *BDNF* polymorphisms and non-veridical decision-making performance in healthy subjects. Similarly, no studies on TMS effects according to BDNF Val66Met genotype relating to non-veridical decision-making could be found in peer-reviewed published sources. Prior research using the CBT task has indicated that there are sex and handedness (Goldberg, Podell, & Lovell, 1994a) as well as age (Aihara, Aoyagi, Goldberg, & Nakazawa, 2003) related differences within healthy subjects, but there are no prior studies on genetic factors determining non-veridical cognition. Studies exploring links between personality and the BDNF Val66Met genotype have indicated that Met-carriers have a lower level of conscientiousness (Hiio et al., 2011). As one of the basic traits, conscientiousness can be related to various types of propensities in decision-making, and links between personality traits and genetic factors encourages research on potential genetic determinants of decision-making behaviour.

4.2. Study III: BDNF polymorphism in non-veridical decision-making and differential effects of rTMS

Studies I and II focused exploring the stimulation effects of TMS on non-veridical decision-making without accounting for genetic factors and underlying neurobiological endophenotypes known to be associated to executive functions and activation of the frontal lobes. As noted earlier, to evaluate factors influencing non-veridical decision-making and its susceptibility to non-invasive neuromodulation, the brain-derived neurotrophic factor (BDNF) was a likely candidate for follow-up research. A functional polymorphism in the *BDNF* gene that results in the substitution of valine (Val) to methionine (Met) in codon 66, is associated with structural and functional changes in the DLPFC and known to affect veridical decision-making (e.g., Da Rocha, Malloy-Diniz, Lage, & Correa, 2011; Egan et al., 2003; Gasic et al., 2009). Studies have indicated that in Met-allele carriers, DLPFC volume is decreased (Pezawas et al., 2004). Met-carriers also display selective impairment on certain delayed response memory tasks, while failing to disengage the hippocampus and recruit the DLPFC as typically observed in Val homozygotes (Egan et al., 2003). However, the role of BDNF Val66Met genotype in non-veridical decision-making in healthy individuals has not been specifically studied. Thus, we hypothesized that the *BDNF* genotype may relate to non-veridical cognition by determining the effects of TMS stimulation when comparing Met-allele carriers to Val homozygotes. The study employed the CBT task (Goldberg, Podell, & Lovell, 1994a) which had been used previously (Study I) to evaluate non-veridical decision-making before

and after applying rTMS stimulation. Additionally, we gathered genetic data from participants to determine their BDNF Val66Met genotype.

The results of Study III revealed a significant TMS and genotype interaction: the Met-allele carriers baseline scores were significantly lower compared to Val-homozygotes, indicating a more context-independent, personal preference driven selection behaviour as measured by the CBT task. Furthermore, following TMS stimulation, Met-carriers became even more driven by internal preferences, not allowing external stimuli to substantially affect their choices, whereas Val homozygotes remained more context-dependent, relying on externally presented cues. Study III revealed that there are genetic differences in non-veridical behaviour related to the *BDNF* gene, and that rTMS stimulation can enhance preexisting genetically determined biases in choice preference. Consequently, depending on the specific genetic variant a person has, it is conceivable to adjust TMS protocols to account for genetic factors affecting the response to treatments. More generally, when designing and applying (r)TMS interventions for experimental or clinical purposes, it is relevant to incorporate genotyping data to account for the variance of the genes knowingly involved in decision-making behaviour.

5. GENERAL SUMMARY AND CONCLUSIONS

The goal of this work was to explore the neurobiological mechanisms of non-veridical decision-making by examining how TMS affects non-veridical behaviour. Neural activity at the DLPFC was modulated using both, low- and high frequency rTMS stimulation protocols, to deliver either inhibitory or excitatory TMS-induced currents to the target region of the brain. As decision-making is also regulated by several neurotransmitters and neurobiological endophenotypes associated with prefrontal functions, the impact of the BDNF Val66Met genotype on non-veridical performance was evaluated.

To summarise the empirical findings obtained within the scope of the thesis, the following statements can be made:

1. Non-veridical behaviour can be modulated by applying rTMS to the DLPFC, but the size and nature of the effect depends on the characteristics of the task, the lateralization of task-related brain mechanisms and stimulation site (Studies I-III), as well as the neurobiological endophenotypes involved (Study III).
2. Selective modulation of non-veridical behaviour without affecting performance on a veridical visuo-spatial task was also achieved by targeting the left DLPFC (Study I).
3. TMS effects do not necessarily mimic brain lesions, even if the target of TMS is located in the same cortical region. Instead of resembling prefrontal lesions, some of the behavioural effects following TMS stimulation of the DLPFC were more similar to posterior lesions (Study I). The mismatch between TMS-induced virtual lesions and real lesions may be due to the spread of local TMS effects to interconnected remote regions in the brain. In case of a risky decision-making task with a motor response (Study II), the effects of inhibitory right DLPFC stimulation closely resembled right DLPFC lesions, both leading to loss of inhibitory control and increase in risk taking.
4. In non-veridical cognition, neurobiological endophenotypes may determine the baseline as well as the neuromodulation effects of a behavioural measure. In Study III, the BDNF Val66Met genotype was associated with a bias in non-veridical preferences: Val/Val and Val/Met subjects had a significantly different choice preferences on a non-veridical task and they responded differently to rTMS stimulation of the right DLPFC, further enhancing their preexisting biases. Without controlling for genotype differences, the pre-existing non-veridical biases would not have been detected and the differential TMS effects would have remained hidden.

More generally, in regard to the two main application areas of brain stimulation – experimental and clinical – this thesis emphasizes several factors that determine the cortical and behavioural effects of TMS.

In a research setting, TMS protocols do not necessarily have the same effect across subjects. Several factors are known to influence the effect of TMS on an individual subject including age, handedness, sex, the initial neural activation state (Eldaief, Press, & Pascual-Leone, 2013; Rossini, Rossini, & Ferreri, 2010; Silvanto, Bona, Marelli, & Cattaneo, 2018; Valero-Cabré, Amengual, Stengel, Pascual-Leone, & Coubard, 2017; Wassermann, Epstein, Ziemann, Welsh, Paus, & Lisanby, 2008). TMS can be adjusted to accommodate the individual characteristics of the subject by determining the individual motor threshold (MT) for each participant prior to stimulation. Based on the MT, the intensity of the magnetic field is regulated. However, this "personalization" of stimulation treatments does not fully cover the variation exhibited in neurobiological and behavioural responses to TMS. The current thesis, namely Study III, illustrates the significant genetic component in how an individual responds to TMS treatment just by looking at a single determinant (BDNF Val66Met genotype). Most likely, a plethora of genetic determinants exist that–individually or in interaction–affect TMS responses, calling for researchers and clinicians to account for genetic determinants when using neuromodulation techniques. As our knowledge of relevant genetic factors expands, the current research protocols and subject preparation checklists need to be revised in order to account for new factors to be considered when applying TMS to a subject.

In clinical practice, the guidelines for TMS devices and protocols are cleared by regulatory authorities such as the Federal Drug Administration and NICE to enforce the use of evidence-based protocols for treatment of specific clinical conditions (e.g., major depressive disorder). Subjects are screened according to inclusion-exclusion criteria and the response to treatment is monitored throughout the course of treatment sessions. Therapeutic interventions of major depression are based on left-right DLPFC imbalance model, according to which clinical depression is characterized by hypoactivity of the left and hyperactivity of the right DLPFC. The antidepressant efficacy of high-frequency rTMS over the left DLPFC has been established and recognized (e.g., Schutter, 2009; Perera et al., 2016). Research findings also suggests that depressed patients benefit from low-frequency stimulation of the right DLPFC (Grimm et al., 2008; Bermpohl et al., 2006). The results of the current thesis, whereby low-frequency stimulation of the right DLPFC triggered elevated risk-taking in healthy subjects (Study II), suggest that right DLPFC excitability is characterised by a continuum: relative to left, the right DLPFC is hyperactive in major depression, but hypoactive in healthy subjects following low-frequency TMS. By discriminating veridical vs. non-veridical cognition, the diagnosis and subsequent treatment of clinical conditions with established stimulation protocols–such as major depressive disorder–may be enhanced to improve the precision of diagnosis as well as to afford a more efficient technique for predicting and monitoring the response of the patient to TMS treatment.

Reliable biomarkers for predicting treatment outcome for patients on an individual level would be of great clinical utility, but are hard to identify (Silverstein et al., 2015). Currently, the response of an individual patient to rTMS treatment of major depression is hard to predict. A reliable and more accurate option to evaluate the early response of a patient to TMS therapy by focusing exclusively on non-veridical short-term effects may provide relevant feedback on the responsiveness or unresponsiveness of the patient. Again, as genetic factors contribute to determining the left-right DLPFC balance and response to TMS interventions (Study III), this knowledge is potentially relevant to be included in clinical TMS guidelines in the future as knowledge of genetic factors and accessibility to genotyping facilities expands.

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SUMMARY IN ESTONIAN

Otsustusprotsesside mõjutamine transkraniaalse magnetstimulatsiooniga

Inimese käitumist kontrollivate otsustusprotsesside mõistmiseks on oluline tuvastada nii erinevat tüüpi otsuste neurobioloogilised mehhanismid kui ka välja selgitada nende otsustusprotsesside seosed frontaalsagara poolt juhitavate eksekutiivsete funktsioonidega. Eksekutiivsed ehk täidesaatvad funktsioonid on kontrollitud käitumise alustalaks ning hõlmavad nii käitumise planeerimist, alternatiivsete käitumisstrateegiate kaalumist kui ka impulsiivse käitumise pidurdamist (Welsh jt, 1991). Otsustusprotsesse võib vaadelda eksekutiivsete funktsioonide osana, mille eesmärgiks on säilitada sihipäraste tegevuste toimumise ajal pidev eesmärgi saavutamisele suunatud kontroll käitumise üle (Fellows, 2013).

Kuigi otsustusprotsesside neuropsühholoogilisel uurimisel on siiani kasutatud peamiselt õige/vale vastusega nn. veridikaalseid ülesandeid, siis inimese igapäevaelus on olulisel kohal ka subjektiivsed, "suhteliselt õiged" otsused. Subjektiivsete otsuste korral puudub sageli üheselt mõistetav vastus, mille on dikteerinud testikoostaja või faktid; selliste otsuste puhul sõltub vastus vastaja enda subjektiivsetest eelistustest, maitsest või olukorrast (Goldberg jt, 1994; 2012). Siiski on enamik neuropsühholoogilisi teste, sh Wisconsini kaarditest (Wisconsin Card Sorting Test; Grant ja Berg, 1948), oma põhimõttelt veridikaalsed (Podell jt, 2012). Isegi riski ja teadmatuse komponenti hõlmavad neuropsühholoogilised ülesanded, näiteks Iowa Gambling Task (Bechara jt, 1994), on oma olemuselt mingis osas veridikaalsed, sest eeldavad inimeselt kindlate, esialgu varjatud mängureeglite äratundmist ning katse-eksituse meetodil kasulikumate valikute tegemist (Brand jt, 2006). Samas on inimene vaba (st veridikaalset tüüpi otsuste reeglitest piiramata) valima riskeerimismäära oma parema äranägemise järgi. Seega on valik riskida suuremal või vähemal määral mitte-veridikaalne.

Käesolev väitekiri keskendub mitte-veridikaalsete otsustusprotsesside uurimisele, kasutades selleks transkraniaalse magnetstimulatsiooni (TMS) meetodit. Magnetimpulssidega otsustusprotsessidega seotud dorsolateraalse prefrontaalkorteksi (DLPFK) piirkondi mõjutades on võimalik tuvastada mitte-veridikaalsete otsuste neurobioloogilisi korrelaate ning uurida veridikaalseid ja mitte-veridikaalseid otsuseid vastandava teoreetilise mudeli paikapidavust. Erinevalt veridikaalsetest otsustest, mille puhul on teada üldtunnustatud ning objektiivne õige või vale vastus (nt. Kumb objekt on suurem? või Kumba eset esineb mingis hulgas rohkem?), puudub mitte-veridikaalse otsuse puhul ühene, objektiivne vastus, mille äraarvamist vastajalt oodatakse. Mitte-veridikaalse otsuse puhul on vastus subjektiivne, sõltudes vastaja eelistustest, maitsest või tahtest, vastamisel lähtutakse printsiibist "mis mulle rohkem meeldib või mis on mulle parim?".

Täpsemalt keskendub töö otsustusprotsessidega seotud ajupiirkondade mõjutamisele, jälgides magnetstimulatsiooni tagajärjel tekkivaid käitumuslikke

muutusi. Selleks, et hinnata, kas veridikaalseid ja mitte-veridikaalseid otsustusprotsesse on võimalik teineteisest sõltumatult manipuleerida, stimuleeriti ajukoore frontaalsagara parem- ja vasakpoolset DLPFK piirkonda nii madal- kui kõrgsagedusliku magnetstimulatsiooniga (Uurimus I). Uurimistulemused näitasid, et kummagi ajupoolkera stimuleerimine nii madalatel kui kõrgetel sagedustel kutsus esile muutusi mitte-veridikaalses nn. Kognitiivse Kallutatuse Ülesandes (KKÜ, ingl. k. Cognitive Bias Task, Goldberg jt, 1994b). Seejuures tõi ainult parema DLPFK madalsageduslik (pidurdav) stimuleerimine esile muutusi ka veridikaalses soorituses.

Selleks, et parempoolse DLPFK piirkonna rolli otsustusprotsessides paremini mõista, rakendasime järgmisena riskeeriva käitumise ülesannet Game of Skill (Otsa jt, 2016). Ka seda hea tulemuse saavutamiseks riskeerimist eeldavatel pallivisetel põhinevat ülesannet võib käsitleda mitte-veridikaalsena, kuna katseisikul on vaba voli valida, kui suurt riski ta soovib võtta. Palli katseruumi laele võimalikult lähedale visates saab katseisik küll rohkem punkte, kuid suureneb ka tõenäosus, et pall puudutab lage, millega kaasneb kas osade (madalama riskitasemega mängurežiim) või kõigi (kõrgema riskitasemega mäng) eelnevalt kogutud punktide kaotamine. Uurimuse II tulemused näitasid, et kui normaaltingimustes käitusid katseisikud kõrgema riskitasemega mängurežiimi puhul ettevaatlikumalt, pigem hoidudes laepuudutuseni viivatest visetest, siis parempoolse DLPFK pidurdava stimuleerimise tagajärjel riskivõtmine suurenes ning oluliselt suurenes ka lae palliga puudutamise osakaal. Katse kinnitas parempoolse DLPFK rolli pidurdavas käitumises mitte-veridikaalse riskeeriva ülesande näitel. Kuna riskeeriva käitumise puhul on tegemist käitumise kontrollis oluliste pidurdusmehhanismide nõrgema panusega (ettevaatlikkuse vähema määraga), siis on arusaadav, miks parempoolse DLPFK kui teadaolevalt tegevuse pidurdamises oluliselt osaleva ajupiirkonna erutuvuse kunstlik pärssimine päädib vähenenud ettevaatlikkusega.

Kuna otsustusprotsesside neurobioloogiat mõjutavad ka frontaalsagara aktiivsusega seotud geneetilised tegurid ning nende poolt kujundatud neurobioloogilised endofenotüübid, siis on tõenäoline, et mitte-veridikaalseid otsustusprotsesse ning nendes TMS poolt esilekutsutavaid muutusi mõjutavad ka geenid. Järgnevalt uuritigi (Uurimus III) ajus toodetavat närvikasvu faktorit kodeeriva geeni *BDNF* rolli mitte-veridikaalsetes otsustes. *BDNF* geenis esinevat polümorfismi (SNP rs6265), mille tagajärjel valiin on asendunud metioniiniga (Val66Met), on varem seostatud strukturaalsete ja anatoomiliste muutustega dorsolateraalses prefrontaalkorteksis ning mõjutustega veridikaalsetele otsustusprotessidele (nt. Egan jt, 2003; Gasic jt, 2009). Met-alleeli kandjatel on täheldatud vähenenud DLPFK mahtu (Pezawas jt, 2004) ning madalamat võimekust teatud tüüpi töömälu ülesannete sooritustes, mida ilmestavad muutused hippokampuse ja DLPFK aktivatsioonimustrites (Egan jt, 2003). Tulemused näitasid Val66Met olulist mõju mitte-veridikaalsele otsustamisele: Met-alleeli kandjad järgisid KKÜ-ülesandes selgeid väljakujunenud eelistusi ja valikukriteeriume, samas kui Val homosügoodid lähtusid valikutes rohkem välise stiimuli mõjutustest, ilmutades suuremat sõltuvust kontekstist.

Täiendavalt ilmnes ka oluline genotüübi ja TMS mõju interaktsioon: Met-alleeli kandjatel süvenes internaalsetel eelistustel põhinev valikute tegemine veelgi, samas kui Val homosügootide käitumine TMS mõjutuste tagajärjel oluliselt ei muutunud. Selles tulemuses peitub võimalus TMS-põhiste teraapiameetodite väljaarendamiseks neuroloogiliste või psühhiaatriliste diagnooside korral, mille oluliseks sümptomiks on käitumise liigne pidurdatus vastusena keskkonna-tegurite mõjule.

Tervikuna näitavad väitekirja uuringud, et mitte-veridikaalseid otsustus-protsesse on võimalik TMS-i abil selektiivselt mõjutada, kusjuures vasakpoolne DLPFK näib olevat rohkem spetsialiseerunud mitte-veridikaalsetele kognitiiv-setele otsustele kui parempoolne (Uurimus I). Väitekirjas leidis täiendavat kinnitust parempoolse DLPFK oluline roll impulsiivses ja riskantses käitumises: parempoolse DLPFK väsitamine madalsagedusliku magnetstimulatsiooniga toob kaasa pidurduse vähenemise ning oluliselt riskeerivama käitumisstrateegia (Uurimus II). Uuring III kinnitas *BDNF* geeni polümorfismi rs6265 olulist mõju nii mitte-veridikaalsetele otsustusprotsessidele kui ka sellele, kuidas prefrontaalsete piirkondade mõjutamine TMS-iga mitte-veridikaalset käitumist muudab. Autorile teadaolevalt ei ole mitte-veridikaalsete otsustusprotsesside TMS-mõjutusi ning seoseid *BDNF* geeniga varem uuritud. Tulemused ilmes-tavad ühtlasi ka seda, et TMS rakendamine avaldab korteksi piirkondadele nii lokaalset kui distaalset (TMS lookusest eemal avalduvat) mõju ning et TMS-i meetodil esile kutsutud "virtuaalne ajukahjustus" ei pruugi käitumuslikult matkida sama ajupiirkonna fokaalset ajukahjustust. Väitekiri illustreerib geneetiliste tegurite olulisust mitte-veridikaalsete otsustusprotsessides ning näitab, et geneetiliste teguritega tuleb arvestada, kui eksperimentaalses või kliinilises töös rakendatakse TMS meetodit.

PUBLICATIONS

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Education:

2011–2019	University of Tartu, psychology, doctoral studies
2003–2009	University of Tartu, entrepreneurship and technology management (MBA)
2001	University of Vienna, Austria, cognitive neuropsychology (1 semester)
1999–2000	Rutgers University, NJ, USA, psychology (2 semesters)
1997–2003	University of Tartu, psychology, BSc

Professional experience:

2017/09–	Cognuse, Chief Scientific Officer
2015/01–	European Commission, expert evaluator (external)
2011–2016	Biominerata, founder, R&D manager
2003–2012	Cognuse, founder, Chief Scientific Officer
2005–2006	Estonian Science Foundation, international projects manager
2003–2005	Estonian Biocentre, R&D projects manager
2005–	Civitta Estonia, council member

Professional training:

2016	Quality Assurance of Clinical Research, Karolinska Institute, Sweden
2015	TMS User and Safety Course, Aalto University, Finland
2013	Coupling to the dynamics of the brain with TMS-EEG, Aalto University, Finland
2013	PET imaging of the CNS, Karolinska Institute, Stockholm, Sweden
2011	TMS in theory and practice, Aalto University/University of Helsinki, Finland
2011	EACCME/UCB Brain Aging and Cognition Academy, France
2010	Psychotherapeutic Interventions for TBI, Käpylä Rehabilitation Center, Finland
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Membership in professional organizations:
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Publications:

1. Tulviste, J., Goldberg, E., Podell, K., Vaht, M., Harro, J. & Bachmann, T. (2019). BDNF polymorphism in non-veridical decision-making and differential effects of rTMS, *Behavioural Brain Research, 364,* 177–182, https://doi.org/10.1016/j.bbr.2019.02.027
2. Tulviste, J., & Bachmann, T. (2019). Diminished risk-aversion after right DLPFC stimulation: Effects of rTMS on a risky ball throwing task. *Journal of the International Neuropsychological Society, 25*(1), 72–78. https://doi.org/10.1017/S1355617718000930
3. Tulviste, J., Goldberg, E., Podell, K., & Bachmann, T. (2016). Effects of repetitive transcranial magnetic stimulation on non-veridical decision-making. Acta Neurobiologiae *Experimentalis, 76*, 182–191.
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2017–	Cognuse OÜ, teadusjuht
2015–	Euroopa Komisjon, eksperthindaja (väline)
2011–2016	Biominerata, asutaja, arendusjuht
2003–2012	Cognuse OÜ, asutaja, teadusjuht
2005–2006	Sihtasutus Eesti Teadusfond, projektijuht
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Publikatsioonid:

1. Tulviste, J., Goldberg, E., Podell, K., Vaht, M., Harro, J. & Bachmann, T. (2019). BDNF polymorphism in non-veridical decision-making and differential effects of rTMS, *Behavioural Brain Research, 364,* 177–182, https://doi.org/10.1016/j.bbr.2019.02.027
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