A gut feeling

DOCTORAL THESIS

A GUT FEELING

NONINVASIVE BRAIN STIMULATION, GUT MICROBIOTA AND DECISION-MAKING UNDER RISK

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*To my dear friend **Gabriela Matos**.*
Gaby, you are always in my heart.

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1

GENERAL INTRODUCTION

Risk-taking behavior is an important topic across multiple fields, including finance, marketing, management, sociology, and anthropology. It is crucial to understand how we make decisions when faced with risk because most of our daily choices have an element of risk to them, from small decisions, such as which route to take to work, to large ones, such as financial investments, insurance purchases, health management, and even high-level governmental decisions, such as quarantine regulations during a pandemic like COVID-19.

At the individual level, being unable to properly assess and manage risk-taking behavior can have serious consequences, such as social isolation, health-compromising behavior, and financial insecurity (Eckel & Wilson, 2004; Galvan et al., 2006; Xue et al., 2010). Similarly, poor decision-making under risk can cause significant social and economic costs at the societal level (Bateson, 1966; Josef et al., 2016; Vickerstaff & Cox, 2005). Thus, it is of utmost importance to better understand risk-taking behavior.

To do so, different fields develop theories and models to inform the development of more efficient public policies, marketing, managerial strategies, and political or financial choices (Knight, 1921; Levav & Argo, 2010). Much of this work draws on findings from fields such as neuroscience, psychology, and microeconomics to study individual risk-taking behavior. Due to the complexity of risk-taking behavior and its dependence on internal and external factors (e.g., emotional state, social influence, and time constraints), many research questions remain to be explored (Das & Teng, 2001; Houser et al., 2010; Josef et al., 2016).

This dissertation seeks to address these questions by combining state-of-the-art neuroscientific methods and economic models to investigate risk-taking behavior through the lens of decision neuroscience. It is aimed at an interdisciplinary audience such that researchers from different fields can clearly understand the concepts and methods used.

1.1 WHAT IS RISK-TAKING BEHAVIOR?

Risk-taking behavior is commonly understood as any behavior that could expose the decision-maker to some level of risk. In psychology, it is often defined as a behavior that involves the perception and evaluation of risks and rewards as well as the decision to act despite potential risks (Trimpop, 1994). This involves some degree of uncertainty regarding the outcomes or the probabilities of such outcomes (Josef et al., 2016). However, the definitions of risk in economics are more stringent (Schonberg et al., 2011). According to the economics literature, risk is a situation in which there is a known probability distribution over certain outcomes, but it is unknown as to which outcome will be obtained (Charness et al., 2013; Chuang & Schechter, 2015). Clarifying such a

definition is essential for the proper identification and subsequent measurement of risk-taking behavior. Clearly defining risk-taking behavior also helps to create tools and models to elicit, estimate, and properly understand risk-taking behavior. This dissertation explores what is defined in economic theory as risk, with clear probabilities and outcomes.

1.2 HOW CAN RISK-TAKING BEHAVIOR BE ESTIMATED?

A great deal of research has been conducted on risk-taking behavior, with a particular focus on understanding why some people are more willing to take risks than others (Chuang & Schechter, 2015). To that end, different methodologies are used to estimate individual risk-taking behavior. One common approach is to use surveys to ask people about their willingness to take risks in different domains (e.g., financial, physical and social) (Armin et al., 2016). Surveys have the advantage of being relatively cheap and quick to administer, but they have the disadvantage of being subject to self-reporting biases, where participants answer imprecisely, according to beliefs, expectations, or distortions related to their actual behavior (Chuang & Schechter, 2015; Wölbert & Riedl, 2013).

In behavioral economics, multiple price lists (MPL) are usually the preferred methodology to measure one's risk preferences (Drichoutis & Lusk, 2016). MPL are a series of binary options where the participant chooses between a gamble and a certain outcome with a lower expected value or between two gambles with varying levels of risk (a safer versus a riskier gamble). The options are either presented simultaneously in a list layout or in a pair at the time. The point at which participants shift from one column to the other (from certain to gamble or from safer to riskier gamble) is used as an indicator of her risk preferences (Andersen et al., 2006; Donkers et al., 2013). A limitation of this method resides in exposing participants to numeric input for probabilities, which stimulates a mental calculation that could otherwise not happen. It is, therefore, a less naturalistic choice environment compared to the tasks described above. The second limitation of the MPL is that when all alternatives are presented at once or in a sequential fashion, participants tend to keep consistent choices to avoid cognitive dissonance. This means that they might accept (reject) options that they would otherwise reject (accept) to avoid contradicting their own previous choices (Andersen et al., 2006; Chuang & Schechter, 2015; Drichoutis & Lusk, 2016).

Cognitive tests, such as the Balloon Analog Risk Task (BART) (Lejuez et al., 2002) and the Risk Task (Rogers, 1999), are also used to study risk-taking behavior. These tests are more common in psychology and cognitive neuroscience studies and provide insight into how people make decisions when faced with risky choices. (Chuang & Schechter, 2015; Lejuez et al., 2002).

The BART is a widely used computer task used to estimate risk-taking behavior (Guo et al., 2018; Lighthall et al., 2009; Rao et al., 2008; Sela et al., 2012). In this task, participants must decide how much air to pump into a virtual balloon on each trial – pumping more air into the balloon increases the potential reward but also raises the chance of it bursting and losing everything (Lejuez et al., 2002). The number of pumps is therefore taken as a measure of risk-taking behavior. However, one of the main limitations of this task is that the probabilities of winning are unclear to the participants. Therefore, this task measures ambiguity rather than risk according to economic definitions (Lejuez et al., 2002).

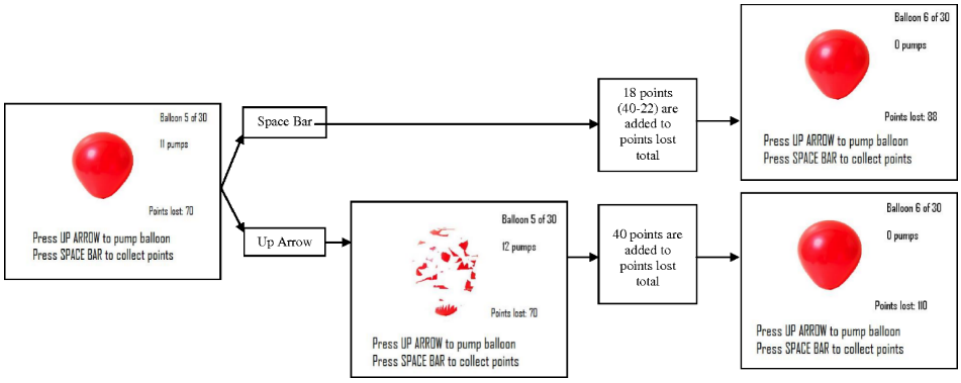


Figure 1.1 - Balloon Analog Risk Task – Task description and layout (Parkinson et al., 2012)

The Risk Task (Rogers, 1999) is another computerized task in which participants need to guess the color (among two options) of the box hiding a token, with the correct guess earning a specific number of points and the incorrect guess losing the same number of points. of the box hiding a token. Each color has a different probability of hiding the token and is associated with a specific payoff. Both probabilities and payoffs vary in each trial. The task is presented in a sequential fashion with the aim of obtaining the highest number of points overall. Although the task is widely used (i.e., Fecteau, Knoch, et al., 2007; Fecteau, Pascual-Leone, et al., 2007; Knoch et al., 2006), it has two main limitations. The first limitation is that participants' choices are likely affected by loss aversion since participants can lose points accumulated along the game. Second, due to its sequential nature, responses can also be affected by memory effects and reactions to previous gains and losses.

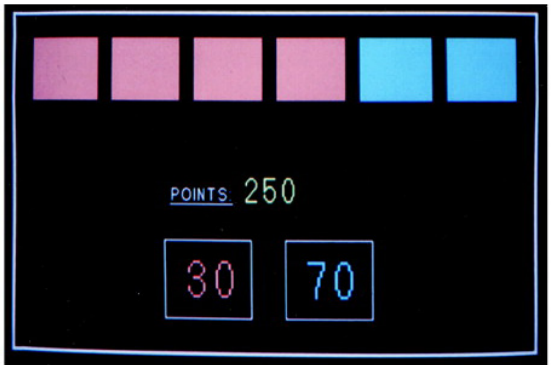


Figure 1.2 - Risk Task – Example screen (Rogers et al., 1999)

Tasks and games, such as the BART and the Risk Task, can be more expensive and time-consuming to set up than a survey. Yet, they provide more detailed data than surveys, and it is possible to obtain a less biased estimation of participants' risk attitudes and risk-taking behavior (Chuang & Schechter, 2015). Either of these methodologies can be implemented using online data collection or in a laboratory setting. It is important to highlight that there is a current debate regarding the time consistency and predictive power of many methods used to estimate risk-taking behavior (Chuang & Schechter, 2015; Csermely & Rabas, 2016; Lejuez et al., 2002). Hence, the choice of methodology depends on a series of factors such as cost, accuracy, financial compensation, sample size, and so on. At times, a combination of measurement methods is advisable.

In this dissertation, I use a novel task named Maastricht Gambling Task (MGT), introduced in Dantas et al. (2021) and developed with the guidance of the Maastricht Center for Neuroeconomics (MU-CEN) that aims at correcting for the limitations detected in other methods to estimate risk-taking behavior (Dantas et al., 2021). This task employs a user-friendly and easily comprehensible layout adapted from the widely studied Risk Task (Rogers et al., 1999), also known as the Cambridge Gambling Task (CGT) (Yazdi et al., 2019).

Unlike the other methods described here, the MGT attains strict economic definitions of risk, with clear probabilities and payoffs presented to the participant. Another important improvement is the control for loss aversion and memory effects, with independent and randomized trials in which participants can either win the payoff associated with their choice or end the trial with zero points. Moreover, the task does not include any level of deception, and all the possible combinations of payoffs and probabilities are combined in 125 unique trials, each repeated once in a random order. With this design, the MGT allows the analysis of each participant's risk-taking behavior in a wide variety of choice

scenarios. The MGT's full description can be seen in Chapter 2 (Dantas et al., 2021).

1.3 HOW CAN NEUROSCIENCE HELP US UNDERSTAND RISK-TAKING BEHAVIOR?

An important approach to further understanding human decision-making in general and risk-taking behavior in particular is the use of neuroscientific methods. Psychologists and economists have increasingly been looking at neuroscientific findings to better understand how humans make decisions (Camerer et al., 2005; Karmarkar & Yoon, 2016; Plassmann et al., 2015). This field of research, known as decision neuroscience, has gained considerable traction in recent years, with a growing body of literature. When combined with economic models and behavioral economics methods (such as economic games), this research field is named neuroeconomics (Epper & Fehr-Duda, 2012; Gianotti et al., 2009).

Neuroscientific methods include both technologies that interact with the central nervous system, such as brain stimulation and neuroimaging techniques, and technologies that measure responses from the peripheral nervous system, such as eye tracking, estimation of skin conductance, and heart rate (Rilling & Sanfey, 2011; Shiv et al., 2005).

Unlike the common behavioral tools used to study risk taking, neuroscientific methods can be used to estimate non-declarative and involuntary neural and physiological responses during the decision-making process. This means that with neuroscientific methods, one can measure in great detail even reactions that might escape the participant's own perception. These responses include, for example, changes in brain activity, heart rate, or sweating (Brunyé & Gardony, 2017; Jongkees & Colzato, 2016; Karmarkar & Yoon, 2016; Smidts et al., 2014).

Neuroimaging methods such as functional magnetic resonance imaging (fMRI) allow measurements of different patterns of brain activity during a specific task or state, such as risk-taking behavior (Thut et al., 2012). fMRI allows the measurement of brain activity, which is estimated based on the blood oxygenation level-dependent (BOLD) responses in different brain areas. With fMRI, one can explore which brain areas and networks are activated during a specific task. Nevertheless, it lacks time accuracy, since the BOLD response is a relatively slow process. fMRI can, however, be used to study subcortical responses, which cannot be done with other neuroimaging methodologies (Logothetis, 2008; Rao et al., 2008).

Electrophysiological measurements such as electroencephalography (EEG) and magnetoencephalography (MEG) are used specifically to read neural electric activity, which is measured as oscillatory patterns or event-related potentials (ERPs) that can be measured during resting-state or during a specific task (Thut et al., 2012). These

methods allow a great temporal resolution, meaning that it is possible to identify different neural responses with an accuracy in the range of milliseconds. However, these methods also have their limitations, with a low space accuracy and impossibility of detecting subcortical activity (Logothetis, 2008).

Finally, risk-taking behavior can also be studied with brain stimulation techniques. In contrast to measurement techniques such as fMRI and EEG, brain stimulation techniques can modulate brain activity, allowing a direct test of a specific area's functional relevance for different behavioral or cognitive processes . Brain stimulation can be done invasively, including surgical procedures, or noninvasively, using noninvasive brain stimulation (NIBS), which is the focus of this thesis (Driver et al., 2009; Nitsche et al., 2008; Polanía et al., 2018; Rossi et al., 2009). These NIBS techniques include methodologies such as transcranial electric stimulation (tES), which includes transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and transcranial magnetic current stimulation (TMS) (Polanía et al., 2018). More details about each technique will be explained in the following sections.

In this dissertation, I used a variety of neuroscientific methods. Chapters 2, 3, and 4 include NIBS, with the use of tACS (Chapters 2 and 3) and TMS (Chapter 4) aiming at investigating the functional relationship between specific oscillatory patterns (tACS) or the activity of specific brain areas (TMS) and risk-taking behavior. Chapters 2 and 3 include EEG measurements, aiming at the measurement of different oscillatory patterns during risk-taking behavior. Moreover, although not specifically a neuroscientific method, I used probiotics as a method to intervene with the gut–brain axis. Figure 1 shows an overview of the methods used in this dissertation and their approximated temporal resolution (the time scale that each technique allows) and intrusiveness (how disturbing or uncomfortable each technique can be in general), loosely based on (Schulte-Mecklenbeck et al., 2017) and Gazzaniga et al. (0(02).

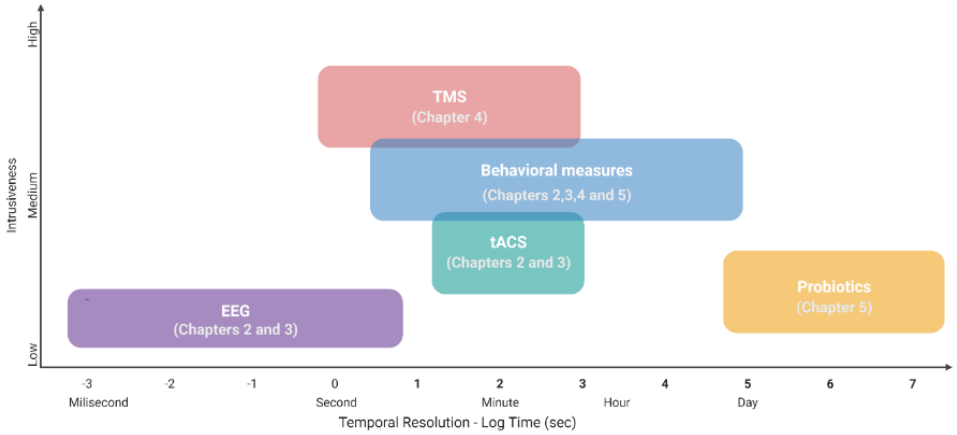
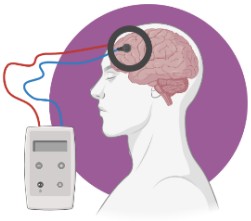


Figure 1.3 - Neuroscientific methods used in this dissertation - Graphic representation of the neuroscientific methods used in this dissertation along the following chapters. Graph depicts a representation of the different methods by temporal resolution and degree of intrusiveness.

1.3.1 tACS

tACS belongs to the family of noninvasive electric stimulation techniques commonly referred to as tES. Electric stimulation uses weak electrical currents applied using electrodes attached to the scalp to stimulate specific brain areas. The most common use of tES is tDCS. This method applies a weak tonic direct current between electrodes mounted on the head. This electric current affects the ionic balance within the synapses (called the synaptic voltage). Synapses are the areas via which neurons communicate with each other. This change in ionic balance can facilitate or inhibit neuronal communication. This process of communication is known as synaptic transmission (Polanía et al., 2018). In general, neurons communicate with each other using electric signals. The changes in ionic balance that trigger these signals are known as action potential (Yamada & Sumiyoshi, 2021).



tACS

tACS belongs to the family of noninvasive electric stimulation commonly referred as tES. tACS generates a sinusoidal shaped electric current, facilitating the occurrence of these same oscillatory patterns in the targeted area (Polanía et al., 2018).

For a neuron to fire, the internal medium of the synaptic membrane needs to reach a specific firing threshold of -55 mV, while the normal balance is around-70 mV. In tDCS, anodal (positive) stimulation leads to widespread subthreshold depolarization, meaning that the inside of the

synapse membrane has a more positive charge, getting closer to the firing threshold, which facilitates neuronal firing and is therefore a facilitating protocol. Cathodal (negative) stimulation leads to the opposite effect, inducing widespread subthreshold hyperpolarization. This means that it increases the negative charge inside the synapse, which is further than the minimum necessary for the neuron to fire an action potential. This increase in negative charge reduces neural excitability and inhibits synaptic transmission (Bland & Sale, 2019; Brunoni et al., 2012; Yamada & Sumiyoshi, 2021). Due to its nature, it is not possible to directly measure the effects of tDCS since while it supposedly affects excitability, it does not elicit neuronal triggering (Guo et al., 2018; Kuo et al., 2013).

tACS employs quite a different mechanism than tDCS. The polarization of the electrodes shifts cyclically at a specific frequency, generating a sinusoidal-shaped electric current according to the frequency chosen. This means that the electric flow between electrodes occurs at specific oscillatory frequencies, which in turn facilitates the occurrence of these same oscillatory patterns in the targeted area (Polanía et al., 2018).

Neural activity occurs naturally in oscillatory patterns. Alpha, beta, theta, and gamma are some of the most widely mentioned frequencies that occur in different areas of our brains (Bland & Sale, 2019). These oscillatory patterns originate from the rhythmic firing of groups of neurons that communicate using different frequencies. This nature of our neural oscillatory communication allows it to be modulated with the imposition of rhythmic stimuli, such as rhythmic light or sound exposition, or electric stimulation, such as tACS. Therefore, tACS biases ongoing neural activity, leading it to approximate the frequency band in which the stimulation is delivered. This mechanism is commonly referred to as entrainment (Bland & Sale, 2019).

By facilitating neuronal activity in specific frequency bands, tACS allows for the study of the relationships between specific neural oscillatory patterns and behavior (Polanía et al., 2018). These studies can be done by increasing or reducing the occurrence of such oscillatory patterns in a specific area using tACS and by measuring consequent behavioral changes. Another approach includes applying the same frequency of stimulation over distinct regions at the same time at different oscillatory phases, aiming at facilitating or hampering the synchronization between these areas to investigate how oscillatory coherence between distinct nodes of neural networks affects behavioral responses (Polanía et al., 2018).

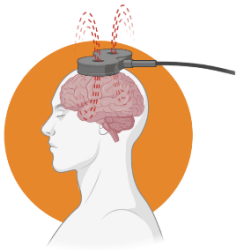
There are numerous examples of studies using tACS to investigate the functional relationships between specific oscillatory frequencies and behavior. These include the causal role of theta–gamma cross-frequency coupling in working memory performance

(Polanía et al., 2012), alpha and beta oscillations in motor bimanual coordination (Heise et al., 2019), and of interest for this dissertation, theta-band oscillations in inhibitory control (Klírová et al., 2021).

The use of EEG allows the measurement of changes in oscillatory patterns in the stimulated areas as well as potential network effects. Nevertheless, the simultaneous use of these methods is still technically challenging due to the noise generated by the stimulation in EEG measurements. Therefore, most studies evaluate changes in oscillatory patterns immediately after tACS, while techniques to improve the signal-to-noise ratio during simultaneous EEG and tACS are at this point being developed and tested (Vosskuhl et al., 2020). In general, tES has a low focality, affecting a greater area than other NIBS methods.

1.3.2 TMS

TMS is another noninvasive brain stimulation technique that uses strong electromagnetic fields to induce small electric currents in the brain (Loo et al., 2000). TMS has been used for a variety of applications, including the treatment of depression (Cui et al., 2022; Perera et al., 2016), as a potential therapy for Parkinson's disease (Brys et al., 2016) and stroke rehabilitation (McDonnell & Stinear, 2017), among others. In addition to these therapeutic uses, TMS can be used to study brain networks by stimulating different areas with varying intensities and protocols, allowing researchers to map out how different regions are connected in the brain (Thut & Pascual-Leone, 2010).



TMS

TMS is a noninvasive brain stimulation technique that uses strong electromagnetic fields to induce small electric currents in the brain (Loo et al., 2000). Thus, it facilitates neural modulation of specific brain areas, making it possible to examine their functional roles (Guse et al., 2010; Kaminski et al., 2011).

Different effects can be obtained with variations in the application of TMS. In general, TMS can be used with single pulse stimulation at a time (single pulse) or with trains of repeated pulses (rTMS). Depending on the frequency and interval between each pulse, different effects are observed. NIBS effects in general can also be distinguished between online effects, which means during stimulation, and offline effects, after stimulation. Low-frequency rTMS generally has an offline inhibitory effect that causes a temporary disruption in the target area's activity, which essentially deactivates it. On the other hand, high-frequency rTMS typically leads to an offline activation of the targeted area due to its excitatory effects (Thut & Pascual-Leone, 2010).

More recently, patterned protocols have been developed, such as theta-burst stimulation (TBS), which employs 50 Hz pulses in 5-Hz intervals (Kaminski et al., 2011). This protocol can be applied continuously for 40 seconds (continuous TBS or cTBS) or intermittently, with trains of bursts repeated every 10 seconds for 192 seconds (intermittent TBS or iTBS) (Cho et al., 2010). In general, cTBS has an inhibitory effect, while iTBS has a mainly excitatory effect (Thut & Pascual-Leone, 2010).

A great advantage offered by TMS compared to tES techniques is its focality. TMS can precisely target specific cortical areas, ensuring that only this area is stimulated and that no other areas are accidentally stimulated (Guse et al., 2010). This focality can be improved with the use of specific coils. The stimulation target can be determined based on anatomical fiduciary points, using the international 10-20 EEG location system or with individual neuronavigation guidance (Kaminski et al., 2011). Neuronavigation is a method via which it is possible to project TMS focus on an area identified based on individual anatomical or functional MRI and properly position the coil to reach the targeted area (Corp et al., 2020; Duecker & Sack, 2015; Thut et al., 2012).

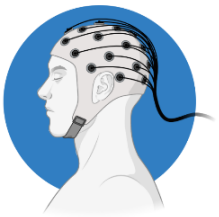
The quick response time of TMS also allows for immediate measurable and observable responses, such as muscular contractions or phosphene generation, something that cannot be directly obtained with tES applications. This combination of focality and observable effects makes TMS an incredibly powerful tool in neuroscience research and clinical practice alike (Corp et al., 2020; Ekhtiari et al., 2019; Enokibara et al., 2016). Thus, it facilitates the neural modulation of specific brain areas, making it possible to examine their functional roles (Guse et al., 2010; Kaminski et al., 2011).

1.3.3 EEG

EEG is a non-invasive technique that records the electrical activity of neurons in the brain. It works by recording the electrical activity of neurons using electrodes placed on the scalp, producing an electroencephalogram (EEG) trace. It has been used for decades to measure neuronal responses, such as sleep stages, seizures, and changes in alertness. This technology has proved invaluable in both clinical settings and research. In clinical diagnosis, it is an important tool for diagnosing diseases such as epilepsy and dementia (Dippel et al., 2016; Michel & Brunet, 2019).

In research, EEG recordings allow for the observation and analysis of neural activity patterns. The analysis of EEG has become much more sophisticated with the development of digital technologies. Instead of merely relying on visual inspection, EEG signals can now be studied in a more comprehensive way. Temporal and spatial characteristics such as amplitude and frequency modulations over time can be studied, providing insights into how conditions like epilepsy, sleep disorders, dementia, or any other disorder that may

affect brain function. This technique also allows valuable insights into the functioning of healthy brains during resting-state or specific tasks or activities. Ultimately, these studies help in understanding how specific electrophysiological brain responses are associated with cognitive processes such as memory, attention, and decision-making (Michel & Brunet, 2019; Smulders et al., 2018).



EEG

The EEG is a non-invasive neuroimaging technique that records the electrical activity of neurons in the brain. It works by recording the electrical activity of neurons using electrodes placed on the scalp (Dippel et al., 2016; Michel & Brunet, 2019).

Perhaps the most important contribution of EEG is that it provides valuable information about neuronal processes with high temporal resolution, allowing us to observe changes in neural activity occurring over millisecond timescales (Michel & Brunet, 2019). Nevertheless, it has a major limitation in its poor spatial resolution. This means that it can be difficult to determine where in the brain certain electrical signals are originating from and what type of neuronal activity is associated with them. As such, while EEG provides useful information about overall levels of brain activity, it cannot always provide detailed insight into which specific areas of the brain are involved in particular cognitive processes or behaviors (Michel & Brunet, 2019; Oostenveld et al., 2011).

1.4 THE NEUROSCIENCE OF RISK-TAKING BEHAVIOR

Decision neuroscience and neuroeconomics have uncovered some important findings about risk-taking behavior. Here, I give a general overview of some of the most relevant findings on this growing field of research, the current state of research, and literature gaps.

The literature on the neuroscience of risk-taking behavior mainly includes neuroimaging studies using fMRI (Mohr et al., 2010). Taken together, these studies suggest the involvement of frontolimbic circuits in the processing and modulation of decision-making under risk. These areas include the basal ganglia (Burke & Tobler, 2011; Kohno et al., 2015; Kuhnen & Knutson, 2005; Mohr et al., 2010; Pollak et al., 2019), the insular cortex (Clark et al., 2017; Kuhnen & Knutson, 2005; Paulus et al., 2003; Xue et al., 2010), and specific areas of the prefrontal cortex (i.e., Brand et al., 2007; Clark et al., 2017; Floden et al., 2008; Galvan et al., 2006; Vorhold et al., 2007).

The basal ganglia has been found to be involved in evaluating the potential reward or punishment associated with a particular action (e.g., taking a risk) (Mohr et al., 2010), while the insular cortex is thought to be involved in processing the emotional aspects

of risk (e.g. fear or excitement) (Clark et al., 2017). The prefrontal cortex, and more specifically the dorsomedial prefrontal cortex (DMPFC), orbitofrontal cortex (OFC), ventromedial prefrontal cortex (VMPFC), and dorsolateral prefrontal cortex (DLPFC), have been related to higher-level cognitive processes such as valuation, planning, inhibitory control, decision-making, and the modulation of risk-taking behavior (Rao et al., 2008).

A meta-analysis published by Moth et al. (2010) reviewed fMRI studies studying risk-taking. Their results indicate that different brain structures are involved in different phases of risky decision-making. Namely, the anterior insula and thalamus are associated with the emotional processing of risk, while the DMPFC would be involved in the cognitive processing of risk, and the decision during risk would be processed by the DLPFC and the parietal cortex (Mohr et al., 2010). This meta-analysis indicates that different neuroimaging studies exploring risk-taking behavior can yield considerably different results, depending on the choice contexts during which participants' risk-taking behavior is evaluated.

Other than fMRI studies, some important insights into the processing of decision-making under risk come from research using EEG. These studies have focused mainly on analyses of feedback-related negativity (FRN), which reflects frontal medial activity (Polezzi et al., 2010). In general, it is accepted that the FRN amplitude reflects the process of coding ongoing evaluation and predicting future gains and losses (Gehring & Willoughby, 2002; Polezzi et al., 2010; Yeung & Sanfey, 2004), which is correlated with risk-taking behavior.

Other EEG studies have explored the correlation between specific oscillatory patterns and risk-taking behavior. For example, a study conducted by Lee and Jeong (2013) found a correlation between cross-frequency phase–amplitude coupling (CFPAC) and risk-taking behavior. A significant negative correlation was found between frontal and centroparietal CFPAC and two independent measures of risk-taking behavior. A positive correlation was found between the right temporal and parietal CFPAC and risk-taking behavior. These results indicate that high risk-taking behavior is correlated with lower communication between frontal control and valuation networks (Lee & Jeong, 2013). In the same direction, different studies indicate a correlation between frontal low-frequency activity (beta and theta range) and risk-taking behavior (Gianotti et al., 2009; Massar et al., 2012, 2014; Schiller et al., 2014; Studer et al., 2013). This relationship will be further explored in the next section.

A third and emerging line of research comes from the study of risk-taking behavior using NIBS. Although less numerous, these studies allow inference of the causal relationship between the activity of specific brain areas and decision-making under risk, which cannot

be obtained with the use of neuroimaging techniques (Levasseur-Moreau & Fecteau, 2012; Minati et al., 2012). Nevertheless, since NIBS methods mainly target cortical areas, the vast majority of these studies target the DLPFC (Boggio, Campanhã, et al., 2010; Boggio, Zaghi, et al., 2010; Dantas, Sack, et al., 2021; Fecteau et al., 2014; Fecteau, Knoch, et al., 2007; Fecteau, Pascual-Leone, et al., 2007; Khaleghi et al., 2020; Levasseur-Moreau & Fecteau, 2012; Minati et al., 2012; Sela et al., 2012), overlooking important brain areas that are involved in the processing of risk-taking behavior due to its size or anatomical positioning. The possibility of exploring the functional role of smaller or deeper cortical areas in risk-taking behavior is frequently compromised by technical limitations.

From the studies using NIBS to study risk-taking behavior, the work of Knoch et al. (2006) is perhaps the most influential. This study demonstrated that stimulating the right DLPFC using low-frequency TMS leads to increases in risk-taking behavior (Knoch et al., 2006). These findings reinforce the importance of the right DLPFC in the modulation of risk-taking behavior. Different studies have tested this relationship using tDCS with different settings (e.g., Boggio, Zaghi, et al., 2010; Fecteau, Knoch, et al., 2007; Gilmore et al., 2018; Khaleghi et al., 2020). However, these studies at times yielded contradictory results. For example, Fecteau et al. (2007) observed a reduction in risk-taking behavior using right anodal/left cathodal tDCS (Fecteau, Knoch, et al., 2007). As previously described, anodal stimulation is thought to facilitate neuronal activity, and therefore this setting would facilitate the activity of the right DLPFC. Considering the results obtained by Knoch et al. (2006), one would expect that this setting would lead to an increase in risk-taking behavior and yet the results obtained by Facteau and colleagues (2007) show a reduction of this type of behavior.

There are still many aspects of the underlying neural basis of risk-taking behavior that remain unclear. For example, it is still unclear how network recruitment during risky decision-making occurs or the causal relationship between each area and risk-taking behavior. Moreover, we still do not fully understand how our brain identifies risk, reacts to it, analyzes the possibilities, and ultimately chooses one of these possibilities. Furthermore, a number of factors have been found to influence an individual's propensity to take risk, including their age, gender, personality type, and previous experiences. Nevertheless, the extent of such an influence is still unclear. Understanding how the brain processes decision-making under risk can help elucidate these questions and guide the consequent development of more accurate models to predict individual risk-taking. In this dissertation, I explore several of these questions, which are divided into three main parts:

PART I - THE CODE: THETA-BAND OSCILLATIONS AND RISK-TAKING BEHAVIOR

The findings of Soutschek et al. in 2021 demonstrated that theta-band oscillations

may play a key role in cognitive control by providing a link between memory and metacognition during decision-making processes. This suggests that theta oscillations may be involved in complex behaviors, such as those related to decision-making under risk, which can include processing memories and evaluating options while considering expected outcomes. The research provides further evidence for an integrative role of theta oscillations within cognitive control mechanisms, potentially leading to an improved understanding of how behavior is regulated by higher brain functions.

Theta-band oscillations appear to be involved in a range of functions, including monitoring performance and adjustments following errors, suggesting that they play an essential role in decision-making. Several studies, including Cavanagh & Frank (2014), Massar et al. (2012), Cohen & Donner (2013), Womelsdorf et al. (2010), and Schiller et al. (2014), reinforce this importance of frontal theta-band activity, proposing that this oscillatory pattern is associated with rule identification and inhibitory control. This has been supported by research that has shown that higher levels of theta-band power are linked to increased accuracy during tasks requiring cognitive control, such as working memory tasks or those involving inhibition or switching between different rules (Cavanagh & Frank, 2014; Cohen & Donner, 2013; Massar et al., 2012, 2014; Pinner & Cavanagh, 2017; Schiller et al., 2014). Hence, this section, named “the code” explores the role of frontal theta-band activity as the “code” used by prefrontal areas to identify rules and recruit inhibitory control during risk-taking behavior.

Studies using EEG suggest that an individual’s resting-state frontal theta-power is correlated with their levels of risk proneness, with higher frontal theta-band asymmetry (right minus left theta-power) correlated to higher risk-taking behavior (Gianotti et al., 2009; Schiller et al., 2014). This indicates that there may be an underlying electrophysiological mechanism involving theta-band activity, which contributes to the processing of decision-making under risk. If this is indeed the case, determining the levels of resting-state frontal theta-band activity might be a measure of risk-proneness independent of any task and explain heterogeneous risk attitudes among individuals.

To investigate the role of frontal theta-band oscillations in the neural processing of risk-taking behavior, in Chapter 2, I explore the functional role of frontal theta-band oscillations in risk-taking behavior, using tACS. With this technique, it is possible to stimulate the brain at this specific oscillatory pattern and modulate risk-taking behavior.

In Chapter 2, I use a single blinded within-subject design, stimulating the left DLPFC with three different tACS protocols (one per session): theta (6.5 Hz), gamma (40 Hz), and sham stimulation. The participants performed the MGT during stimulation. This study also included EEG measurements aimed at measuring frontal theta-power

before task and stimulation and potential changes immediately after the stimulation protocols. With this design, I could investigate the role of frontal theta-band activity in risk-taking behavior by assessing the behavioral changes when left theta-band activity is exogenously increased with tACS.

Chapter 3 follows up on Chapter 2 and investigates the role of laterality in the electrophysiological mechanism of risk-taking modulation. To better understand the electrophysiological role of theta-band activity in the modulation of risk, I evaluated whether the effects are dependent on the hemisphere that is stimulated. Chapter 3 also adds the intensity of stimulation as a factor, in line with recent studies exploring the effects of low-and high-intensity tACS and how the different intensities might affect the results observed. To that end, I used a single blinded within-subject design, with two sessions, during which I stimulated either the right or left DLPFC. In each session, participants received low intensity (1.5 mA), high intensity (3 mA), or sham tACS during task execution in a counterbalanced fashion. Again, I performed EEG measurements before and immediately after each stimulation protocol.

The two studies in this section explored the functional role of frontal theta-band activity in risk-taking behavior and deepened the knowledge of how this electrophysiological mechanism occurs. More details in each chapter follow by the end of this introduction.

PART II - THE CONTROLLER: PREFRONTAL CORTEX AND RISK-TAKING BEHAVIOR

The prefrontal cortex is the part of the brain believed to be responsible for executive function, or cognitive control (Cavanagh & Frank, 2014; Figner et al., 2010), hence “the controller”. This includes higher-level thinking skills like planning, decision-making, working memory and attention span regulation, goal setting and monitoring progress towards achieving goals, self-regulation of emotions and behavior to ensure social appropriateness in interactions with others (Carlén, 2017; Milad & Quirk, 2002). Of interest for this dissertation, the prefrontal cortex is believed to play a pivotal role in risk assessment. When presented with uncertain situations or decisions that involve multiple variables (such as costs vs. benefits), this area is fundamental for evaluating potential consequences before taking action, inhibiting impulsive behaviors that could have negative outcomes in the future, and understanding cause-and-effect relationships between actions taken now and future results they might produce; all of which are essential functions required by humans to be successful in their lives (Carlén, 2017; Figner et al., 2010; Hoban et al., 2016; Milad & Quirk, 2002; Wokke et al., 2017).

There are yet many open gaps in the current literature regarding the specific functional roles of two important brain areas in the prefrontal cortex involved in risk-taking

behavior: the VMPFC and the DLPFC (Knoch et al., 2006; Schiller et al., 2014). Both areas have been linked to risk-taking behavior in numerous neuroimaging studies (Burke & Tobler, 2011; Floden et al., 2008; Lee & Jeong, 2013; Polezzi et al., 2010). The VMPFC is located at the front of the brain, just behind the forehead, and has been associated with a range of cognitive processes, including decision-making, emotion regulation, and evaluation of rewards (S. W. Anderson et al., 1999; Clark et al., 2017). The DLPFC is positioned further back in the frontal lobe and is thought to be involved in executive functions, such as planning and goal-directed behavior (Lowe et al., 2014; Rudorf & Hare, 2014).

As previously mentioned, a number of studies have explored the functional relationship between DLPFC activity and the modulation of risk-taking behavior, establishing the role of this area in executive control (Boggio, Zaghi, et al., 2010; Fecteau et al., 2007; Guo et al., 2018; Knoch et al., 2006; Lowe et al., 2014; McNeill et al., 2018; Minati et al., 2012). Nevertheless, despite their close proximity, access to the VMPFC is compromised by its anatomical positioning, which makes the noninvasive stimulation of this area considerably more challenging (Cho et al., 2010; Zack et al., 2016). Therefore, research into the exact functional relationship between VMPFC activity and risk-taking behavior using brain stimulation techniques, such as transcranial magnetic stimulation, has yet to be explored. Yet, recent coil developments now allow targeting deeper

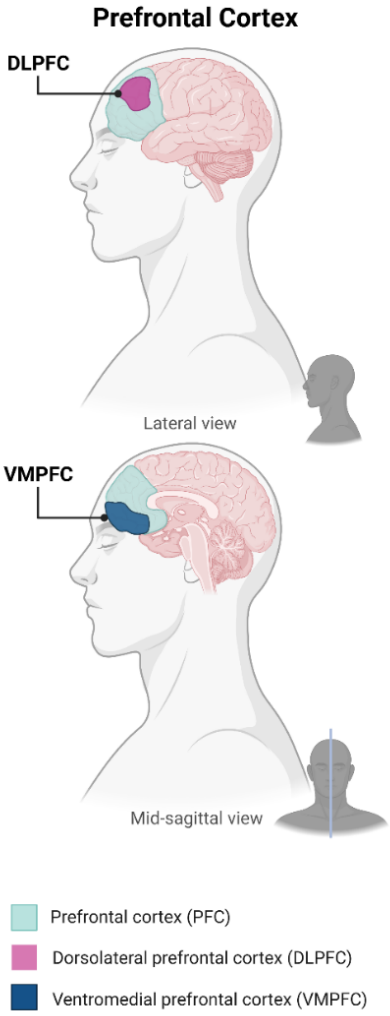


FIGURE 1.4 - PREFRONTAL CORTEX ANA-TOMICAL POSITIONING. FIGURE DEPICTS THE PREFRONTAL CORTEX IN LATERAL (LEFT SIDE VISIBLE) AND MID-SAGITTAL VIEWS (CUT IN THE MINIATURE). DUE TO ITS ANATOMICAL POSITIONING, THE DLPFC AND VMPFC ARE DEPICTED IN DIFFERENT VIEWS OF THE BRAIN, WITH THE DLPFC VISIBLE IN THE LATERAL VIEW AND THE VMPFC IN THE MID-SAGITTAL CUT.

cortical areas, such as the VMPFC (Cho et al., 2015), which was used in Chapter 4.

Chapter 4 includes a study using a generally inhibitory transcranial magnetic stimulation (TMS) protocol in combination with adequate coils to stimulate the VMPFC and the DLPFC independently and evaluate how the inhibition of such areas affects decision-making under risk. This study had two main objectives. First, I replicated the findings of Knoch et al. (2006) by increasing risk-taking behavior after the disruption of rDLPFC activity. However, unlike Knoch et al. (2006), I employed a continuous theta-burst stimulation (cTBS) protocol, which is a mainly inhibitory protocol and yet of faster application. cTBS has an application duration of 40 seconds, while the low-frequency (1 Hz) repeated TMS protocol used by Knoch et al. (2006) has an application duration of 15 minutes. Both protocols have mainly inhibitory effects lasting several minutes after stimulation. Second, I evaluated how the inhibition of the VMPFC (also using the same cTBS protocol) would affect risk-taking behavior.

PART III - THE SECRET RULERS: BACTERIA, AND A CERTAIN GUT FEELING

A crescent and influential line of research in neuroscience indicates that human cognition, and potentially human decision-making, involves networks beyond the brain and the central nervous system (CNS). These studies indicate the involvement of a bidirectional network known as the gut–brain axis (GBA) in human cognition (e.g., de Araujo et al., 2012; Foster et al., 2017; Ganz, 2021; Mayer, 2011). The GBA could therefore be an influential part of this network or a “secret ruler” participating in our decision-making. Following this line of research, I extrapolate the limits of the central nervous system (CNS) by investigating if and how the GBA affects human decision-making and, more specifically, risk-taking behavior.

The GBA is a bidirectional network through which the brain and the enteric nervous system (ENS) communicate and influence each other’s activity. In fact, the ENS has a neuronal complexity only comparable to our central nervous system (Ganz, 2021), being composed of more than 200 million neurons, equal to or more than our spinal cord (Damasio, 2019). In addition, gut epithelial cells are also able to generate and transmit nervous information (Bohórquez et al., 2015), and the production of important neurotransmitters such as dopamine, serotonin, and GABA are dependent on the bacteria present in our gut (Dinan et al., 2013; Het et al., 2009; Messaoudi et al., 2011; O’Mahony et al., 2015; Sarkar et al., 2016).

Studies using both animal models and human participants showed the importance of the GBA in important cognitive processes such as stress reactivity, mood, and higher cognitive functions (C. Anderson et al., 2019; Bercik et al., 2011; Carabotti et al., 2015;

Dantas, Jiao, et al., 2021; Dinan et al., 2013; Enders, 2018; Foster et al., 2017; Ganz, 2021; Messaoudi et al., 2011; Ming et al., 2018). At this point, the mechanism via which this influence happens is still being clarified, but the effects of changes in the gut microbiota in high-order cognitive processes are being demonstrated in a crescent number of studies.

The GBA has also been shown to play a key role in decision-making in animal models, and the potential replication of such findings with humans is remarkable. Despite its constant presence in our everyday language when we talk about our decisions with expressions such as “gut feelings”, “gutted” or “go with your guts”, our guts have been vastly neglected until quite recently by neuroscience (Dinan et al., 2013; Sarkar et al., 2016). And even more so by decision neuroscience. Therefore, I explore in Chapter 5, I explore the role of the gut-brain axis in human decision-making.

In Chapter 5, I demonstrate how both risk-taking behavior and decision-making over time are affected after the prolonged intake of probiotics. In this study, I used a double-blinded placebo-controlled design. Each participant was randomly assigned to a protocol in which she took either 30 days of probiotics or placebo. To evaluate changes in decision-making, I used a sequence of economic games and compared participants’ results before and after the probiotics/placebo protocol (Dantas et al., 2022).

1.8 CHAPTERS OUTLINE

Chapter 2 – Reduced risk-taking behavior during frontal oscillatory theta-band neurostimulation

This study provides direct empirical evidence of the functional relationship between prefrontal theta-band activity and risk-taking behavior. Through a within-subject experiment, thirty-one healthy participants received theta (6.5 Hz), gamma (40 Hz), and sham tACS over the left DLPFC. Risk-taking behavior, response times, sensitivity to value, and outcome probabilities were assessed during the different stimulation protocols.

Chapter 3 – Modulating risk-taking behavior with theta-band tACS

Despite the uncertainty of neural processes underlying decision-making under risk, neuroimaging and electrophysiological studies suggest a crucial role of frontal theta-band activity. However, non-invasive brain stimulation studies have yielded inconsistent findings. Thus, this study aimed to confirm the functional relationship between frontal theta-band activity and risk-taking behavior, as well as to investigate hemispheric lateralization. I tested with theta-band tACS over the left and right dorsolateral prefrontal cortex (DLPFC), with lower (1.5 mA) and higher (3 mA) intensities.

Chapter 4 – The functional relevance of right DLPFC and VMPFC in risk-taking behavior

This study used TMS to investigate the functional relevance of the right dorsolateral prefrontal cortex (rDLPFC) and VMPFC in risk-taking behavior. Based on the current literature, I hypothesized that, compared to sham stimulation, stimulation of the VMPFC would lead to a reduction in risk-taking behavior, while stimulation of the rDLPFC would lead to an increase. To that end, I used cTBS, a mainly inhibitory TMS protocol, to inhibit the activity of each area and compare the resulting behavioral responses.

Chapter 5 – The effects of probiotics on risk and time preferences

Although animal models, human neuroimaging, and lesion studies revealed that the gut microbiota influences the interaction between the central and enteric nervous systems via the gut–brain axis, no studies so far have investigated how it affects human decision-making with healthy participants. To explore this question, I conducted a placebo-controlled double-blinded design to evaluate participants' risk-taking behavior and intertemporal choices. Participants were randomly divided into two groups to receive daily doses of either probiotic or placebo. Their behavioral responses were evaluated in two sessions before and after the probiotics/placebo intake.

1.9 REFERENCES

Andersen, S., Harrison, G. W., Lau, M. I., & Rutström, E. E. (2006). Elicitation using multiple price list formats. Experimental Economics 2006 9:4, 9(4), 383–405. https://doi.org/10.1007/S10683-006-7055-6

Anderson, C., Cryan, J., & Dinan, T. (2019). The Psychobiotic Revolution: Mood, Food, and the New Science of the Gut-Brain Connection. National Geographic.

Anderson, S. W., Bechara, A., Damasio, H., Tranel, D., & Damasio, A. R. (1999). Impairment of social and moral behavior related to early damage in human prefrontal cortex. 2(11).

Armin, F., Becker, A., Dohmen, T. J., Huffman, D., & Sunde, U. (2016). The Preference Survey Module: A Validated Instrument for Measuring Risk, Time, and Social Preferences. SSRN Electronic Journal. https://doi.org/10.2139/ssrn.2725874

Bateson, N. (1966). Familiarization, group discussion, and risk taking. In Journal of Experimental Social Psychology (Vol. 2, Issue 2, pp. 119–129). Academic Press. https://doi.org/10.1016/0022-1031(66)90073-4

Bercik, P., Park, A. J., Sinclair, D., Khoshdel, A., Lu, J., Huang, X., Deng, Y., Blennerhassett, P. A., Fahnestock, M., Moine, D., Berger, B., Huizinga, J. D., Kunze, W., Mclean, P. G., Bergonzelli, G. E., Collins, S. M., & Verdu, E. F. (2011). The anxiolytic effect of Bifidobacterium longum NCC3001 involves vagal pathways for gut-brain communication. Neurogastroenterology and Motility, 23(12), 1132–1139. https://doi.org/10.1111/j.1365-2982.2011.01796.x

Bland, N. S., & Sale, M. V. (2019). Current challenges: the ups and downs of tACS. In Experimental Brain Research (Vol. 237, Issue 12, pp. 3071–3088). Springer. https://doi.org/10.1007/s00221-019-05666-0

Boggio, P. S., Campanhã, C., Valasek, C. A., Fecteau, S., Pascual-Leone, A., & Fregni, F. (2010). Modulation of decision-making in a gambling task in older adults with transcranial direct current stimulation. European Journal of Neuroscience, 31(3), 593–597. https://doi.org/10.1111/j.1460-9568.2010.07080.x

Boggio, P. S., Zaghi, S., Villani, A. B., Fecteau, S., Pascual-Leone, A., & Fregni, F. (2010). Modulation of risk-taking in marijuana users by transcranial direct current stimulation (tDCS) of the dorsolateral prefrontal cortex (DLPFC). Drug and Alcohol Dependence, 112(3), 220–225. https://doi.org/10.1016/j.drugalcdep.2010.06.019

Bohórquez, D. V, Shahid, R. A., Erdmann, A., Kreger, A. M., Wang, Y., Calakos, N., Wang, F., & Liddle, R. A. (2015). Neuroepithelial circuit formed by innervation of sensory enteroendocrine cells. J. Clin. Invest., 125(2), 782–786. https://doi.org/10.1172/JCI78361DS1

Brand, M., Recknor, E. C., Grabenhorst, F., & Bechara, A. (2007). Decisions under ambiguity and decisions under risk: Correlations with executive functions and comparisons of two different gambling tasks with implicit and explicit rules. Journal of Clinical and Experimental Neuropsychology, 29(1), 86–99. https://doi.org/10.1080/13803390500507196

Brunoni, A. R., Nitsche, M. A., Bolognini, N., Bikson, M., Wagner, T., Merabet, L., Edwards, D. J., Valero-Cabre, A., Rotenberg, A., Pascual-Leone, A., Ferrucci, R., Priori, A., Boggio, P. S., & Fregni, F. (2012). Clinical research with transcranial direct current stimulation (tDCS): Challenges and future directions. Brain Stimulation, 5(3), 175–195. https://doi.org/10.1016/J.BRS.2011.03.002

Brunyé, T. T., & Gardony, A. L. (2017). Eye tracking measures of uncertainty during perceptual decision

making. International Journal of Psychophysiology, 120, 60–68. https://doi.org/10.1016/J.IJPSYCHO.2017.07.008

Brys, M., Fox, M. D., Agarwal, S., Biagioni, M., Dacpano, G., Kumar, P., Pirraglia, E., Chen, R., Wu, A., Fernandez, H., Shukla, A. W., Lou, J. S., Gray, Z., Simon, D. K., di Rocco, A., & Pascual-Leone, A. (2016). Multifocal repetitive TMS for motor and mood symptoms of Parkinson disease. Neurology, 87(18), 1907–1915. https://doi.org/10.1212/WNL.0000000000003279

Burke, C. J., & Tobler, P. N. (2011). Coding of reward probability and risk by single neurons in animals. Frontiers in Neuroscience, 0(OCT), 121. https://doi.org/10.3389/fnins.2011.00121

Camerer, C., Loewenstein, G., & Prelec, D. (2005). Neuroeconomics: How neuroscience can inform economics. Journal of Economic Literature, 43(1), 9–64. https://doi.org/10.1257/0022051053737843

Carabotti, M., Scirocco, A., Maselli, M. A., & Severi, C. (2015). The gut-brain axis: Interactions between enteric microbiota, central and enteric nervous systems. Annals of Gastroenterology, 28(2).

Carlén, M. (2017). What constitutes the prefrontal cortex? Science, 358(6362), 478–482. https://doi.org/10.1126/SCIENCE.AAN8868/SUPPL_FILE/AAN8868S5.MP4

Cavanagh, J. F., & Frank, M. J. (2014). Frontal theta as a mechanism for cognitive control. Trends in Cognitive Sciences, 18(8), 414–421. https://doi.org/10.1016/j.tics.2014.04.012

Charness, G., Gneezy, U., & Imas, A. (2013). Journal of Economic Behavior & Organization Experimental methods : Eliciting risk preferences. Journal of Economic Behavior and Organization, 87, 43–51. https://doi.org/10.1016/j.jebo.2012.12.023

Cho, S. S., Ko, J. H., Pellecchia, G., van Eimeren, T., Cilia, R., & Strafella, A. P. (2010). Continuous theta burst stimulation of right dorsolateral prefrontal cortex induces changes in impulsivity level. Brain Stimulation, 3(3), 170–176. https://doi.org/10.1016/j.brs.2009.10.002

Cho, S. S., Koshimori, Y., Aminian, K., Obeso, I., Rusjan, P., Lang, A. E., Daskalakis, Z. J., Houle, S., & Strafella, A. P. (2015). Investing in the future: Stimulation of the medial prefrontal cortex reduces discounting of delayed rewards. Neuropsychopharmacology, 40(3), 546–553. https://doi.org/10.1038/npp.2014.211

Chuang, Y., & Schechter, L. (2015). Stability of experimental and survey measures of risk, time, and social preferences: A review and some new results. Journal of Development Economics, 117, 151–170. https://doi.org/10.1016/j.jdeveco.2015.07.008

Clark, L., Bechara, A., Damasio, H., Aitken, M. R. F., & Sahakian, B. J. (2017). Differential effects of insular and ventromedial prefrontal cortex lesions on risky decision-making. November. https://doi.org/10.1093/brain/awn066

Cohen, M. X., & Donner, T. H. (2013). Midfrontal conflict-related theta-band power reflects neural oscillations that predict behavior. Journal of Neurophysiology, 110(12), 2752–2763. https://doi.org/10.1152/JN.00479.2013/ASSET/IMAGES/LARGE/Z9K0241322250006.JPEG

Corp, D. T., Bereznicki, H. G. K., Clark, G. M., Youssef, G. J., Fried, P. J., Jannati, A., Davies, C. B., Gomes-Osman, J., Stamm, J., Chung, S. W., Bowe, S. J., Rogasch, N. C., Fitzgerald, P. B., Koch, G., di Lazzaro, V., Pascual-Leone, A., & Enticott, P. G. (2020). Large-scale analysis of interindividual variability in theta-burst stimulation data: Results from the 'Big TMS Data Collaboration.' Brain Stimulation, 13(5), 1476–1488. https://doi.org/10.1016/j.brs.2020.07.018

Csermely, T., & Rabas, A. (2016). How to reveal people's preferences: Comparing time consistency and

predictive power of multiple price list risk elicitation methods. Journal of Risk and Uncertainty, 53(2–3), 107–136. https://doi.org/10.1007/s11166-016-9247-6

Cui, Y., Fang, H., Bao, C., Geng, W., Yu, F., & Li, X. (2022). Efficacy of Transcranial Magnetic Stimulation for Reducing Suicidal Ideation in Depression: A Meta-Analysis. Frontiers in Psychiatry, 12, 764183. https://doi.org/10.3389/FPSYT.2021.764183/FULL

Damasio, A. (2019). The strange order of things: Life, feeling, and the making of cultures. Vintage.

Dantas, A. M., Jiao, P., Sack, A., Bruggen, E., & Schuhmann, T. (2021, October 25). A gut feeling: how your gut and brain changes your risk and time preferences. Mendeley Data. https://doi.org/10.17632/nbz385mhny.1

Dantas, A. M., Sack, A. T., Bruggen, E., Jiao, P., & Schuhmann, T. (2021). Reduced risk-taking behavior during frontal oscillatory theta-band neurostimulation. Brain Research, 1759, 147365. https://doi.org/10.1016/j.brainres.2021.147365

Dantas, A. M., Sack, A. T., Bruggen, E., Jiao, P., & Schuhmann, T. (2022). The effects of probiotics on risk and time preferences. Scientific Reports, 12(1), 1–10. https://doi.org/10.1038/s41598-022-16251-x

Das, T. K., & Teng, B.-S. (2001). Strategic risk behaviour and its temporalities: between risk propensity and decision context. Journal of Management Studies, 38(4), 515–534. https://doi.org/10.1111/1467-6486.00247

de Araujo, I. E., Ferreira, J. G., Tellez, L. A., Ren, X., & Yeckel, C. W. (2012). The gut-brain dopamine axis: A regulatory system for caloric intake. Physiology and Behavior, 106(3), 394–399. https://doi.org/10.1016/j.physbeh.2012.02.026

Dinan, T. G., Stanton, C., & Cryan, J. F. (2013). Psychobiotics: A novel class of psychotropic. Biological Psychiatry, 74(10), 720–726. https://doi.org/10.1016/j.biopsych.2013.05.001

Dippel, G., Chmielewski, W., Mückschel, M., & Beste, C. (2016). Response mode-dependent differences in neurofunctional networks during response inhibition: an EEG-beamforming study. Brain Structure and Function, 221(8), 4091–4101. https://doi.org/10.1007/s00429-015-1148-y

Donkers, B., Lourenço, C. J. S., Dellaert, B. G. C., & Goldstein, D. G. (2013). Using Preferred Outcome Distributions to Estimate Value and Probability Weighting Functions in Decisions under Risk. SSRN Electronic Journal. https://doi.org/10.2139/ssrn.2262354

Drichoutis, A. C., & Lusk, J. L. (2016). What can multiple price lists really tell us about risk preferences? Journal of Risk and Uncertainty, 53(2–3), 89–106. https://doi.org/10.1007/s11166-016-9248-5

Driver, J., Blankenburg, F., Bestmann, S., Vanduffel, W., & Ruff, C. C. (2009). Concurrent brain-stimulation and neuroimaging for studies of cognition. Trends in Cognitive Sciences, 13(7), 319–327. https://doi.org/10.1016/J.TICS.2009.04.007

Duecker, F., & Sack, A. T. (2015). The hybrid model of attentional control: New insights into hemispheric asymmetries inferred from TMS research. Neuropsychologia, 74, 21–29. https://doi.org/10.1016/j.neuropsychologia.2014.11.023

Eckel, C. C., & Wilson, R. K. (2004). Is trust a risky decision? Journal of Economic Behavior and Organization, 55(4 SPEC.ISS.), 447–465. https://doi.org/10.1016/j.jebo.2003.11.003

Ekhtiari, H., Tavakoli, H., Addolorato, G., Baeken, C., Bonci, A., Campanella, S., Castelo-Branco, L., Challet-Bouju, G., Clark, V. P., Claus, E., Dannon, P. N., del Felice, A., den Uyl, T., Diana, M., di Giannantonio,

M., Fedota, J. R., Fitzgerald, P., Gallimberti, L., Grall-Bronnec, M., … Hanlon, C. A. (2019). Transcranial electrical and magnetic stimulation (tES and TMS) for addiction medicine: A consensus paper on the present state of the science and the road ahead. Neuroscience & Biobehavioral Reviews, 104, 118–140. https://doi.org/10.1016/J.NEUBIOREV.2019.06.007

Enders, G. (2018). Gut: The Inside Story of Our Body's Most Underrated Organ (Revised Ed). Greystone Books Ltd.

Enokibara, M., Trevizol, A., Shiozawa, P., & Cordeiro, Q. (2016). Establishing an effective TMS protocol for craving in substance addiction: Is it possible? The American Journal on Addictions, 25(1), 28–30. https://doi.org/10.1111/AJAD.12309

Epper, T. F., & Fehr-Duda, H. (2012). The Missing Link: Unifying Risk Taking and Time Discounting. SSRN Electronic Journal. https://doi.org/10.2139/ssrn.2175461

Fecteau, S., Agosta, S., Hone-blanchet, A., Fregni, F., Boggio, P., Ciraulo, D., & Pascual-leone, A. (2014). Modulation of smoking and decision-making behaviors with transcranial direct current stimulation in tobacco smokers : A preliminary study. Drug and Alcohol Dependence, 140, 78–84. https://doi.org/10.1016/j.drugalcdep.2014.03.036

Fecteau, S., Knoch, D., Fregni, F., Sultani, N., Boggio, P., & Pascual-leone, A. (2007). Diminishing Risk-Taking Behavior by Modulating Activity in the Prefrontal Cortex : A Direct Current Stimulation Study. 27(46), 12500–12505. https://doi.org/10.1523/JNEUROSCI.3283-07.2007

Fecteau, S., Pascual-Leone, A., Zald, D. H., Liguori, P., Théoret, H., Boggio, P. S., Fregni, F., The, H., Boggio, P. S., Fregni, F., & Ht, C. (2007). Activation of Prefrontal Cortex by Transcranial Direct Current Stimulation Reduces Appetite for Risk during Ambiguous Decision Making. Journal of Neuroscience, 27(23), 6212–6218. https://doi.org/10.1523/JNEUROSCI.0314-07.2007

Figner, B., Knoch, D., Johnson, E. J., Krosch, A. R., Lisanby, S. H., Fehr, E., & Weber, E. U. (2010). Lateral prefrontal cortex and self-control in intertemporal choice. Nature Neuroscience, 13(5), 538–539. https://doi.org/10.1038/nn.2516

Floden, D., Alexander, M. P., Kubu, C. S., Katz, D., & Stuss, D. T. (2008). Impulsivity and risk-taking behavior in focal frontal lobe lesions. Neuropsychologia, 46(1), 213–223. https://doi.org/10.1016/j.neuropsychologia.2007.07.020

Foster, J. A., Rinaman, L., & Cryan, J. F. (2017). Stress & the gut-brain axis: Regulation by the microbiome. Neurobiology of Stress, 7, 124–136. https://doi.org/10.1016/j.ynstr.2017.03.001

Galvan, A., Hare, T. A., Parra, C. E., Penn, J., Voss, H., Glover, G., & Casey, B. J. (2006). Earlier Development of the Accumbens Relative to Orbitofrontal Cortex Might Underlie Risk-Taking Behavior in Adolescents. 26(25), 6885–6892. https://doi.org/10.1523/JNEUROSCI.1062-06.2006

Ganz, J. (2021). Revealing the complexity of the gut's brain. In Nature Neuroscience (Vol. 24, Issue 1, pp. 1–2). Nature Research. https://doi.org/10.1038/s41593-020-00769-2

Gazzaniga, M. S., Ivry. R. B., & Mangun, G. R. (2002). Cognitive neuroscience: the biology of the mind (2nd ed.). Norton.

Gehring, W. J., & Willoughby, A. R. (2002). The medial frontal cortex and the rapid processing of monetary gains and losses. Science, 295(5563), 2279–2282. https://doi.org/10.1126/SCIENCE.1066893/ASSET/5F1FF110-03AE-4F8A-AE77-C260E9428914/ASSETS/GRAPHIC/SE1120294004.JPEG

Gianotti, L. R. R., Knoch, D., Faber, P. L., Lehmann, D., Pascual-Marqui, R. D., Diezi, C., Schoch, C., Eisenegger, C., & Fehr, E. (2009). Tonic activity level in the right prefrontal cortex predicts individuals' risk taking. Psychological Science, 20(1), 33–38. https://doi.org/10.1111/j.1467-9280.2008.02260.x

Gilmore, C. S., Dickmann, P. J., Nelson, B. G., Lamberty, G. J., & Lim, K. O. (2018). Transcranial Direct Current Stimulation (tDCS) paired with a decision-making task reduces risk-taking in a clinically impulsive sample. Brain Stimulation, 11(2), 302–309. https://doi.org/10.1016/j.brs.2017.11.011

Guo, H., Zhang, Z., Da, S., Sheng, X., & Zhang, X. (2018). High-definition transcranial direct current stimulation (HD-tDCS) of left dorsolateral prefrontal cortex affects performance in Balloon Analogue Risk Task (BART). Brain and Behavior, 8(2), e00884. https://doi.org/10.1002/brb3.884

Guse, B., Falkai, P., & Wobrock, T. (2010). Cognitive effects of high-frequency repetitive transcranial magnetic stimulation: A systematic review. Journal of Neural Transmission, 117(1), 105–122. https://doi.org/10.1007/S00702-009-0333-7/TABLES/4

Heise, K. F., Monteiro, T. S., Leunissen, I., Mantini, D., & Swinnen, S. P. (2019). Distinct online and offline effects of alpha and beta transcranial alternating current stimulation (tACS) on continuous bimanual performance and task-set switching. Scientific Reports, 9(1). https://doi.org/10.1038/s41598-019-39900-0

Het, S., Rohleder, N., Schoofs, D., Kirschbaum, C., & Wolf, O. T. (2009). Neuroendocrine and psychometric evaluation of a placebo version of the "Trier Social Stress Test." Psychoneuroendocrinology, 34(7), 1075–1086. https://doi.org/10.1016/j.psyneuen.2009.02.008

Hoban, A. E., Stilling, R. M., Ryan, F. J., Shanahan, F., Dinan, T. G., Claesson, M. J., Clarke, G., & Cryan, J. F. (2016). Regulation of prefrontal cortex myelination by the microbiota. Translational Psychiatry, 6(4), e774–e774. https://doi.org/10.1038/tp.2016.42

Houser, D., Schunk, D., & Winter, J. (2010). Distinguishing trust from risk: An anatomy of the investment game. Journal of Economic Behavior and Organization, 74(1–2), 72–81. https://doi.org/10.1016/j.jebo.2010.01.002

Jongkees, B. J., & Colzato, L. S. (2016). Spontaneous eye blink rate as predictor of dopamine-related cognitive function—A review. In Neuroscience and Biobehavioral Reviews (Vol. 71, pp. 58–82). Elsevier Ltd. https://doi.org/10.1016/j.neubiorev.2016.08.020

Josef, A. K., Richter, D., Samanez-Larkin, G. R., Wagner, G. G., Hertwig, R., & Mata, R. (2016). Stability and change in risk-taking propensity across the adult life span. Journal of Personality and Social Psychology, 111(3), 430–450. https://doi.org/10.1037/pspp0000090

Kaminski, J. A., Korb, F. M., Villringer, A., & Ott, D. V. M. (2011). Transcranial Magnetic Stimulation Intensities in Cognitive Paradigms. PLOS ONE, 6(9), e24836. https://doi.org/10.1371/JOURNAL.PONE.0024836

Karmarkar, U. R., & Yoon, C. (2016). Consumer neuroscience: Advances in understanding consumer psychology. In Current Opinion in Psychology (Vol. 10, pp. 160–165). Elsevier. https://doi.org/10.1016/j.copsyc.2016.01.010

Khaleghi, A., Pirzad Jahromi, G., Zarafshan, H., Mostafavi, S. A., & Mohammadi, M. R. (2020). Effects of transcranial direct current stimulation of prefrontal cortex on risk-taking behavior. In Psychiatry and Clinical Neurosciences (Vol. 74, Issue 9, pp. 455–465). Blackwell Publishing. https://doi.org/10.1111/pcn.13025

Klírová, M., Voráčková, V., Horáček, J., Mohr, P., Jonáš, J., Dudysová, D. U., Kostýlková, L., Fayette, D., Krejčová, L., Baumann, S., Laskov, O., & Novák, T. (2021). Modulating Inhibitory Control Processes Using Individualized High Definition Theta Transcranial Alternating Current Stimulation (HD ϑ-tACS) of the Anterior Cingulate and Medial Prefrontal Cortex. Frontiers in Systems Neuroscience, 0, 25. https://doi.org/10.3389/FNSYS.2021.611507

Knight, F. H. (1921). Risk, uncertainty and profit (Vol. 31). Houghton Mifflin.

Knoch, D., Gianotti, L. R. R., Pascual-leone, A., Treyer, V., Regard, M., Hohmann, M., & Brugger, P. (2006). Disruption of Right Prefrontal Cortex by Low-Frequency Repetitive Transcranial Magnetic Stimulation Induces. 26(24), 6469–6472. https://doi.org/10.1523/JNEUROSCI.0804-06.2006

Kohno, M., Ghahremani, D. G., Morales, A. M., Robertson, C. L., Ishibashi, K., Morgan, A. T., Mandelkern, M. A., & London, E. D. (2015). Risk-taking behavior: Dopamine D2/D3 receptors, feedback, and frontolimbic activity. Cerebral Cortex, 25(1), 236–245. https://doi.org/10.1093/cercor/bht218

Kuhnen, C. M., & Knutson, B. (2005). The Neural Basis of Financial Risk Taking. Neuron, 47, 763–770. https://doi.org/10.1016/j.neuron.2005.08.008

Kuo, H. I., Bikson, M., Datta, A., Minhas, P., Paulus, W., Kuo, M. F., & Nitsche, M. A. (2013). Comparing cortical plasticity induced by conventional and high-definition 4 × 1 ring tDCS: A neurophysiological study. Brain Stimulation, 6(4), 644–648. https://doi.org/10.1016/j.brs.2012.09.010

Lee, J., & Jeong, J. (2013). Correlation of risk-taking propensity with cross-frequency phase–amplitude coupling in the resting EEG. Clinical Neurophysiology, 124(11), 2172–2180. https://doi.org/10.1016/J.CLINPH.2013.05.007

Lejuez, C. W., Read, J. P., Kahler, C. W., Richards, J. B., Ramsey, S. E., Stuart, G. L., Strong, D. R., Brown, R. A., York, N., Ramsey, S. E., Stuart, G. L., & Strong, D. R. (2002). Evaluation of a Behavioral Measure of Risk Taking : The Balloon Analogue Risk Task (BART). 8(2), 75–84. https://doi.org/10.1037//1076-898X.8.2.75

Levasseur-Moreau, J., & Fecteau, S. (2012). Translational application of neuromodulation of decision-making. In Brain Stimulation (Vol. 5, Issue 2, pp. 77–83). Elsevier. https://doi.org/10.1016/j.brs.2012.03.009

Levav, J., & Argo, J. J. (2010). Physical contact and financial risk taking. Psychological Science : A Journal of the American Psychological Society / APS, 21(6), 804–810. https://doi.org/10.1177/0956797610369493

Lighthall, N. R., Mather, M., & Gorlick, M. A. (2009). Acute stress increases sex differences in risk seeking in the Balloon Analogue Risk Task. PLoS ONE, 4(7), e6002. https://doi.org/10.1371/journal.pone.0006002

Logothetis, N. K. (2008). What we can do and what we cannot do with fMRI. Nature 2008 453:7197, 453(7197), 869–878. https://doi.org/10.1038/nature06976

Loo, C. K., Taylor, J. L., Gandevia, S. C., McDarmont, B. N., Mitchell, P. B., & Sachdev, P. S. (2000). Transcranial magnetic stimulation (TMS) in controlled treatment studies: are some "sham" forms active? Biological Psychiatry, 47(4), 325–331. https://doi.org/10.1016/S0006-3223(99)00285-1

Lowe, C. J., Hall, P. A., & Staines, W. R. (2014). The Effects of Continuous Theta Burst Stimulation to the Left Dorsolateral Prefrontal Cortex on Executive Function, Food Cravings, and Snack Food Consumption. Psychosomatic Medicine, 76(7), 503–511. https://doi.org/10.1097/PSY.0000000000000090

Massar, S. A. A., Kenemans, J. L., & Schutter, D. J. L. G. (2014). Resting-state EEG theta activity and risk learning: Sensitivity to reward or punishment? International Journal of Psychophysiology, 91(3), 172–177. https://doi.org/10.1016/j.ijpsycho.2013.10.013

Massar, S. A. A., Rossi, V., Schutter, D. J. L. G., & Kenemans, J. L. (2012). Baseline EEG theta/beta ratio and punishment sensitivity as biomarkers for feedback-related negativity (FRN) and risk-taking. Clinical Neurophysiology, 123(10), 1958–1965. https://doi.org/10.1016/j.clinph.2012.03.005

Mayer, E. A. (2011). Gut feelings: the emerging biology of gut–brain communication. Nature Reviews Neuroscience 2011 12:8, 12(8), 453–466. https://doi.org/10.1038/nrn3071

McDonnell, M. N., & Stinear, C. M. (2017). TMS measures of motor cortex function after stroke: A meta-analysis. Brain Stimulation, 10(4), 721–734. https://doi.org/10.1016/J.BRS.2017.03.008

McNeill, A., Monk, R. L., Qureshi, A. W., Makris, S., & Heim, D. (2018). Continuous Theta Burst Transcranial Magnetic Stimulation of the Right Dorsolateral Prefrontal Cortex Impairs Inhibitory Control and Increases Alcohol Consumption. Cognitive, Affective and Behavioral Neuroscience, 18(6), 1198–1206. https://doi.org/10.3758/s13415-018-0631-3

Messaoudi, M., Lalonde, R., Violle, N., Javelot, H., Desor, D., Nejdi, A., Bisson, J. F., Rougeot, C., Pichelin, M., Cazaubiel, M., & Cazaubiel, J. M. (2011). Assessment of psychotropic-like properties of a probiotic formulation (Lactobacillus helveticus R0052 and Bifidobacterium longum R0175) in rats and human subjects. British Journal of Nutrition, 105(5), 755–764. https://doi.org/10.1017/S0007114510004319

Michel, C. M., & Brunet, D. (2019). EEG source imaging: A practical review of the analysis steps. Frontiers in Neurology, 10(APR), 325. https://doi.org/10.3389/FNEUR.2019.00325/BIBTEX

Milad, M. R., & Quirk, G. J. (2002). Neurons in medial prefrontal cortex signal memory for fear extinction. Nature 2002 420:6911, 420(6911), 70–74. https://doi.org/10.1038/nature01138

Minati, L., Campanhã, C., Critchley, H. D., & Boggio, P. S. (2012). Effects of transcranial direct-current stimulation (tDCS) of the dorsolateral prefrontal cortex (DLPFC) during a mixed-gambling risky decision-making task. Cognitive Neuroscience, 3(2), 80–88. https://doi.org/10.1080/17588928.2011.628382

Ming, X., Chen, N., Ray, C., Brewer, G., Kornitzer, J., & Steer, R. A. (2018). A Gut Feeling. Child Neurology Open, 5(6408), 2329048X1878679. https://doi.org/10.1177/2329048X18786799

Mohr, P. N. C., Biele, G., & Heekeren, H. R. (2010). Neural processing of risk. Journal of Neuroscience, 30(19), 6613–6619. https://doi.org/10.1523/JNEUROSCI.0003-10.2010

Nitsche, M. A., Cohen, L. G., Wassermann, E. M., Priori, A., Lang, N., Antal, A., Paulus, W., Hummel, F., Boggio, P. S., Fregni, F., & Pascual-Leone, A. (2008). Transcranial direct current stimulation: State of the art 2008. Brain Stimulation, 1(3), 206–223. https://linkinghub.elsevier.com/retrieve/pii/S1935861X08000405

O'Mahony, S. M., Clarke, G., Borre, Y. E., Dinan, T. G., & Cryan, J. F. (2015). Serotonin, tryptophan metabolism and the brain-gut-microbiome axis. Behavioural Brain Research, 277, 32–48. https://doi.org/10.1016/j.bbr.2014.07.027

Oostenveld, R., Fries, P., Maris, E., & Schoffelen, J.-M. (2011). FieldTrip: Open Source Software for Advanced Analysis of MEG, EEG, and Invasive Electrophysiological Data. Computational Intelligence and Neuroscience, 2011, 1–9. https://doi.org/10.1155/2011/156869

Parkinson, B., Phiri, N., & Simons, G. (2012). Bursting with anxiety: adult social referencing in an interpersonal balloon analogue risk task (BART). Emotion (Washington, D.C.), 12(4), 817–826. https://doi.org/10.1037/A0026434

Paulus, M. P., Rogalsky, C., Simmons, A., Feinstein, J. S., & Stein, M. B. (2003). Increased activation in the right insula during risk-taking decision making is related to harm avoidance and neuroticism. NeuroImage, 19(4), 1439–1448. https://doi.org/10.1016/S1053-8119(03)00251-9

Perera, T., George, M. S., Grammer, G., Janicak, P. G., Pascual-Leone, A., & Wirecki, T. S. (2016). The Clinical TMS Society Consensus Review and Treatment Recommendations for TMS Therapy for Major Depressive Disorder. Brain Stimulation, 9(3), 336–346. https://doi.org/10.1016/J.BRS.2016.03.010

Pinner, J. F. L., & Cavanagh, J. F. (2017). Frontal theta accounts for individual differences in the cost of conflict on decision making. Brain Research, 1672, 73–80. https://doi.org/10.1016/j.brainres.2017.07.026

Plassmann, H., Venkatraman, V., Huettel, S., & Yoon, C. (2015). Consumer neuroscience: Applications, challenges, and possible solutions. Journal of Marketing Research, 52(4), 427–435. https://doi.org/10.1509/jmr.14.0048

Polanía, R., Nitsche, M. A., Korman, C., Batsikadze, G., & Paulus, W. (2012). The Importance of Timing in Segregated Theta Phase-Coupling for Cognitive Performance. Current Biology, 22(14), 1314–1318. https://doi.org/10.1016/J.CUB.2012.05.021

Polanía, R., Nitsche, M. A., & Ruff, C. C. (2018). Studying and modifying brain function with non-invasive brain stimulation. In Nature Neuroscience (Vol. 21, Issue 2, pp. 174–187). Nature Publishing Group. https://doi.org/10.1038/s41593-017-0054-4

Polezzi, D., Sartori, G., Rumiati, R., Vidotto, G., & Daum, I. (2010). Brain correlates of risky decision-making. NeuroImage, 49(2), 1886–1894. https://doi.org/10.1016/J.NEUROIMAGE.2009.08.068

Pollak, Y., Dekkers, T. J., Shoham, R., & Huizenga, H. M. (2019). Risk-Taking Behavior in Attention Deficit/Hyperactivity Disorder (ADHD): a Review of Potential Underlying Mechanisms and of Interventions. In Current Psychiatry Reports (Vol. 21, Issue 5, pp. 1–11). Current Medicine Group LLC 1. https://doi.org/10.1007/s11920-019-1019-y

Rao, H., Korczykowski, M., Pluta, J., Hoang, A., & Detre, J. A. (2008). Neural correlates of voluntary and involuntary risk taking in the human brain: An fMRI Study of the Balloon Analog Risk Task (BART). NeuroImage, 42(2), 902–910. https://doi.org/10.1016/j.neuroimage.2008.05.046

Rilling, J. K., & Sanfey, A. G. (2011). The neuroscience of social decision-making. Annual Review of Psychology, 62, 23–48. https://doi.org/10.1146/annurev.psych.121208.131647

Rogers, R. D. R., Everitt, B. J., Baldacchino, A., Blackshaw, A. J., Swainson, R., Wynne, K., Baker, N. B., Hunter, J., Carthy, T., Booker, E., London, M., Deakin, J. F. W., Sahakian, B. J., & Robbins, T. W. (1999). Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan-depleted normal volunteersEvidence for monoaminergic mechanisms. ..., 20(4), 322–339. https://doi.org/10.1016/S0893-133X(98)00091-8

Rossi, S., Hallett, M., Rossini, P. M., Pascual-Leone, A., Avanzini, G., Bestmann, S., Berardelli, A., Brewer, C., Canli, T., Cantello, R., Chen, R., Classen, J., Demitrack, M., di Lazzaro, V., Epstein, C. M., George, M. S., Fregni, F., Ilmoniemi, R., Jalinous, R., … Ziemann, U. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research.

Clinical Neurophysiology, 120(12), 2008–2039. https://doi.org/10.1016/J.CLINPH.2009.08.016

Rudorf, S., & Hare, T. A. (2014). Interactions between dorsolateral and ventromedial prefrontal cortex underlie context-dependent stimulus valuation in goal-directed choice. Journal of Neuroscience, 34(48), 15988–15996. https://doi.org/10.1523/JNEUROSCI.3192-14.2014

Sarkar, A., Lehto, S. M., Harty, S., Dinan, T. G., Cryan, J. F., & Burnet, P. W. J. (2016). Psychobiotics and the Manipulation of Bacteria–Gut–Brain Signals. Trends in Neurosciences, 39(11), 763–781. https://doi.org/10.1016/j.tins.2016.09.002

Schiller, B., Gianotti, L. R. R., Nash, K., & Knoch, D. (2014). Individual differences in inhibitory control - Relationship between baseline activation in lateral PFC and an electrophysiological index of response inhibition. Cerebral Cortex, 24(9), 2430–2435. https://doi.org/10.1093/cercor/bht095

Schonberg, T., Fox, C. R., & Poldrack, R. A. (2011). Mind the gap : bridging economic and naturalistic risk-taking with cognitive neuroscience. Trends in Cognitive Sciences, 15(1), 11–19. https://doi.org/10.1016/j.tics.2010.10.002

Schulte-Mecklenbeck, M., Johnson, J. G., Böckenholt, U., Goldstein, D. G., Russo, J. E., Sullivan, N. J., & Willemsen, M. C. (2017). Process-Tracing Methods in Decision Making: On Growing Up in the 70s. Current Directions in Psychological Science, 26(5), 442–450. https://doi.org/10.1177/0963721417708229/ASSET/IMAGES/LARGE/10.1177_0963721417708229-FIG1.JPEG

Sela, T., Kilim, A., & Lavidor, M. (2012). Transcranial alternating current stimulation increases risk-taking behavior in the Balloon Analog Risk Task. Frontiers in Neuroscience, 6(FEB), 1–11. https://doi.org/10.3389/fnins.2012.00022

Shiv, B., Bechara, A., Levin, I., Alba, J. W., Bettman, J. R., Dube, L., Isen, A., Mellers, B., Smidts, A., Grant, S. J., & Mcgraw, A. P. (2005). Decision neuroscience. Marketing Letters, 16(3–4), 375–386. https://doi.org/10.1007/s11002-005-5899-8

Smidts, A., Hsu, M., Sanfey, A. G., Boksem, M. A. S., Ebstein, R. B., Huettel, S. A., Kable, J. W., Karmarkar, U. R., Kitayama, S., Knutson, B., Liberzon, I., Lohrenz, T., Stallen, M., & Yoon, C. (2014). Advancing consumer neuroscience. Marketing Letters, 25(3), 257–267. https://doi.org/10.1007/s11002-014-9306-1

Smulders, F. T. Y., ten Oever, S., Donkers, F. C. L., Quaedflieg, C. W. E. M., & van de Ven, V. (2018). Single-trial log transformation is optimal in frequency analysis of resting EEG alpha. European Journal of Neuroscience, 48(7), 2585–2598. https://doi.org/10.1111/ejn.13854

Studer, B., Pedroni, A., & Rieskamp, J. (2013). Predicting Risk-Taking Behavior from Prefrontal Resting- State Activity and Personality. PLoS ONE, 8(10), 1–8. https://doi.org/10.1371/journal.pone.0076861

Thut, G., Miniussi, C., & Gross, J. (2012). The Functional Importance of Rhythmic Activity in the Brain. Current Biology, 22(16), R658–R663. https://doi.org/10.1016/J.CUB.2012.06.061

Thut, G., & Pascual-Leone, A. (2010). A review of combined TMS-EEG studies to characterize lasting effects of repetitive TMS and assess their usefulness in cognitive and clinical neuroscience. In Brain Topography (Vol. 22, Issue 4, pp. 219–232). Springer. https://doi.org/10.1007/s10548-009-0115-4

Trimpop, R. (1994). The psychology of risk taking behavior. North-Holland.

Vickerstaff, S., & Cox, J. (2005). Retirement and Risk: The Individualisation of Retirement Experiences? The Sociological Review, 53(1), 77–95. https://doi.org/10.1111/j.1467-954X.2005.00504.x

Vorhold, V., Giessing, C., Wiedemann, P. M., Schütz, H., Gauggel, S., & Fink, G. R. (2007). The neural basis of risk ratings: Evidence from a functional magnetic resonance imaging (fMRI) study. Neuropsychologia, 45(14), 3242–3250. https://doi.org/10.1016/J.NEUROPSYCHOLOGIA.2007.06.023

Vosskuhl, J., Mutanen, T. P., Neuling, T., Ilmoniemi, R. J., & Herrmann, C. S. (2020). Signal-Space Projection Suppresses the tACS Artifact in EEG Recordings. Frontiers in Human Neuroscience, 14, 525. https://doi.org/10.3389/fnhum.2020.536070

Wokke, M. E., Cleeremans, A., & Ridderinkhof, K. R. (2017). Sure I'm Sure: Prefrontal Oscillations Support Metacognitive Monitoring of Decision Making. Journal of Neuroscience, 37(4), 781–789. https://doi.org/10.1523/JNEUROSCI.1612-16.2016

Wölbert, E., & Riedl, A. (2013). Measuring Time and Risk Preferences: Reliability, Stability, Domain Specificity. www.RePEc.org

Xue, G., Lu, Z., Levin, I. P., & Bechara, A. (2010). The impact of prior risk experiences on subsequent risky decision-making: The role of the insula. NeuroImage, 50(2), 709–716. https://doi.org/10.1016/j.neuroimage.2009.12.097

Yamada, Y., & Sumiyoshi, T. (2021). Neurobiological Mechanisms of Transcranial Direct Current Stimulation for Psychiatric Disorders; Neurophysiological, Chemical, and Anatomical Considerations. Frontiers in Human Neuroscience, 15, 21. https://doi.org/10.3389/FNHUM.2021.631838/BIBTEX

Yazdi, K., Rumetshofer, T., Gnauer, M., Csillag, D., Rosenleitner, J., & Kleiser, R. (2019). Neurobiological processes during the Cambridge gambling task. Behavioural Brain Research, 356, 295–304. https://doi.org/10.1016/j.bbr.2018.08.017

Yeung, N., & Sanfey, A. G. (2004). Independent Coding of Reward Magnitude and Valence in the Human Brain. Journal of Neuroscience, 24(28), 6258–6264. https://doi.org/10.1523/JNEUROSCI.4537-03.2004

Zack, M., Cho, S. S., Parlee, J., Jacobs, M., Li, C., Boileau, I., & Strafella, A. (2016). Effects of High Frequency Repeated Transcranial Magnetic Stimulation and Continuous Theta Burst Stimulation on Gambling Reinforcement, Delay Discounting, and Stroop Interference in Men with Pathological Gambling. Brain Stimulation, 9(6), 867–875. https://doi.org/10.1016/j.brs.2016.06.003

THE CODE

PART I

THETA-BAND OSCILLATIONS AND COGNITIVE CONTROL

2

REDUCED RISK-TAKING BEHAVIOR DURING FRONTAL OSCILLATORY THETA BAND NEUROSTIMULATION

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ABSTRACT

Most of our decisions involve a certain degree of risk regarding the outcomes of our choices. People vary in the way they make decisions, resulting in different levels of risk-taking behavior. These differences have been linked to prefrontal theta-band activity. However, a direct functional relationship between prefrontal theta-band activity and risk-taking has not yet been demonstrated. We used noninvasive brain stimulation to test the functional relevance of prefrontal oscillatory theta activity for the regulatory control of risk-taking behavior.

In a within-subject experiment, 31 healthy participants received theta (6.5 Hertz [Hz]), gamma (40 Hz), and sham transcranial alternating current stimulation (tACS) over the left prefrontal cortex (lPFC). During stimulation, participants completed a task assessing their risk-taking behavior as well as response times and sensitivity to value and outcome probabilities. Electroencephalography (EEG) was recorded before and immediately after stimulation to investigate possible long-lasting stimulation effects.

Theta-band, but not gamma band or sham, tACS led to a significant reduction in risk-taking behavior, indicating a frequency-specific effect of prefrontal brain stimulation on the modulation of risk-taking behavior. Moreover, theta-band stimulation led to increased response times and decreased sensitivity to reward values. EEG data analyses did not show an offline increase in power in the stimulated frequencies after the stimulation protocol. These findings provide direct empirical evidence for the effects of prefrontal theta-band stimulation on behavioral risk-taking regulation.

KEYWORDS: TACS, RISK-TAKING BEHAVIOR, THETA ACTIVITY, THETA FREQUENCY, DECISION NEUROSCIENCE

2.1 INTRODUCTION

Human decision-making often includes a certain degree of risk regarding its outcomes and outcome probabilities. Take, for example, financial investments, driving above the speed limit, or simply trying a new cuisine. In all of these situations, and many others, the outcomes of our decisions and actions cannot be predicted with absolute certainty. A decision-maker exhibits risk-taking behavior in these situations. Risk-taking is inevitable and may not only have (un)desired personal but also social and economic impacts (Trimpop, 1994). Therefore, the regulatory control of risk-taking behavior is of utmost importance for human decision-making.

During decision-making under risk, a complex mechanism is at work. This mechanism codes and flexibly evaluates the context, outcome probabilities, and previous information to define the optimal level of risk to be taken (Kuhnen and Knutson, 2005). Despite what is expected from pure rational models, risk-taking behavior is not consistent across different contexts, and the optimal decision is often rejected (Brand et al., 2007). These inconsistencies are likely a consequence of the complexity of the neural mechanisms involved in risk-taking behavior and the control thereof, which have been extensively explored by previous studies (e.g., 3–6). Namely, risk-taking behavior is the result of a complex interplay between emotional responses to possibilities of reward (limbic activity) and the inhibition of such responses via the activation of frontal control regions (Floden et al., 2008). Among these, the ventromedial prefrontal cortex (VMPFC) and dorsolateral prefrontal cortex (DLPFC) are critical areas responsible for signaling the need for strategy adjustment and executive control, respectively (Galvan et al., 2006). However, the exact mechanism underlying such signaling processes remains unclear.

Electroencephalography (EEG) studies have shown that participants with a higher theta power (4–8 Hertz [Hz]) in the right prefrontal cortex (rPFC) compared to the left, i.e., a higher frontal theta-band asymmetry, displayed more risk-taking behavior during gambling tasks (Gianotti et al., 2009; Studer et al., 2013a). Recent literature confirms the inverse relationship between risk-taking behavior and frontal theta power, where more risk aversion is observed in participants with higher frontal theta power and vice-versa (Schmidt et al., 2019b, 2018). Furthermore, other studies show a positive correlation between error detection, cognitive control, and increased right VMPFC theta power (Gallagher et al., 2009).

Moreover, theta oscillations are involved in neural network communication when cognitive control is required (Cavanagh and Frank, 2014). Prefrontal theta oscillations may therefore represent part of the signaling mechanism by which the VPMFC recruits the DLPFC in case recruitment of regulatory mechanisms is needed upon the detection of a risky context. However, although these EEG studies indicate that theta oscillations

are related to risk-taking behavior, the functional behavioral relevance of this oscillatory pattern in the regulation of risk-taking has yet not been shown.

Noninvasive brain stimulation, such as transcranial alternating current stimulation (tACS), offers the possibility of inducing temporary oscillatory patterns in specific brain regions by applying changing electric currents on the scalp, transiently modulating brain activity. This allows the probing of the relationship between frequency patterns and behavioral responses (Reato et al., 2013a). To investigate the role of theta-band frontal asymmetry in risk-taking behavior, Sela and colleagues (2012) applied theta-band tACS over the right and left DLPFC while participants performed the Balloon Analog Risk Task. After left, but not right, DLPFC theta-band stimulation, an increase in risk-taking behavior was found. This was not in line with prior EEG studies hypothesizing that right DLPFC stimulation increases risk-taking behavior by increasing frontal asymmetry, while left DLPFC tACS reduces risk-taking behavior due to an increase in theta-band activity in the left hemisphere and consequent asymmetry reduction (Gianotti et al., 2009; Studer et al., 2013a). Sela and colleagues (2010) speculated that their findings may be due to a disruption of interhemispheric balance in participants' natural frontal asymmetry (Sela et al., 2012). The authors were not able to make conclusions about the frequency specificity of the stimulation as no control frequencies had been applied (Feurra et al., 2012). Moreover, they opted for using the Balloon Analog Task to estimate risk. This task mostly measures impulsivity and evaluates uncertainty rather than risk, which is a different economic construct (Lejuez et al., 2002) since the probabilities are not explicit to participants.

The present study aims at investigating this functional relationship between frontal theta-band oscillations and risk-taking behavior. Although previous studies (Gianotti et al., 2009; Studer et al., 2013b) have shown a correlation between resting-state frontal theta-band asymmetry and risk-taking behavior, no direct causal relationship between theta-band activity and risk-taking behavior regulation has thus far been shown. We therefore applied tACS to the left DLPFC in theta-band (6.5 Hz) while participants performed a risk-taking task to affect frontal theta-band activity and, as proposed by Sela and colleagues (2012), disrupt frontal theta-band asymmetry. Moreover, we applied gamma band (40 Hz) tACS and sham stimulation as controls. We chose gamma band tACS as a control frequency as it has not been linked to risk-taking behavior thus far. We also implemented a new behaviorally controlled risk-taking protocol paired with financial incentives for more robust measures of risk-taking behavior.

Considering that the EEG recording during tACS protocols is still a suboptimal option (Bland and Sale, 2019), we used EEG recordings before and immediately after the transcranial brain stimulation to monitor possible long-lasting power changes in the stimulated frequencies. These measurements aimed to investigate a possible functional

relationship between electrophysiological effects and behavioral results.

We hypothesized that, compared to sham and gamma band stimulation, theta-band stimulation to the left DLPFC decreases risk-taking behavior, confirming the central regulatory role of theta frequencies on the electrophysiological mechanism underlying the modulation of risk-taking behavior (Başar et al., 2001; Gianotti et al., 2009).

To test this hypothesis, we used a within-subjects design in which participants went through three different tACS protocols. In each session, participants received either theta (6.5 Hz), gamma (40 Hz), or sham stimulation. During the period of stimulation, participants were asked to play a computer gambling game in which they had to opt between two different bets with various payoffs and probabilities of winning, named the Maastricht Gambling Task (MGT). EEG recordings were performed before and after the stimulation period for three minutes in each block. More details of the experimental design and procedure can be found in Section 2.2.

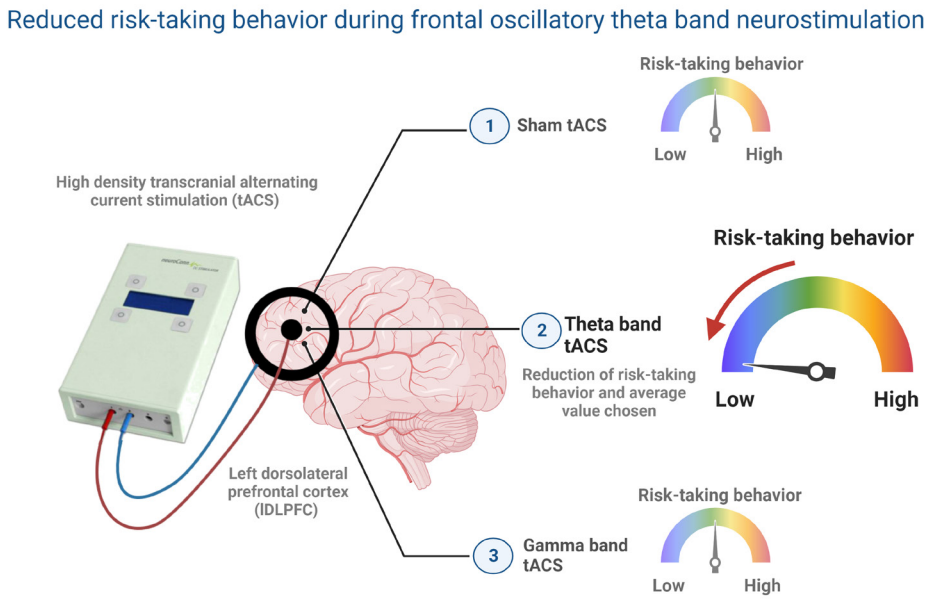

Figure 2.1 – Graphical abstract

2.2 METHODS

2.2.1 Sample

Thirty-two healthy, right-handed students (16 female, mean age 23.8 years, range 18–31 years, SD = 3.45) participated in this study. All participants had normal or corrected-to-normal vision and gave written informed consent after being introduced to the experiment. They were screened for tACS safety, following the recommended procedures of Antal and colleagues (2017) (Antal et al., 2017), screening for, e.g., skin diseases, implants, neurological disorders, pregnancy, and medication.

The study was approved by the Ethics Review Committee Psychology and Neuroscience (ERCPN) of Maastricht University, The Netherlands (ERCPN 188_07_02_2018). Participants were compensated, in the form of vouchers with monetary value, based on the choices they made and luck in the risk-taking task and for participating in the experiment. The stimulation was well tolerated by 31 out of 32 participants. One participant reported skin redness in the area of the stimulation after participating in session 1 and therefore decided to stop participation in the experiment. The results of this participant were excluded from the analyses.

2.2.2 Procedure

Each participant received theta-band (6.5 Hz), gamma band (40 Hz), and sham tACS in three separate sessions. The sessions were separated by an average of seven days (+/-1) to avoid carry-over effects. Figure 2.2 provides an overview of our procedure and experimental design. The order of stimulation conditions (interventions) was randomized across participants.

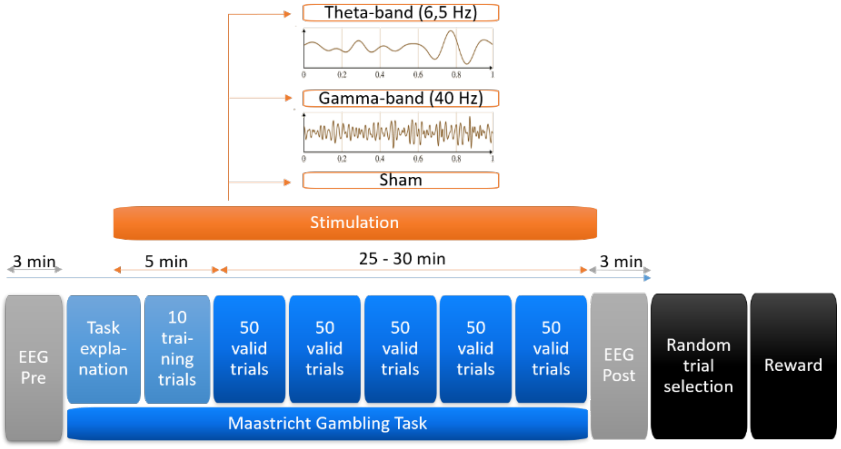

Figure 2.2 – Experimental Design
General experimental procedures showing timing, EEG recordings, task presentation, and experimental conditions.

Participants were invited to the laboratory, where they reviewed the participant information and signed the safety pre-experimental check and the written consent form. In each session, participants were informed about the experimental procedures and task and positioned at the workstation where the tACS and EEG electrodes were placed. EEG was measured before and after the stimulation. During tACS, participants had to perform the computerized MGT.

Participants were informed at the beginning of the session that by the end of it, one random trial of the task would be selected for payment. They were asked to use an online random number generator to determine the number of the trial that would be paid out. This was done in each of the three sessions. During the task, experimental currency was expressed as points. Every point earned in the selected trial was converted to € .10. All participants also received a participation fee of € 7.5 per hour (1.5 hours per session). The payments varied between € 33.75 and € 63.75 and were made only after the third session. All task details and payment rules were explained before the task (Figure 2.2).

2.2.3 Maastricht Gambling Task (MGT)

A customized experimental protocol to elicit and assess risk-taking behavior was developed based on the widely used "risk task" (Rogers et al., 1999), also known as the Cambridge Gambling Task (CGT). The CGT is a valid measurement of risk-taking behavior (Deakin et al., 2004; Yazdi et al., 2019), controlling for impulsivity, and has been used in multiple studies using noninvasive brain stimulation (Boggio et al., 2010; Fecteau et al., 2014; Knoch et al., 2006; Valasek et al., 2010). However, the CGT does not control for memory and wealth effects because the trials are not independent, meaning that participants carry gains and losses from the previous trials; moreover, it is confounded by loss aversion as participants can lose points during the task.

Therefore, we developed a revised protocol, the MGT. This computerized task presents six boxes (see Figure 2.3 for an example screen) to the participant, which can be colored either pink or blue. The number of pink boxes is randomized and ranges from 1 to 5, with the remaining boxes being blue. One of the colored boxes hides a token (represented by a yellow X), and the participant has to guess the color of the box that hides the token by choosing left (pink) or right (blue).

Each color has a different bet value representing the potential earnings if the chosen color is correct (hit). A wrong guess results in zero payoff. For example, in Figure 2.3, the trial offers a chance of 3/6 (50%) of earning 50 points if pink is chosen and 3/6 (50%) of earning 100 points if blue is chosen. The bet values were selected randomly among five different values (5, 25, 50, 75, or 100) for each color in each trial independently. The

participant's goal was to obtain the maximum of points in each trial. To remove the impact of loss aversion, the MGT does not allow for losses. Trials have no interdependency in the MGT. Payoffs are calculated for each trial independently and are not cumulated over trials. This avoids memory and wealth effects.

Finally, participants see all the possible combinations of the five different bet values with the different probabilities, resulting in 125 unique trials; therefore, participants can perceive that there is no deception and that all possibilities are randomly assigned. Each trial is displayed twice, which yields a total of 250 trials in random order to guarantee consistent results. Participants had an average of consistency of 100% in the probabilities chosen and 93% (standard deviation 4%, median 93%) in terms of risk-taking and average value chosen across the repeated trials. No participant made significantly inconsistent decisions comparing the two repetitions of each trial in a session.

The tokens' location, color distribution, and bet values are determined independently and randomly across trials. With this, we guaranteed that there was no deception and full randomization. This also minimizes the chance of any specific strategy development. All participants were informed explicitly that there was no winning strategy since all results were random.

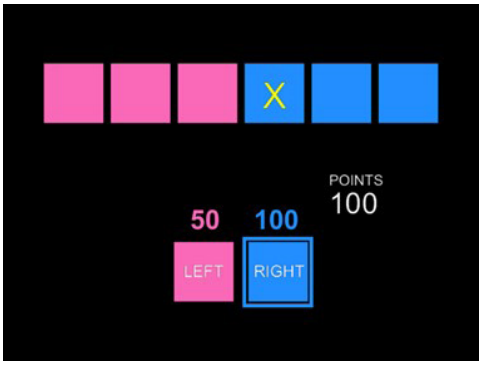

Figure 2.3 – Maastricht Gambling Task (MGT)
Example screen presenting a trial where choosing blue offers a payout of 100 points with a probability of 3/6 (EV= 50) and pink offers a payout of 50 points and a probability of 3/6 (EV=25). In this example, the participant chose the highlighted option (blue), and the token (yellow x) was revealed to be hidden behind one of the blue boxes. In this example, the participant gained 100 points, presented in white.

When a participant chooses a color, the choice is highlighted, and the position of the token is revealed (Figure 2.3). Therefore, in this same example, if the participant had

chosen blue, and the tokens were hidden behind a blue box, she/he would receive 100 points (as indicated in the white text on the right).

To gain more insight into the different types of trials, we divided them into three clusters according to the differences (or contrasts) in expected values offered by the two options (pink and blue), which could capture the difficulty of making a choice in the trial. The lower this difference, the more difficult it is for a subject to make a choice. This led to the division of trials into the following clusters: low, medium, and high contrast. In our analysis, we excluded trials with no difference in expected value since this group of options includes fewer trials than the remaining clusters and would not allow balanced analyses. Trials with one strictly dominant option, meaning (for simplicity) trials where the options have differences in expected value > |65|, were excluded. This exclusion was made since these were considered non-informative because these choices are considered obvious and would hardly be affected by any environmental or intrinsic factor. In total, 204 out of 250 trials were analyzed per session. The cluster division can be seen in detail in the supplementary material 2.A.1.

2.2.4 Transcranial alternating current stimulation (tACS)

We aimed at stimulating the left DLPFC. A small circular (diameter: 2.1cm, thickness: 2mm) electrode and a large (outer diameter: 11cm; inner diameter: 9cm, thickness: 2mm) rubber ring tACS electrode (neuroConn, Ilmenau, Germany) were placed using conductive gel (Ten20 conductive Neurodiagnostic electrode paste, WEAVER and company, Aurora, CO, USA) onto the left DLPFC, with the small electrode positioned over F3 (based on the international 10-20 EEG system) and the large electrode around it. Electrode positioning and tACS simulation were modeled with SimNIBS (Thielscher et al., 2015), as shown in Figure 2.4.

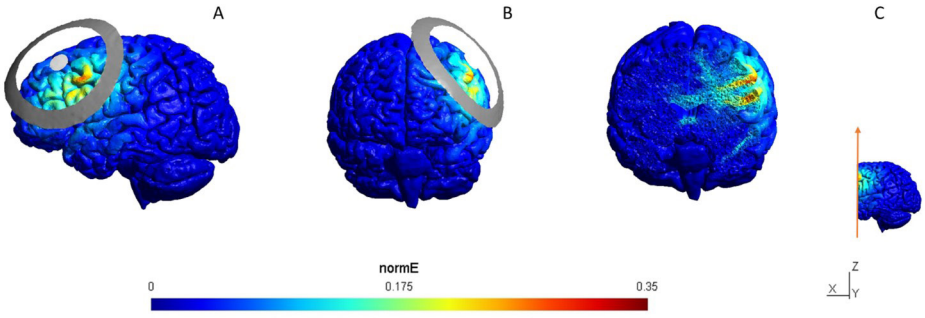

Figure 2.4 – SimNIBS tACS Simulation
Left lateral (A) and frontal (B) view of the stimulation and coronal cut at F3 to show the potential subcortical reach of the stimulation (C). Colors stand for the normalized electric field (0–0.35), meaning that the red areas are the areas where the electric stimulation has a higher incidence.

This ring electrode montage enables a higher spatial focality compared to standard rectangular electrodes (Kuo et al., 2013). Alternating current was applied using a neuroConn DC-stimulator with remote triggering (neuroConn, Ilmenau, Germany) and DataStreamer software (ten Oever et al., 2016), for which we created stimulus protocols on Matlab2018b (The Mathworks Inc., Massachusetts, USA) for each condition. Stimulation frequency and intensity were set to 6.5 Hz (theta-range stimulation) and 40 Hz (gamma-range stimulation), and a stimulation intensity of 1.5mA peak to peak, phase offset set to 0 and 100 cycles were used for ramping up. Intensities and frequencies were defined based on settings used previously in similar experiments (Santarnecchi et al., 2019; Sela et al., 2012). For the sham tACS, the current was ramped up at a 6.5 Hz frequency for 30 seconds and ramped down immediately after. The impedance of the tACS electrodes was kept below 15 kΩ during stimulation. The average stimulation time lasted 30 minutes. Participants were blind to the stimulation protocol and the experimental hypotheses. Questionnaires applied after the experimental session confirmed that participants were unaware of the stimulation protocol.

2.2.5 Electroencephalography (EEG)

EEG electrodes were positioned according to the 10-20 international EEG system around the stimulation site (F1 and F5), contralateral to the stimulation site (F2 and F6) and on the parietal cortex (P5 and P6), with Cz being used as reference and the left mastoid used as ground. EEG measurements were done immediately before and after the tACS, each lasting three minutes, to measure resting-state theta-band activity (measurement before the stimulation) and the effects of the entrainment (after stimulation). Participants were asked to stay with their eyes closed, relaxed and to avoid any movement.

Data were recorded (DC-200 Hz, sampling rate 500 Hz) with a BrainAmp Standard EEG amplifier and the BrainVision Recorder software (BrainProducts GmbH, Munich, Germany). Impedance levels were kept below 15 kΩ. Offline preprocessing was conducted using the Fieldtrip toolbox (Oostenveld et al., 2011) and custom MATLAB scripts. EEG recordings were low pass-filtered in the analog domain (cutoff frequency: 250 Hz) and then digitized (sampling rate: 1000 Hz). Offline preprocessing was performed with a notch-filter (50 Hz) to remove electrical noise and demean the data over the full dataset. After that, it was segmented into 90 trials of two seconds each. Trials with high variance and excessive noise were excluded by visual inspection and variance analyses.

2.2.6 Statistical methodology

To assure transparency and facilitate the reproducibility of our study, all data collected and codes used to analyze them are available at http://dx.doi.org/10.17632/vtz4vt9z5w.1. We analyzed the four following different behavioral dependent variables: 1) Risk, 2) Probability scores 3) Value, and 4) Response time.

2.2.6.1 RISK

The measure of risk-taking behavior should be dependent on both the probabilities of outcomes and the value associated with each outcome. In our experiment, betting on color x (X=blue or pink) in a trial with probability p and a payoff of x would have an expected payoff of *xp*. For instance, when choosing pink, the probability of being correct (a hit) and getting the reward is equal to the proportion of pink boxes during that trial, and the probability of being incorrect and getting no reward is equal to the proportion of blue boxes. Therefore, the expected payoff from choosing color X in a trial is given by the following:

$$EX=xp. \quad (1)$$

For example, in a trial with one blue box with a bet value of 100 and five pink boxes with a bet value of five, the expected payoff for blue and pink are, respectively, 16.67 and 4.17. This makes blue more attractive for a risk-neutral participant. Therefore, an option is strictly dominant for a risk-neutral participant if it has a higher expected payoff.

The measure of risk takes into account the level of variation (Tobler et al., 2007). The variance of payoffs from choosing color X is given by the following:

$$VarXi=\sum px-E(X)2. \quad (2)$$

For example, in a trial with one blue box with a bet value of 25, and five pink boxes with a bet value of five, the expected payoffs of both options are the same, 4.17. However, the variance of blue (86.81) is much higher than that of pink (3.47). Therefore, the option blue is considered riskier than pink. Therefore, for two bets with the same *expected value*, the one with a larger variance is considered riskier. From variance, we calculated standard deviation (SD) as our measure of risk-taking behavior (e.g., Myerson, 2005), which is our main dependent variable, from now on referred to as "Risk."

$$Risk= SD=VarX \quad (3)$$

2.2.6.2 PROBABILITY SCORES

Previous studies have considered only the choice of specific outcome probabilities as an indicator of risk (Boggio et al., 2010; Fecteau et al., 2007b; Knoch et al., 2006), meaning that in these studies, a choice is typically considered risky if the probability is below 50% and safe if its probability is above 50%. To allow a more refined analysis of participant's preferences of probabilities, they were transformed into a scale ranging from -2 to 2. The choice of a higher probability was classified with a negative score and that of a lower probabilities received a positive score. In simple terms, these scores indicate that

options with a higher level of uncertainty have positive scores, while safer options have negative scores. These probability scores can be seen in Table 2.1.

Table 2.1 - Probability Scores Higher scores indicate that participants chose the trials with lower probabilities (risk prone), while lower scores indicate that participants chose higher probabilities (risk averse). For example, if a participant chooses blue in a trial where the distribution of blue boxes is 1/6 (and pink boxes 5/6), the participant would receive a score of 2, indicating that the participant chose the lowest probability possible. If in this same trial the participant chooses pink, the score would be -2, indicating that this participant chose the highest possible probability.

Pink	Blue	Choice	Probability
5	1	Blue	2
1	5	Pink	2
4	2	Blue	1
2	4	Pink	1
3	3	Pink	0
3	3	Blue	0
4	2	Pink	-1
2	4	Blue	-1
5	1	Pink	-2
1	5	Blue	-2

3.2.6.3 VALUE AND RESPONSE TIME

To analyze the average value chosen by a participant in each session, their choices of bet values independent of the trial result (being correct or incorrect) were averaged. That variable is named Value. Furthermore, response times (RT) were also recorded for every decision.

2.2.6.4 BEHAVIORAL DATA ANALYSES

The behavioral data were preprocessed using custom MATLAB (The Mathworks Inc., Massachusetts, USA). We performed a series of linear mixed model analyses to estimate the effects of stimulation (sham, theta, and gamma) on risk-taking behavior. Our final models were fixed effects models, with participant-specific random effects. All the analyses presented normally distributed residuals and showed no heteroscedasticity, and no observations were removed as outliers.

Overall, we constructed linear mixed models where each observation is a unique subject-cell pair. Each cell is a unique combination of session and contrast. That is, three sessions by three levels clusters (LC [low contrast], MC [medium contrast], and HC [high contrast]), resulting in nine unique observations (cells) per subject. The resulting models

can be represented as follows:

$$Yij = \gamma 0 + u0i + \gamma 1 Stimij + \gamma 2 Clusterij + \varepsilon ij$$

Yij stands for each of the behavioral outcome variables; *i* stands for the i-th participant,

and *j* represents the j-th cell; $\gamma 0$ stands for fixed effect intercept; $u0i$ stands for the subject-specific random effect; *Stim* stands for Stimulation condition (sham, theta, gamma); and *Cluster* stands for the three different levels of contrast of the trials (low, medium, high contrast). *Stim* and Cluster are subject-cell specific, hence the subscript *ij*. To analyze the effects of stimulation on risk-taking behavior, measured as the average standard deviation of the chosen option (as described above), we fitted a linear mixed model, estimated using maximum likelihood (ML) and compound symmetry heterogeneous (CSH) covariance structure to predict Risk, with Stimulation and Cluster as factors (formula = Risk ~ Stimulation + Cluster + Stimulation * Cluster).

The analyses of the effects of stimulation on the probability scores used reduced maximum likelihood (REML) and heterogeneous Toeplitz (TPH) covariance structure to predict Probability scores with Stimulation and Cluster as factors (formula = Probability score ~ Stimulation + Cluster + Stimulation * Cluster).

To estimate the effect of stimulation on the average values, we fitted a linear mixed model estimated using REML and CSH as covariance structure to predict Value with Stimulation and Cluster as factors (formula = Value ~ Stimulation + Cluster + Stimulation * Cluster).

Finally, to analyze the participant's RT, we used a linear mixed model with RT as the dependent variable, estimated using ML and TPH as covariance structure, with Stimulation and Cluster as factors (formula = RT ~ Stimulation + Cluster + Stimulation * Cluster).

We checked the correlation among the behavioral dependent variables and checked the robustness of our results for each behavioral dependent variable when using appropriate controls of other behavioral outcomes. These controls did not affect the main results, which were confirmed with additional repeated measures ANOVA analyses, omitted here for conciseness.

2.2.6.5 EEG ANALYSES

We preprocessed the data separately for low (1–20 Hz) and high (20–90 Hz) frequencies. For low frequencies, a fast Fourier transformation was performed with hanning tapers

and output frequencies between 1 and 20 Hz. For high frequencies, a fast Fourier transformation was performed with discrete prolate spheroidal sequences (DPSS) tapers, a smoothing factor of 5 Hz, and output frequencies between 20 and 90 Hz. Then, the data were log normalized to control for discrepancies driven by individual variability (Smulders et al., 2018).

To look for differences in theta and gamma power before and after the stimulation protocols, the power spectra were averaged for the pre- and post-stimulation measurements. Theta-band was defined between 5 and 8 Hz, with 1.5 Hz above and 1.5 Hz below the stimulation frequency (6.5 Hz). Gamma band was defined between 35 and 45 Hz, with 5 Hz above and 5 Hz below the stimulation frequency (40 Hz). Since gamma frequencies include a greater frequency range, we opted for a greater range (5 Hz instead of 1.5 Hz) around the stimulation frequency.

Theta and gamma power were analyzed for all channels pre- and post-stimulation, with focus on the frontal left channels (F1 and F5) around the stimulation focus and the frontal right channels (F2 and F6) contralateral to the stimulation.

To investigate whether a change in the hemispheric relationship in theta power took place, we calculated the average of the theta power in the right hemisphere minus the average in the left hemisphere, named frontal asymmetry (right–left) (Gianotti et al., 2009). Moreover, we compared the changes in theta as well as gamma power in the parietal channels before and after stimulation to analyze how focal the stimulation effects were.

The effects of stimulation in each condition were compared within participants for an interval of three minutes, followed by a *post hoc* analysis of the first minute after stimulation to investigate in detail possible fading effects. Moreover, a time frequency analysis was performed to provide a clear view of the power changes across frequencies over time in each condition. Signal processing and EEG data preprocessing were conducted using MATLAB (The Mathworks Inc., Massachusetts, USA) custom scripts and the Fieldtrip toolbox (Oostenveld et al., 2011). The difference in theta power across conditions was correlated with the behavioral results using both the theta-asymmetry before stimulation as a covariate and the changes in theta and gamma frequencies as dependent variables by performing a repeated measures ANCOVA with Bonferroni correction.

2.3 RESULTS

2.3.1 Behavioral results

In this section, we present the main behavioral results of our experiment. The detailed statistical methodology can be found in Section 2.2.6.

2.3.1.1 MAIN RESULTS: RISK

The estimated fixed effects analysis of the effects of the different protocols of stimulation on risk-taking behavior showed a significant reduction, of -0.301, on risk-taking behavior during theta-band stimulation, t(66.69)=-2.04, p=.05, SE= .15, d=-.50, indicating a medium negative effect of theta-band stimulation on risk when compared to sham (Figure 2.5). Moreover, gamma stimulation did not affect the participant's average risk-taking significantly compared to sham, t(69.992)=-1.22, p=.23, SE= .10, d=-.29, confirming that the effects observed are frequency specific.

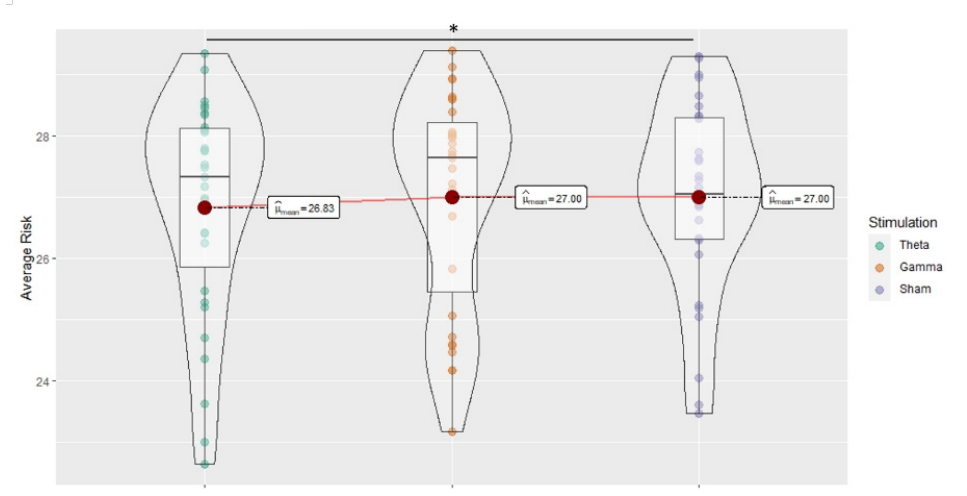

Figure 2.5 – Average Risk-taking Behavior (n=31)
Average risk-taking estimated by the average standard deviation of each participant's choice across stimulation conditions (theta [6.5 Hz] in green, gamma [40 Hz] in orange, and sham in purple). Risk can vary between 11.75 and 36.15. Dark red marks indicate the mean risk per condition.

2.3.1.2 PROBABILITY SCORES

The linear mixed model analyses with probability as the dependent variable did not yield significant main effects for stimulation, F(2,47.29)= .76, p=.92. The estimated fixed effects analyses also did not yield significant effects of theta-band stimulation, t(35.08)=.32, p=.75, SE= .01, d=.11, or gamma stimulation, t(67.70)=-.80, p=.43, SE=

.01, d=-.19, when compared to sham, meaning that no significant differences in the probability scores were observed after the different stimulation protocols.

2.3.1.3 VALUE

These analyses of the effect of stimulation on the average values yielded a non-significant main effect of stimulation, F(2,91.89)=2.43, p=.09. Further analyses of estimated fixed effects yielded significant effects of theta stimulation on value, with a reduction of-0.67 compared to sham, t (64.33)=-2.13, p=.04, SE= .32, d=-.53, indicating a medium negative effect of theta-band stimulation on the average value chosen by the participants when compared to sham. No significant effects were observed after gamma stimulation, t(71.19)=-1.27, p=.21, SE= .21, d=-.30, compared to sham. This means that there was a significant reduction in the average value chosen by the participants due to the theta stimulation, confirming that this is a frequency-exclusive effect (Figure 2.6). These findings reinforce the strong relationship between risk-taking behavior and valuation since both processes were affected by the same pattern of stimulation.

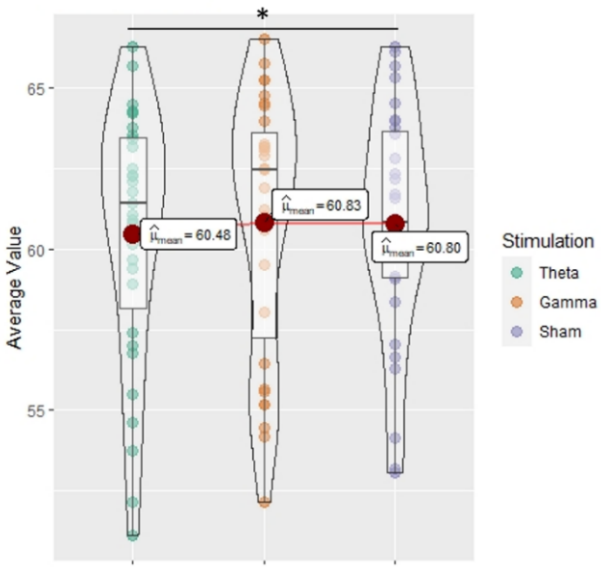

Figure 2.6 – Average Value (n=31)
Average value per condition (theta [6.5 Hz] in green, gamma [40 Hz] in orange, and sham in purple). Dark red marks indicate the mean value per condition.

2.3.1.4 RESPONSE TIME

Estimated fixed effects analyses of the effects of stimulation on response time showed strong significant effects of stimulation, F(2,50.24) =35.80, p<.001. Furthermore, these

analyses yielded significant results for theta stimulation, t(24.26) =5.16, p<.001, SE= .07, d=2.10, indicating a large effect of theta-band stimulation on response time and a nearly significant medium effect for gamma stimulation, t(63.86)=1.88, p=.07, SE= .03, d=.47, when compared to sham. Theta stimulation led to an increase of 41.11% in response time (compared to sham). This implies that the theta stimulation led to an increase in the deliberation time, which cannot be attributed to the stimulation per se since this effect was only marginally significant in the gamma stimulation condition. Details can be observed in Figure 2.7, where response time is plotted against contrast, or trial difficulty level, based on the cluster division previously explained, from easier decisions (which are clear, with big differences in EV between pink and blue) to difficult decisions in which the mental calculation to define the most advantageous option is more challenging.

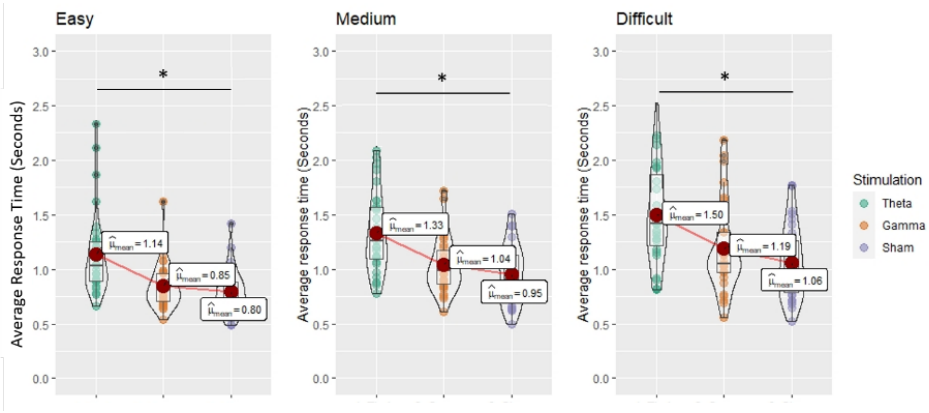

Figure 2.7 – Average Response Time by Task Difficulty Level (n=31)
Average response time per trial difficulty in seconds by stimulation protocol (theta [6.5 Hz] in green, gamma [40 Hz] in orange, and sham in purple). Dark red marks indicate the average response time per condition.

2.3.2 EEG results

2.3.2.1 THETA-BAND ENTRAINMENT

To investigate the effects of theta-band stimulation on EEG results, we ran a repeated measures ANOVA with theta power as the dependent variable, considering the entire interval of three minutes of data. The repeated measures ANOVA used a 3 (stimulation condition: theta, gamma, and sham) by 2 (time: before and after stimulation) by 6 (theta power averaged over 3 minutes on each electrode: F1, F5, F2, F6, P5, P6) within-subject design, with Bonferroni correction for multiple comparisons.

The results showed a significant main effect of time, with theta power increasing from

an average of-0.135 to an average of-0.056 after stimulation, F(1,6) =3.38, p=.01. There was no significant main effect of stimulation, F(1,12) =.82, p=.63, and no significant interaction effect between stimulation and time, F(1,12) =.82, p=.63 (for descriptives, please see the Table S2).

Further analyses included a 3 (stimulation condition) by 2 (time) repeated measures ANOVA using frontal asymmetry as the dependent variable. There was no significant effect of stimulation on frontal asymmetry, F(1,2) =1.19, p=.17; time, F(1,1) =.06, p=.81, or of the interaction between time and stimulation, F(1,2) =.81, p=.46.

Most studies looking at tACS aftereffects using EEG have not found electrophysiological effects lasting beyond the stimulation offset [37–39]. Therefore, we ran *post hoc* analyses to investigate whether the effects were visible only at the very beginning of the period after stimulation, fading during the full interval of three minutes. To do so, we ran a repeated measures ANOVA using as the dependent variable the difference in theta power between the first minute before stimulation and the first minute immediately after it. We used a 3 (stimulation conditions: theta, gamma, and sham) by 7 (theta power difference on each electrode: F1, F5, F2, F6, P5, P6 and change in frontal asymmetry) within-subject design, with Bonferroni correction for multiple comparisons. These analyses yielded a significant effect of stimulation, F(1,12) =4.44, p<.001.

Further contrasts showed significant effects of both theta and gamma band stimulation. There was a large and significant effect of theta-band stimulation (and not gamma) on asymmetry change (pre-post) when compared to sham t(2)= 2.53, p=.01, d=3.58. However, this effect was mainly driven by a decrease in asymmetry in the sham condition, indicating that the decrease is due to the task execution and not to the stimulation.

Following these steps, we ran a time frequency analysis considering all times recorded before and after stimulation. These analyses yielded no significant difference between the experimental conditions (theta and gamma band stimulation) compared to sham. The frequency spectrum contrasting pre- vs. post-power spectrum for each condition can be seen in supplementary material 2.A.3.

We also conducted a partial correlation analysis between the frontal theta asymmetry, theta power in F1, F3, F5, F6, P2, and P6, and the behavioral responses (probabilities chosen, average value chosen, risk, and response time). The level of asymmetry before or after the stimulation did not significantly correlate with either of the behavioral measures. Theta power in F1 and F2 was significantly correlated to the probabilities chosen (r= .11 and p=.02 and r= .01 and p=.01, respectively) although there were no significant effects of stimulation on the probabilities chosen by the participants. The

results also indicate trends regarding the correlations between theta power in F1 and F2 and the average values chosen (r=.0 and p=.10 and r=.08 and p=.09, respectively) and between theta power in these same electrodes and risk (r=.08 and p=.08 and r=.08 and p=.07, respectively).

The inclusion of asymmetry in theta power in any of the electrodes in the regression models used to analyze the behavioral results did not improve the fit of these models and therefore was discarded.

2.3.2.2 GAMMA BAND ENTRAINMENT

The effects of gamma band stimulation were investigated using a 3 (stimulation condition: theta, gamma, and sham) by 2 (time: before and after stimulation) by 6 (theta power averaged over 3 minutes on each electrode: F1, F5, F2, F6, P5, P6) within-subject repeated measures ANOVA, with Bonferroni correction for multiple comparisons. No significant effect of stimulation condition, $F(1,12) = .85$, $p = .60$, nor of time, $F(1,6) = 1.05$, $p = .42$, or the interaction between stimulation and time, $F(1,12) = 1.04$, $p = .47$, was observed. Therefore, there was no significant gamma entrainment, or its effects were not visible in the behavioral or EEG results.

2.4 DISCUSSION

The present study aimed at investigating the functional relationship between frontal theta-band oscillations and risk-taking behavior. Although previous studies (Gianotti et al., 2009; Studer et al., 2013b) have shown a correlation between resting-state frontal theta-band asymmetry and risk-taking behavior, no direct causal relationship has thus far been shown. We hypothesized that theta oscillations underlie the neuronal communication for recruiting the DLPFC when the decision-making process includes risk, being fundamental for the modulation of risk-taking behavior (Cavanagh and Frank, 2014). We therefore expected theta-band stimulation to cause a reduction in risk-taking behavior and that this effect is frequency specific.

As predicted, we were able to effectively reduce risk-taking behavior in healthy participants using theta-band tACS over the left DLPFC compared to sham and gamma band stimulation. These findings confirm the functional relationship between theta-band frequencies and risk-taking behavior regulation, being a fundamental part of the electrophysiological mechanism responsible for this modulation. Theta-band tACS leads to a significant decrease, of 1.12%, in risk-taking behavior compared to sham. This was not the case during gamma stimulation.

To our knowledge, our study is the first to show the frequency specificity of this effect. Moreover, we observed a significant reduction in value sensitivity due to theta-band (and

not gamma) stimulation, meaning that participants opted for lower values after theta-band stimulation compared to the results obtained in the sham or gamma conditions. These results are in line with previous studies, where participants became more risk-averse after noninvasive brain stimulation with reduced sensitivity to value (Boggio et al., 2010; Fecteau et al., 2007a; Gilmore et al., 2018; Levasseur-Moreau and Fecteau, 2012). However, our study was able to show that this effect is also frequency-specific. Therefore, it is expected that theta frequencies would play a fundamental role in the reduction in value sensitivity, meaning the recruitment of the DLPFC as the executive control to modulate the VMPFC response to the value (Hare et al., 2011).

The stimulation did not affect the probabilities chosen by the participants, indicating that the choice of probabilities might be regulated by a different electrophysiological mechanism. Even though our results indicate that probabilities and value are evaluated independently in our brain, behaviorally and in terms of neurological activity, these processes are at least strongly correlated (Knutson et al., 2001; Kuhnen and Knutson, 2005; Tobler et al., 2007). This means that both inputs (bet value and its probabilities) are considered to inform the decision process, which justifies the use of standard deviation as an estimation of risk. Our approach considers the option's expected value (meaning the bet's probabilities and value) to estimate risk, which is in our perspective a more naturalistic evaluation of risk. Our findings indicate that participants' reductions in risk-taking behavior were mainly driven by a reduction in the average value sensitivity.

Although we did not have a specific hypothesis regarding the response time, it is interesting to notice that theta stimulation increased response time compared to sham and gamma stimulation. It may be speculated that the increased response time reflects a longer deliberation process (Rubinstein, 2013).

It is important to note that our results contradict the study by Sela and colleagues (2012). Their results indicated an increase in risk-taking behavior after theta-band stimulation, which might be explained by their choice of the Balloon Analog Task as the experimental paradigm. Since this task has a strong factor of impulsivity, the effect observed should reflect an increase in impulsivity and not in risk-taking behavior (Lejuez et al., 2002; Schonberg et al., 2011). Moreover, they considered the tolerability to losses (measured as sequential explosions) as an indicator of riskier choices (Sela et al., 2012), which means that their results might also indicate a reduction in loss-aversion. Since our experimental paradigm (MGT) avoids loss-aversion and impulsivity, we may have more directly assessed risk-taking behavior. Finally, we must consider the impact of the use of real monetary incentives in economic decision-making (Xu et al., 2016). Since our task was monetarized, the observed results have a higher reliability.

It is also interesting to highlight that our results showed considerable robustness despite the use of random trial selection for payment. This compensation method, despite being widely used in economics experiments, might have led to a decrease in risk-taking behavior and electrophysiological responses to monetary feedback (Schmidt et al., 2019a; Schmidt and Hewig, 2015). However, since we used the same method of compensation across sessions and treatment conditions, it should not influence a specific treatment effect.

In addition to assessing the behavioral effects of our oscillatory brain state neuromodulation on risk-taking modulation, we also used EEG to measure oscillatory activity before and after tACS. It is important to highlight, however, that up to this point, to our knowledge, there is no evidence of long-lasting effects of theta or gamma band tACS on frequency modulation (Heise et al., 2019; Reato et al., 2013c; Strüber et al., 2015a). This means that significant effects on EEG data after stimulation would also depend on long-lasting effects of our stimulation protocol, considering the technical limitations of online recording already discussed (Bland and Sale, 2019).

When comparing theta power before and after theta tACS, no significant changes were found, nor did we reveal significant changes in hemispheric theta-band asymmetry after theta-band stimulation. This may seem surprising and in contrast to our behavioral effects being attributed to and interpreted as being caused by tACS-induced increase in left theta power. However, it is important to note here that while behavioral effects were assessed during tACS being applied simultaneously with task execution, the EEG measurements, due to tACS artifacts, were restricted to assessing the oscillatory activity after both the behavioral performance and tACS had ended. Especially the latter may be a straightforward explanation for the absence of significant EEG effects in a pre-post tACS design as such effects rely on a significant longer-lasting neurophysiological effect of tACS beyond the period of stimulation itself.

However, the question as to whether tACS-induced entrainment is longer lasting is far from being settled (Strüber et al., 2015a). Offline effects of tACS are rarely reported, and various previous studies have also reported difficulties in establishing longer-lasting effects of tACS on excitability or neural plasticity (Bland and Sale, 2019; Reato et al., 2013a; Schutter, 2016; Strüber et al., 2015b). Considering our results, we may therefore speculate that the EEG effects were only present during the task and stimulation and faded away immediately after tACS had ended. Our *post hoc* analyses focusing only on the first minute of post-EEG measurements after TACS and contrasting these effects against the entire post-EEG period indicate time-sensitive changes in theta-band asymmetry in line with this speculation. Yet, our study was not designed to conclusively test any other related hypotheses regarding the difference between the immediate

versus lasting effects of tACS on neural oscillatory activity. Follow-up studies with online measurements using algorithms to remove stimulation artifacts could be used to investigate such possibility although, currently, this methodology is still under debate (Bland and Sale, 2019).

In addition, we also revealed that the task execution itself had lasting effects on theta-band asymmetry, as indicated by *post hoc* analyses of the EEG measures immediately after the task execution in the sham condition. In other words, unrelated to tACS, the mere behavioral performance in risk-taking modulation tasks considerably affected theta-band asymmetry after task execution had been completed. At the same time, our behavioral results showed no significant correlation with resting-state frontal theta-band asymmetry at baseline, indicating that these effects cannot be explained only by the resting-state frontal asymmetry or by changes in asymmetry due to the stimulation. The stimulation frequency specificity of our significant behavioral findings, however, confirming our *a priori* hypothesis that specifically theta, not gamma or sham, neurostimulation should affect risk-taking behavior, clearly represents supporting evidence for the functional relationship between theta-band stimulation and risk-taking regulation driven by a reduction in sensibility to reward. This work also contributes to the understanding of the frontal areas' interaction in the regulation of risk-taking behavior as much as the role of theta-band oscillations in this process. Moreover, it gives insights into the causes of individual differences in risk-taking, granting the analysis of frontal resting-state brain activity a potential role in inferring differences in individual risk-proneness. This can be used in the construction of more accurate economic models of risk-taking.

Moreover, these findings can potentially contribute to the development of diagnosis and intervention techniques for patients with abnormal risk-taking behavior since this is characteristic of a range of psychiatric and neurological disorders (Rao et al., 2008). For example, the use of theta-band stimulation might be an interesting tool to compensate increases in risk-taking behavior due to the use of L-dopa in patients with Parkinson's disease (Cools et al., 2003, 2002) or help patients with attention deficit/hyperactivity disorder (ADHD), which is known to be associated with abnormal risk-taking behavior (Pollak et al., 2019). Nevertheless, these suggestions should be explored in future studies.

2.5 CONCLUSION

Although it is widely accepted that the DLPFC has an important role in risk-taking regulation, it is not clear how the recruitment of this area occurs in the presence of risk. Theta oscillations are potentially responsible for neuron communication when cognitive control is needed [13]. In our study, we provided empirical evidence for the

direct functional relationship between prefrontal theta-band activity and risk-taking regulation using high definition theta-band tACS with gamma band entrainment and sham as control. A significant reduction in risk-taking behavior was observed after theta-band, but not gamma band or sham tACS over the left DLPFC, confirming the specific role of theta frequencies in risk-taking behavior regulation. Such findings indicate that prefrontal theta-band oscillations are potentially the basis for communication between frontal areas during risk-taking regulation.

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2.6 REFERENCES

Andersen, S., Harrison, G. W., Lau, M. I., & Rutström, E. E. (2008). Eliciting risk and time preferences. Econometrica, 76(3), 583–618. https://doi.org/10.1111/j.1468-0262.2008.00848.x

*Andreoni, J., & Sprenger, C. (2012). Estimating Time Preferences from Convex Budgets † By J ames A ndreoni and C harles S prenger *. 102(7), 3333–3356.*

Antal, A., Alekseichuk, I., Bikson, M., Brockmöller, J., Brunoni, A. R., Chen, R., Cohen, L. G., Dowthwaite, G., Ellrich, J., Flöel, A., Fregni, F., George, M. S., Hamilton, R., Haueisen, J., Herrmann, C. S., Hummel, F. C., Lefaucheur, J. P., Liebetanz, D., Loo, C. K., … Paulus, W. (2017). Low intensity transcranial electric stimulation: Safety, ethical, legal regulatory and application guidelines. In Clinical Neurophysiology (Vol. 128, Issue 9, pp. 1774–1809). Elsevier Ireland Ltd. https://doi.org/10.1016/j.clinph.2017.06.001

Bagga, D., Aigner, C. S., Reichert, J. L., Cecchetto, C., Fischmeister, F. P. S., Holzer, P., Moissl-Eichinger, C., & Schöpf, V. (2019). Influence of 4-week multi-strain probiotic administration on resting-state functional connectivity in healthy volunteers. European Journal of Nutrition, 58(5), 1821–1827. https://doi.org/10.1007/s00394-018-1732-z

Bagga, D., Reichert, J. L., Koschutnig, K., Aigner, C. S., Holzer, P., Koskinen, K., Moissl-Eichinger, C., & Schöpf, V. (2018). Probiotics drive gut microbiome triggering emotional brain signatures. Gut Microbes, 9(6), 486–496. https://doi.org/10.1080/19490976.2018.1460015

Başar, E., Başar-Eroglu, C., Karakaş, S., & Schürmann, M. (2001). Gamma, alpha, delta, and theta oscillations govern cognitive processes. International Journal of Psychophysiology, 39(2–3), 241–248. https://doi.org/10.1016/S0167-8760(00)00145-8

Bercik, P., Denou, E., Collins, J., Jackson, W., Lu, J., Jury, J., Deng, Y., Blennerhassett, P., MacRi, J., McCoy, K. D., Verdu, E. F., & Collins, S. M. (2011). The intestinal microbiota affect central levels of brain-derived neurotropic factor and behavior in mice. Gastroenterology, 141(2), 599-609.e3. https://doi.org/10.1053/j.gastro.2011.04.052

Bercik, P., Park, A. J., Sinclair, D., Khoshdel, A., Lu, J., Huang, X., Deng, Y., Blennerhassett, P. A., Fahnestock, M., Moine, D., Berger, B., Huizinga, J. D., Kunze, W., Mclean, P. G., Bergonzelli, G. E., Collins, S. M., & Verdu, E. F. (2011). The anxiolytic effect of Bifidobacterium longum NCC3001 involves vagal pathways for gut-brain communication. Neurogastroenterology and Motility, 23(12), 1132–1139. https://doi.org/10.1111/j.1365-2982.2011.01796.x

Bland, N. S., & Sale, M. v. (2019). Current challenges: the ups and downs of tACS. In Experimental Brain Research (Vol. 237, Issue 12, pp. 3071–3088). Springer. https://doi.org/10.1007/s00221-019-05666-0

Boggio, P. S., Campanhã, C., Valasek, C. A., Fecteau, S., Pascual-Leone, A., & Fregni, F. (2010). Modulation of decision-making in a gambling task in older adults with transcranial direct current stimulation. European Journal of Neuroscience, 31(3), 593–597. https://doi.org/10.1111/j.1460-9568.2010.07080.x

Boggio, P. S., Zaghi, S., Beatriz, A., Fecteau, S., Pascual-leone, A., & Fregni, F. (2010). Modulation of risk-taking in marijuana users by transcranial direct current stimulation (tDCS) of the dorsolateral prefrontal cortex (DLPFC). Drug and Alcohol Dependence, 112(3), 220–225. https://doi.org/10.1016/j.drugalcdep.2010.06.019

Bohórquez, D. V, Shahid, R. A., Erdmann, A., Kreger, A. M., Wang, Y., Calakos, N., Wang, F., & Liddle, R. A. (2015). Neuroepithelial circuit formed by innervation of sensory enteroendocrine cells. J. Clin. Invest., 125(2), 782–786. https://doi.org/10.1172/JCI78361DS1

Bradley, M. M., & Lang, P. J. (1994). Measuring emotion: The self-assessment manikin and the semantic differential.

Journal of Behavior Therapy and Experimental Psychiatry, 25(1), 49–59. https://doi.org/10.1016/0005-7916(94)90063-9

Brand, M., Recknor, E. C., Grabenhorst, F., & Bechara, A. (2007). Decisions under ambiguity and decisions under risk: Correlations with executive functions and comparisons of two different gambling tasks with implicit and explicit rules. Journal of Clinical and Experimental Neuropsychology, 29(1), 86–99. https://doi.org/10.1080/13803390500507196

Bravo, J. A., Forsythe, P., Chew, M. v, Escaravage, E., Savignac, H. M., Dinan, T. G., Bienenstock, J., & Cryan, J. F. (2011). Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. Proceedings of the National Academy of Sciences, 108(38), 16050–16055. https://doi.org/10.1073/pnas.1102999108

Carabotti, M., Scirocco, A., Maselli, M. A., & Severi, C. (2015). The gut-brain axis: Interactions between enteric microbiota, central and enteric nervous systems. Annals of Gastroenterology, 28(2).

Cavanagh, J. F., & Frank, M. J. (2014). Frontal theta as a mechanism for cognitive control. Trends in Cognitive Sciences, 18(8), 414–421. https://doi.org/10.1016/j.tics.2014.04.012

Clark, L., Bechara, A., Damasio, H., Aitken, M. R. F., & Sahakian, B. J. (2017). Differential effects of insular and ventromedial prefrontal cortex lesions on risky decision-making. November. https://doi.org/10.1093/brain/awn066

Colzato, L. S., Steenbergen, L., de Kwaadsteniet, E. W., Sellaro, R., Liepelt, R., & Hommel, B. (2013). Tryptophan Promotes Interpersonal Trust. Psychological Science, 24(12), 2575–2577. https://doi.org/10.1177/0956797613500795

Cools, R., Barker, R. A., Sahakian, B. J., & Robbins, T. W. (2003). L-Dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease. Neuropsychologia, 41(11), 1431–1441. https://doi.org/10.1016/S0028-3932(03)00117-9

Cools, R., Stefanova, E., Barker, R. A., Robbins, T. W., & Owen, A. M. (2002). Dopaminergic modulation of high-level cognition in Parkinson's disease: the role of the prefrontal cortex revealed by PET. Brain, 125(3), 584–594. https://doi.org/10.1093/brain/awf052

Cryan, J. F., & Dinan, T. G. (2012). Mind-altering microorganisms: The impact of the gut microbiota on brain and behaviour. In Nature Reviews Neuroscience (Vol. 13, Issue 10, pp. 701–712). Nature Publishing Group. https://doi.org/10.1038/nrn3346

Damasio, A. (2019). The strange order of things: Life, feeling, and the making of cultures. Vintage.

Dantas, A. M., Sack, A. T., Bruggen, E., Jiao, P., & Schuhmann, T. (2021). Reduced risk-taking behavior during frontal oscillatory theta-band neurostimulation. Brain Research, 1759, 147365. https://doi.org/10.1016/j.brainres.2021.147365

Davis, S. C., Yadav, J. S., Barrow, S. D., & Robertson, B. K. (2017). Gut microbiome diversity influenced more by the Westernized dietary regime than the body mass index as assessed using effect size statistic. MicrobiologyOpen, 6(4), 476. https://doi.org/10.1002/mbo3.476

Deakin, J., Aitken, M., Robbins, T., & Sahakian, B. J. (2004). Risk taking during decision-making in normal volunteers changes with age. Journal of the International Neuropsychological Society, 10(4), 590–598. https://doi.org/10.1017/S1355617704104104

Deans, J. K., Powell, A. D., & Jefferys, J. G. R. (2007). Sensitivity of coherent oscillations in rat hippocampus to AC

electric fields. Journal of Physiology, 583(2), 555–565. https://doi.org/10.1113/jphysiol.2007.137711

Desbonnet, L., Garrett, L., Clarke, G., Bienenstock, J., & Dinan, T. G. (2008). The probiotic Bifidobacteria infantis: An assessment of potential antidepressant properties in the rat. Journal of Psychiatric Research, 43(2), 164–174. https://doi.org/10.1016/j.jpsychires.2008.03.009

Dinan, T. G., Stanton, C., & Cryan, J. F. (2013). Psychobiotics: A novel class of psychotropic. Biological Psychiatry, 74(10), 720–726. https://doi.org/10.1016/j.biopsych.2013.05.001

Dinan, T. G., Stilling, R. M., Stanton, C., & Cryan, J. F. (2015). Collective unconscious: How gut microbes shape human behavior. Journal of Psychiatric Research, 63, 1–9. https://doi.org/10.1016/j.jpsychires.2015.02.021

Enders, G. (2018). Gut: The Inside Story of Our Body's Most Underrated Organ (Revised Ed). Greystone Books Ltd.

Falk, A., Becker, A., Dohmen, T., Enke, B., Huffman, D., & Sunde, U. (2018). Global Evidence on Economic Preferences. The Quarterly Journal of Economics, 133(4), 1645–1692. https://doi.org/10.1093/qje/qjy013*

Fecteau, S., Agosta, S., Hone-blanchet, A., Fregni, F., Boggio, P., Ciraulo, D., & Pascual-leone, A. (2014). Modulation of smoking and decision-making behaviors with transcranial direct current stimulation in tobacco smokers : A preliminary study. Drug and Alcohol Dependence, 140, 78–84. https://doi.org/10.1016/j.drugalcdep.2014.03.036

Fecteau, S., Knoch, D., Fregni, F., Sultani, N., Boggio, P., & Pascual-leone, A. (2007). Diminishing Risk-Taking Behavior by Modulating Activity in the Prefrontal Cortex : A Direct Current Stimulation Study. 27(46), 12500–12505. https://doi.org/10.1523/JNEUROSCI.3283-07.2007

Fecteau, S., Pascual-leone, A., Zald, D. H., Liguori, P., The, H., Boggio, P. S., Fregni, F., & Ht, C. (2007). Activation of Prefrontal Cortex by Transcranial Direct Current Stimulation Reduces Appetite for Risk during Ambiguous Decision Making. 27(23), 6212–6218. https://doi.org/10.1523/JNEUROSCI.0314-07.2007

Feurra, M., Galli, G., & Rossi, S. (2012). Transcranial Alternating Current Stimulation Affects Decision Making. Frontiers in Systems Neuroscience, 6, 39. https://doi.org/10.3389/fnsys.2012.00039

Figner, B., Knoch, D., Johnson, E. J., Krosch, A. R., Lisanby, S. H., Fehr, E., & Weber, E. U. (2010). Lateral prefrontal cortex and self-control in intertemporal choice. Nature Neuroscience, 13(5), 538–539. https://doi.org/10.1038/nn.2516

Floden, D., Alexander, M. P., Kubu, C. S., Katz, D., & Stuss, D. T. (2008). Impulsivity and risk-taking behavior in focal frontal lobe lesions. 46, 213–223. https://doi.org/10.1016/j.neuropsychologia.2007.07.020

Foster, J. A., Rinaman, L., & Cryan, J. F. (2017). Stress & the gut-brain axis: Regulation by the microbiome. Neurobiology of Stress, 7, 124–136. https://doi.org/10.1016/j.ynstr.2017.03.001

Gallagher, M., McMahan, R., Schoenbaum, G., & O'Doherty, J. P. (2009). Orbitofrontal Cortex and Representation of Incentive Value in Associative Learning. Journal of Neuroscience, 19(15), 6610–6614. https://doi.org/10.1523/jneurosci.2575-09.2009

Galvan, A., Hare, T. A., Parra, C. E., Penn, J., Voss, H., Glover, G., & Casey, B. J. (2006). Earlier Development of the Accumbens Relative to Orbitofrontal Cortex Might Underlie Risk-Taking Behavior in Adolescents. 26(25), 6885–6892. https://doi.org/10.1523/JNEUROSCI.1062-06.2006

Ganz, J. (2021). Revealing the complexity of the gut's brain. In Nature Neuroscience (Vol. 24, Issue 1, pp. 1–2). Nature Research. https://doi.org/10.1038/s41593-020-00769-2

Gianotti, L. R. R., Knoch, D., Faber, P. L., Lehmann, D., Roberto, D., Diezi, C., Schoch, C., Eisenegger, C., & Fehr, E. (2009). Tonic Activity Level in the Right Prefrontal Cortex Predicts Individuals ' Risk Taking. 20(1), 33–38.

Gilmore, C. S., Dickmann, P. J., Nelson, B. G., Lamberty, G. J., & Lim, K. O. (2018). Transcranial Direct Current Stimulation (tDCS) paired with a decision-making task reduces risk-taking in a clinically impulsive sample. Brain Stimulation, 11(2), 302–309. https://doi.org/10.1016/j.brs.2017.11.011

Guillermo A Calvo, & Carmen M Reinhart. (2002). The Global Preferences Survey. Source: The Quarterly Journal of Economics, 117(2), 379–408. https://doi.org/10.1162/003355301556310

Hare, T. A., Malmaud, J., & Rangel, A. (2011). Focusing attention on the health aspects of foods changes value signals in vmPFC and improves dietary choice. The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 31(30), 11077–11087. https://doi.org/10.1523/JNEUROSCI.6383-10.2011

Heise, K. F., Monteiro, T. S., Leunissen, I., Mantini, D., & Swinnen, S. P. (2019). Distinct online and offline effects of alpha and beta transcranial alternating current stimulation (tACS) on continuous bimanual performance and task-set switching. Scientific Reports, 9(1). https://doi.org/10.1038/s41598-019-39900-0

Hoban, A. E., Stilling, R. M., Ryan, F. J., Shanahan, F., Dinan, T. G., Claesson, M. J., Clarke, G., & Cryan, J. F. (2016). Regulation of prefrontal cortex myelination by the microbiota. Translational Psychiatry, 6(4), e774–e774. https://doi.org/10.1038/tp.2016.42

Jiao, P. (2020). Payoff-Based Belief Distortion. The Economic Journal, 130(629), 1416–1444. https://doi.org/10.1093/ej/ueaa019

Knoch, D., Gianotti, L. R. R., Pascual-leone, A., Treyer, V., Regard, M., Hohmann, M., & Brugger, P. (2006). Disruption of Right Prefrontal Cortex by Low-Frequency Repetitive Transcranial Magnetic Stimulation Induces. 26(24), 6469–6472. https://doi.org/10.1523/JNEUROSCI.0804-06.2006

Knutson, B., Adams, C. M., Fong, G. W., & Hommer, D. (2001). Anticipation of increasing monetary reward selectively recruits nucleus accumbens. The Journal of Neuroscience, 21(16). https://doi.org/10.1523/jneurosci.21-16-j0002.2001

Kohn, N., Szopinska-Tokov, J., Llera, A., Beckmann, C., Arias Vasquez, A., & Aarts, E. (2020). Multivariate associative patterns between the gut microbiota and large-scale brain network connectivity. In bioRxiv (p. 2020.08.25.266122). Cold Spring Harbor Laboratory. https://doi.org/10.1101/2020.08.25.266122

Kohno, M., Ghahremani, D. G., Morales, A. M., Robertson, C. L., Ishibashi, K., Morgan, A. T., Mandelkern, M. A., & London, E. D. (2015). Risk-taking behavior: Dopamine D2/D3 receptors, feedback, and frontolimbic activity. Cerebral Cortex, 25(1), 236–245. https://doi.org/10.1093/cercor/bht218

Koul, A., Soriano, M., Avenanti, A., Cavallo, A., & Becchio, C. (2019). Investigating the causal role of frontal and parietal cortices in intention understanding: a cTBS study. Brain Stimulation, 12(2), 485. https://doi.org/10.1016/j.brs.2018.12.585

Kuhnen, C. M., & Knutson, B. (2005). The neural basis of financial risk taking. Neuron, 47(5), 763–770. https://doi.org/10.1016/j.neuron.2005.08.008

Kuo, H. I., Bikson, M., Datta, A., Minhas, P., Paulus, W., Kuo, M. F., & Nitsche, M. A. (2013). Comparing cortical plasticity induced by conventional and high-definition 4 × 1 ring tDCS: A neurophysiological study. Brain Stimulation, 6(4), 644–648. https://doi.org/10.1016/j.brs.2012.09.010

Lejuez, C. W., Read, J. P., Kahler, C. W., Richards, J. B., Ramsey, S. E., Stuart, G. L., Strong, D. R., Brown, R. A., York, N., Ramsey, S. E., Stuart, G. L., & Strong, D. R. (2002). Evaluation of a Behavioral Measure of Risk Taking : The Balloon Analogue Risk Task (BART). 8(2), 75–84. https://doi.org/10.1037//1076-898X.8.2.75

Levasseur-Moreau, J., & Fecteau, S. (2012). Translational application of neuromodulation of decision-making. In

Brain Stimulation (Vol. 5, Issue 2, pp. 77–83). Elsevier. https://doi.org/10.1016/j.brs.2012.03.009

Luna, R. A., & Foster, J. A. (2015). Gut brain axis: Diet microbiota interactions and implications for modulation of anxiety and depression. Current Opinion in Biotechnology, 32(Figure 1), 35–41. https://doi.org/10.1016/j.copbio.2014.10.007

Mani, A., Mullainathan, S., Shafir, E., & Zhao, J. (2013). Poverty impedes cognitive function. Science, 341(6149), 976–980. https://doi.org/10.1126/science.1238041

Messaoudi, M., Lalonde, R., Violle, N., Javelot, H., Desor, D., Nejdi, A., Bisson, J. F., Rougeot, C., Pichelin, M., Cazaubiel, M., & Cazaubiel, J. M. (2011). Assessment of psychotropic-like properties of a probiotic formulation (Lactobacillus helveticus R0052 and Bifidobacterium longum R0175) in rats and human subjects. British Journal of Nutrition, 105(5), 755–764. https://doi.org/10.1017/S0007114510004319

Messaoudi, M., Violle, N., Bisson, J. F., Desor, D., Javelot, H., & Rougeot, C. (2011). Beneficial psychological effects of a probiotic formulation (Lactobacillus helveticus R0052 and Bifidobacterium longum R0175) in healthy human volunteers. Gut Microbes, 2(4). https://doi.org/10.4161/gmic.2.4.16108

Myerson, R. B. (2005). Probability Models for Economic Decisions. Technometrics, 48(1), 159–159. https://doi.org/10.1198/tech.2006.s374

O'Mahony, S. M., Clarke, G., Borre, Y. E., Dinan, T. G., & Cryan, J. F. (2015). Serotonin, tryptophan metabolism and the brain-gut-microbiome axis. Behavioural Brain Research, 277, 32–48. https://doi.org/10.1016/j.bbr.2014.07.027

Oostenveld, R., Fries, P., Maris, E., & Schoffelen, J.-M. (2011). FieldTrip: Open Source Software for Advanced Analysis of MEG, EEG, and Invasive Electrophysiological Data. Computational Intelligence and Neuroscience, 2011, 1–9. https://doi.org/10.1155/2011/156869

Oriach, C. S., Robertson, R. C., Stanton, C., Cryan, J. F., & Dinan, T. G. (2016). Food for thought: The role of nutrition in the microbiota-gut-brain axis. Clinical Nutrition Experimental, 6, 25–38. https://doi.org/10.1016/j.yclnex.2016.01.003

Papalini, S., Michels, F., Kohn, N., Wegman, J., van Hemert, S., Roelofs, K., Arias-Vasquez, A., & Aarts, E. (2019). Stress matters: Randomized controlled trial on the effect of probiotics on neurocognition. Neurobiology of Stress, 10, 100141. https://doi.org/10.1016/J.YNSTR.2018.100141

Pollak, Y., Dekkers, T. J., Shoham, R., & Huizenga, H. M. (2019). Risk-Taking Behavior in Attention Deficit/Hyperactivity Disorder (ADHD): a Review of Potential Underlying Mechanisms and of Interventions. In Current Psychiatry Reports (Vol. 21, Issue 5, pp. 1–11). Current Medicine Group LLC 1. https://doi.org/10.1007/s11920-019-1019-y

R Core team. (2015). R Core Team. In R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing , Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org/. (Vol. 55, pp. 275–286). https://www.r-project.org/

Rao, H., Korczykowski, M., Pluta, J., Hoang, A., & Detre, J. A. (2008). Neural correlates of voluntary and involuntary risk taking in the human brain: An fMRI Study of the Balloon Analog Risk Task (BART). NeuroImage, 42(2), 902–910. https://doi.org/10.1016/j.neuroimage.2008.05.046

Reato, D., Rahman, A., Bikson, M., & Parra, L. C. (2013a). Effects of weak transcranial alternating current stimulation on brain activity-a review of known mechanisms from animal studies. In Frontiers in Human Neuroscience (Vol. 7, Issue OCT, p. 687). Frontiers Media S. A. https://doi.org/10.3389/fnhum.2013.00687

Reato, D., Rahman, A., Bikson, M., & Parra, L. C. (2013b). Effects of weak transcranial alternating current stimulation on brain activity-a review of known mechanisms from animal studies. In Frontiers in Human Neuroscience (Vol. 7, Issue OCT). Frontiers Media S. A. https://doi.org/10.3389/fnhum.2013.00687

Reato, D., Rahman, A., Bikson, M., & Parra, L. C. (2013c). Effects of weak transcranial alternating current stimulation on brain activity—a review of known mechanisms from animal studies. Frontiers in Human Neuroscience, 7(OCT), 687. https://doi.org/10.3389/fnhum.2013.00687

Rogers, R. D., Everitt, B. J., Baldacchino, A., Blackshaw, A. J., Swainson, R., Wynne, K., Baker, N. B., Hunter, J., Carthy, T., Booker, E., London, M., Deakin, J. F. W., Sahakian, B. J., & Robbins, T. W. (1999). Dissociable Deficits in the Decision-Making Cognition of Chronic Amphetamine Abusers, Opiate Abusers, Patients with Focal Damage to Prefrontal Cortex, and Tryptophan-Depleted Normal Volunteers: Evidence for Monoaminergic Mechanisms. Neuropsychopharmacology, 20(4), 322–339. https://doi.org/10.1016/S0893-133X(98)00091-8

Rogers, R. D. R., Everitt, B. J., Baldacchino, A., Blackshaw, A. J., Swainson, R., Wynne, K., Baker, N. B., Hunter, J., Carthy, T., Booker, E., London, M., Deakin, J. F. W., Sahakian, B. J., & Robbins, T. W. (1999). Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan-depleted normal volunteersEvidence for monoaminergic mechanisms. ..., 20(4), 322–339. https://doi.org/10.1016/S0893-133X(98)00091-8

Roman, P., Estévez, A. F., Miras, A., Sánchez-Labraca, N., Cañadas, F., Vivas, A. B., & Cardona, D. (2018). A Pilot Randomized Controlled Trial to Explore Cognitive and Emotional Effects of Probiotics in Fibromyalgia. Scientific Reports, 8(1), 10965. https://doi.org/10.1038/s41598-018-29388-5

Rubinstein, A. (2013). Response time and decision making: An experimental study. In Judgment and Decision Making (Vol. 8, Issue 5).

Rudorf, S., & Hare, T. A. (2014). Interactions between dorsolateral and ventromedial prefrontal cortex underlie context-dependent stimulus valuation in goal-directed choice. Journal of Neuroscience, 34(48), 15988–15996. https://doi.org/10.1523/JNEUROSCI.3192-14.2014

Sanfey, A. G. (2007). Social decision-making: Insights from game theory and neuroscience. In Science (Vol. 318, Issue 5850, pp. 598–602). American Association for the Advancement of Science. https://doi.org/10.1126/science.1142996

Santarnecchi, E., Sprugnoli, G., Bricolo, E., Costantini, G., Liew, S. L., Musaeus, C. S., Salvi, C., Pascual-Leone, A., Rossi, A., & Rossi, S. (2019). Gamma tACS over the temporal lobe increases the occurrence of Eureka! moments. Scientific Reports, 9(1), 1–12. https://doi.org/10.1038/s41598-019-42192-z

Sarkar, A., Lehto, S. M., Harty, S., Dinan, T. G., Cryan, J. F., & Burnet, P. W. J. (2016). Psychobiotics and the Manipulation of Bacteria–Gut–Brain Signals. Trends in Neurosciences, 39(11), 763–781. https://doi.org/10.1016/j.tins.2016.09.002

Scheperjans, F., Aho, V., Pereira, P. A. B., Koskinen, K., Paulin, L., Pekkonen, E., Haapaniemi, E., Kaakkola, S., Eerola-Rautio, J., Pohja, M., Kinnunen, E., Murros, K., & Auvinen, P. (2015). Gut microbiota are related to Parkinson's disease and clinical phenotype. Movement Disorders, 30(3), 350–358. https://doi.org/10.1002/mds.26069

Schmidt, B., & Hewig, J. (2015). Paying Out One or All Trials: A Behavioral Economic Evaluation of Payment Methods in a Prototypical Risky Decision Study. Psychological Record, 65(2), 245–250. https://doi.org/10.1007/s40732-014-0112-1

Schmidt, B., Kanis, H., Holroyd, C. B., Miltner, W. H. R., & Hewig, J. (2018). Anxious gambling: Anxiety is associated with higher frontal midline theta predicting less risky decisions. Psychophysiology, 55(10), e13210. https://doi.org/10.1111/psyp.13210

Schmidt, B., Keßler, L., Hecht, H., Hewig, J., Holroyd, C. B., & Miltner, W. H. R. (2019). What you give is what you get: Payment of one randomly selected trial induces risk-aversion and decreases brain responses to monetary feedback. Cognitive, Affective and Behavioral Neuroscience, 19(1), 187–196. https://doi.org/10.3758/s13415-018-00656-1

Schmidt, B., Kessler, L., Holroyd, C. B., & Miltner, W. H. R. (2019). Wearing a bike helmet leads to less cognitive control, revealed by lower frontal midline theta power and risk indifference. Psychophysiology, 56(12). https://doi.org/10.1111/psyp.13458

Schonberg, T., Fox, C. R., & Poldrack, R. A. (2011). Mind the gap : bridging economic and naturalistic risk-taking with cognitive neuroscience. Trends in Cognitive Sciences, 15(1), 11–19. https://doi.org/10.1016/j.tics.2010.10.002

Schutter, D. J. L. G. (2016). Cutaneous retinal activation and neural entrainment in transcranial alternating current stimulation: A systematic review. NeuroImage, 140, 83–88. https://doi.org/10.1016/j.neuroimage.2015.09.067

Sela, T., Kilim, A., & Lavidor, M. (2012). Transcranial alternating current stimulation increases risk-taking behavior in the Balloon Analog Risk Task. Frontiers in Neuroscience, 6(FEB), 1–11. https://doi.org/10.3389/fnins.2012.00022

Smulders, F. T. Y., ten Oever, S., Donkers, F. C. L., Quaedflieg, C. W. E. M., & van de Ven, V. (2018). Single-trial log transformation is optimal in frequency analysis of resting EEG alpha. European Journal of Neuroscience, 48(7), 2585–2598. https://doi.org/10.1111/ejn.13854

Sprenger, C. (2015). An Endowment Effect for Risk: Experimental Tests of Stochastic Reference Points. Journal of Political Economy, 123(6), 1456–1499. https://doi.org/10.1086/683836

Strüber, D., Rach, S., Neuling, T., & Herrmann, C. S. (2015a). On the possible role of stimulation duration for after-effects of transcranial alternating current stimulation. Frontiers in Cellular Neuroscience, 9(AUGUST), 311. https://doi.org/10.3389/fncel.2015.00311

Strüber, D., Rach, S., Neuling, T., & Herrmann, C. S. (2015b). On the possible role of stimulation duration for after-effects of transcranial alternating current stimulation. Frontiers in Cellular Neuroscience, 9(AUGUST), 311. https://doi.org/10.3389/fncel.2015.00311

Studer, B., Pedroni, A., & Rieskamp, J. (2013a). Predicting Risk-Taking Behavior from Prefrontal Resting- State Activity and Personality. PLoS ONE, 8(10), 1–8. https://doi.org/10.1371/journal.pone.0076861

Studer, B., Pedroni, A., & Rieskamp, J. (2013b). Predicting Risk-Taking Behavior from Prefrontal Resting-State Activity and Personality. PLoS ONE, 8(10), e76861. https://doi.org/10.1371/journal.pone.0076861

Tangney, J. P., Baumeister, R. F., & Boone, A. L. (2004). High Self-Control Predicts Good Adjustment, Less Pathology, Better Grades, and Interpersonal Success. Journal of Personality, 72(2), 271–324. https://doi.org/10.1111/j.0022-3506.2004.00263.x

ten Oever, S., de Graaf, T. A., Bonnemayer, C., Ronner, J., Sack, A. T., & Riecke, L. (2016). Stimulus presentation at specific neuronal oscillatory phases experimentally controlled with tACS: Implementation and applications. Frontiers in Cellular Neuroscience, 10(OCT2016), 240. https://doi.org/10.3389/fncel.2016.00240

Thaler, R. H., & Johnson, E. J. (1990). Gambling with the House Money and Trying to Break Even: The Effects of Prior Outcomes on Risky Choice. Management Science, 36(6), 643–660. https://doi.org/10.1287/mnsc.36.6.643

Thielscher, A., Antunes, A., & Saturnino, G. B. (2015). Field modeling for transcranial magnetic stimulation: A useful tool to understand the physiological effects of TMS? Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS, 2015-November, 222–225. https://doi.org/10.1109/EMBC.2015.7318340

Tillisch, K., Labus, J., Kilpatrick, L., Jiang, Z., Stains, J., Ebrat, B., Guyonnet, D., Legrain-Raspaud, S., Trotin, B., Naliboff, B., & Mayer, E. A. (2013). Consumption of fermented milk product with probiotic modulates brain activity. Gastroenterology, 144(7), 1394-1401.e4. https://doi.org/10.1053/j.gastro.2013.02.043

Tillmann, S., & Wegener, G. (2019). Probiotics reduce risk-taking behavior in the Elevated Plus Maze in the Flinders Sensitive Line rat model of depression. Behavioural Brain Research, 359, 755–762. https://doi.org/10.1016/j.bbr.2018.08.025

Tobler, P. N., O'Doherty, J. P., Dolan, R. J., & Schultz, W. (2007). Reward value coding distinct from risk attitude-related uncertainty coding in human reward systems. Journal of Neurophysiology, 97(2), 1621–1632. https://doi.org/10.1152/jn.00745.2006

Trimpop, R. (1994). The psychology of risk taking behavior. North-Holland.

Wastyk, H. C., Fragiadakis, G. K., Perelman, D., Dahan, D., Merrill, B. D., Yu, F. B., Topf, M., Gonzalez, C. G., Van Treuren, W., Han, S., Robinson, J. L., Elias, J. E., Sonnenburg, E. D., Gardner, C. D., & Sonnenburg, J. L. (2021). Gut-microbiota-targeted diets modulate human immune status. Cell. https://doi.org/10.1016/J.CELL.2021.06.019

Weber, B. J., & Huettel, S. A. (2008). The neural substrates of probabilistic and intertemporal decision making. Brain Research, 1234, 104–115. https://doi.org/10.1016/j.brainres.2008.07.105

Xu, L., Liang, Z. Y., Wang, K., Li, S., & Jiang, T. (2009). Neural mechanism of intertemporal choice: From discounting future gains to future losses. Brain Research, 1261, 65–74. https://doi.org/10.1016/j.brainres.2008.12.061

Xu, S., Pan, Y., Wang, Y., Spaeth, A. M., Qu, Z., & Rao, H. (2016). Real and hypothetical monetary rewards modulate risk taking in the brain. Nature Publishing Group, July, 1–7. https://doi.org/10.1038/srep29520

Yazdi, K., Rumetshofer, T., Gnauer, M., Csillag, D., Rosenleitner, J., & Kleiser, R. (2019a). Neurobiological processes during the Cambridge gambling task. Behavioural Brain Research, 356, 295–304. https://doi.org/10.1016/j.bbr.2018.08.017

Yazdi, K., Rumetshofer, T., Gnauer, M., Csillag, D., Rosenleitner, J., & Kleiser, R. (2019b). Neurobiological processes during the Cambridge gambling task. Behavioural Brain Research, 356, 295–304. https://doi.org/10.1016/j.bbr.2018.08.017

2.A SUPPLEMENTARY MATERIAL

2.A.1 Table. Trials' division in clusters

Cluster	Trials	Expected value
High Contrast	68	65>= |x| >33.33
Medium Contrast	68	16.67<= |x| <= 33.33
Low Contrast	68	1.67< |x| <16.67
No Diff	26	1.67>= |x| >=0
Strictly Dominant Blue	10	x <-65
Strictly Dominant Pink	10	x > 65
Grand Total	**125**	

2.A.2 Table. EEG data:

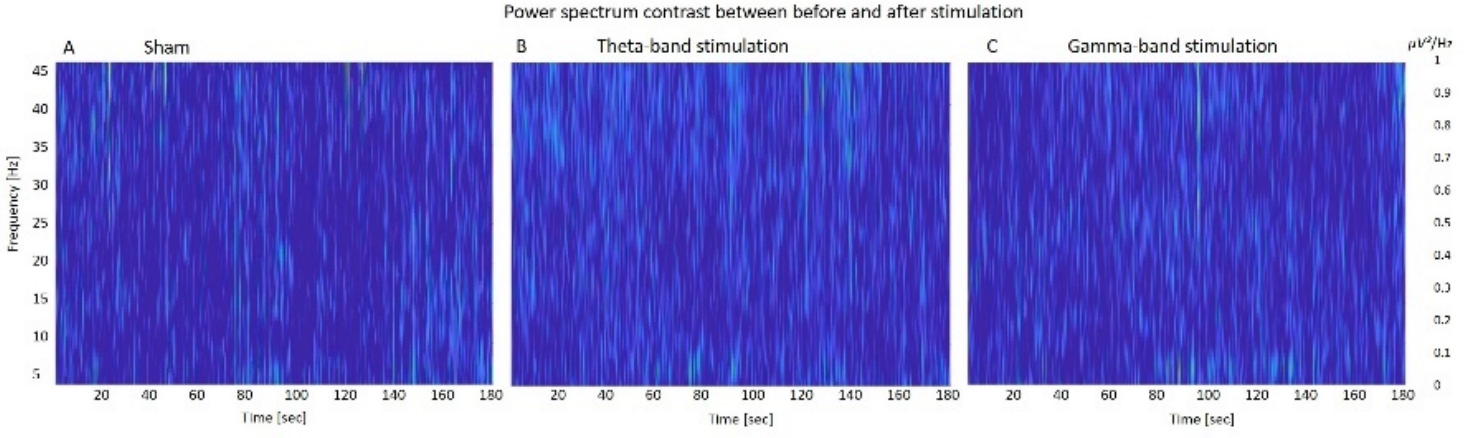
Descriptive statistics (N=31) of theta power (5–8 Hz) estimated pre and post stimulation in each electrode (F1, F5, F2, F6, P5, P6) and stimulation condition (theta, gamma, and sham).

Electrode	Mean theta power	Std. deviation
F1 Pre Theta	-.55	.56
F1 Post Theta	-.47	.61
F1 Pre Gamma	-.54	.54
F1 Post Gamma	-.45	.59
F1 Pre Sham	-.51	.61
F1 Post Sham	-.47	.61
F5 Pre Theta	.06	.53
F5 Post Theta	.12	.58
F5 Pre Gamma	.08	.55
F5 Post Gamma	.17	.58
F5 Pre Sham	.10	.54
F5 Post Sham	.14	.56
P5 Pre Theta	.16	.73
P5 Post Theta	.25	.67
P5 Pre Gamma	.15	.74
P5 Post Gamma	.29	.68
P5 Pre Sham	.16	.74
P5 Post Sham	.22	.71
F2 Pre Theta	-.68	.50
F2 Post Theta	-.61	.50
F2 Pre Gamma	-.66	.53
F2 Post Gamma	-.56	.58
F2 Pre Sham	-.59	.61
F2 Post Sham	-.55	.63
F6 Pre Theta	-.09	.48
F6 Post Theta	-.05	.54

CONTINUED.

Electrode	Mean theta power	Std. deviation
F6 Pre Gamma	-.10	.55
F6 Post Gamma	-.003	.59
F6 Pre Sham	-.04	.59
F6 Post Sham	-.002	.62
P6 Pre Theta	.24	.74
P6 Post Theta	.33	.68
P6 Pre Gamma	.16	.70
P6 Post Gamma	.31	.68
P6 Pre Sham	.23	.74
P6 Post Sham	.31	.70

2.A.3 Time-frequency analyses during the entire interval recorded:



2.A.3 - TIME FREQUENCY RANGE AVERAGED ACROSS THE ELECTRODES SURROUNDING THE STIMULATION FOCUS, F1 AND F5, DURING THREE MINUTES AFTER STIMULATION (180 SECONDS). NO SIGNIFICANT DIFFERENCES IN FREQUENCY ARE OBSERVED. TIME IS DEPICTED ON THE X AND FREQUENCY ON THE Y AXIS. WARM COLORS REFLECT AN INCREASE IN OSCILLATORY POWER. THE FIGURE SHOWS THE POWER SPECTRA FOR THE SHAM CONDITION (A), THETA-BAND STIMULATION AT 6.5 HZ (B), AND GAMMA BAND STIMULATION AT 40 HZ (C) CONTRASTING DATA RECORDED BEFORE AND AFTER EACH PROTOCOL.

3

MODULATING RISK-TAKING BEHAVIOR WITH THETA-BAND TACS

IN PRESS

ABSTRACT

Although risk is prevalent in decision-making, the specific neural processes underlying risk-taking behavior remain unclear. Previous studies have suggested that frontal theta-band activity plays a crucial role in modulating risk-taking behavior. The functional relevance of theta in risk-taking behavior is yet to be clearly established and studies using noninvasive brain stimulation have yielded inconsistent findings. We aimed to investigate this relevance using transcranial alternating current stimulation (tACS) over right or left dorsolateral prefrontal cortex (DLPFC). We also studied the influence of stimulation intensity on risk-taking behavior and electrophysiological effects.

We applied theta-band (6.5 Hz) tACS over the left (F3) and right (F4) DLPFC with lower (1.5 mA) and higher (3 mA) tACS intensities. We employed a single-blinded, sham-controlled, within-subject design and combined tACS with electroencephalography (EEG) measurements and the Maastricht Gambling Task (MGT) to elicit and evaluate risk-taking behavior.

Our results show an increase in risk-taking behavior and average choices of value after left DLPFC stimulation at both intensities and a reduction of risk-taking behavior in average choices of value after 3 mA (and not 1.5 mA) right DLPFC stimulation compared to sham. Further analyses showed a negative correlation between resting-state frontal theta-power and risk-taking behavior. Overall, frontal theta-power was increased after left, but not right, theta-band tACS independent of stimulation intensity.

Our findings confirm the functional relevance of frontal theta-band activity in decision-making under risk and the differential role of left and right DLPFC. We also were able to show that stimulation intensity did have an effect on behavioral effectsresponses, namely risk-taking behavior, average choices of value and response time. S, with significant right hemisphere stimulation effects were observed only after high-intensity stimulation. Nevertheless, electrophysiological effects were only significant after left DLPFC stimulation, regardless of tACS intensity. Furthermore, the results indicate the role of the baseline frontal theta-power in the direction of behavioral effects after theta-band tACS.

KEYWORDS: TACS, RISK-TAKING BEHAVIOR, THETA ACTIVITY, THETA FREQUENCY, DECISION NEUROSCIENCE

3.1 INTRODUCTION

Risk is constant in our lives. In economics, risk refers to a situation in which one is unsure about which outcome out of several potential others will happen; however, the probability distribution of these outcomes can be determined (Drichoutis & Lusk, 2016). Examples of risky decisions are numerous; they include trivial choices, such as taking an umbrella based on the probability of rain displayed on a weather app, and highly impactful decisions, such as financial investments or insurance. Since risk plays such a crucial role in our lives, it is important to understand the neural processes underlying decision-making concerning risks. Evidence from electroencephalography (EEG) studies indicates that frontal theta-band activity is an important component of those neural processes.

Frontal theta-band activity is correlated to processes such as cognitive control (Cavanagh & Frank, 2014a; Klírová et al., 2021; McFerren et al., 2021; Womelsdorf et al., 2010), response inhibition (Dippel et al., 2016, 2017), reward anticipation (Koul et al., 2019; Wischnewski et al., 2016) and conflict detection (Cohen & Donner, 2013), which are fundamental processes in risk-taking behavior. Moreover, frontal theta-band activity is an important component of the electrophysiological mechanism through which the dorsolateral prefrontal cortex (DLPFC) and medial prefrontal cortex (MPFC) communicate with each other (Başar et al., 2001; Cavanagh & Frank, 2014b)—two areas crucial for human decision-making and, specifically, decision-making under risk (Dantas et al., 2021a; Koul et al., 2019; Schmidt et al., 2018, 2019; Sela et al., 2012; D. Zhang & Gu, 2018).

Studies that investigated the role of frontal theta-band activity in individual economic risk-taking behavior can be divided into two groups. The first group focused on the correlation between resting-state frontal theta-power and risk-taking behavior (Gianotti et al., 2009; Massar et al., 2012, 2014; Pinner & Cavanagh, 2017; Schmidt et al., 2018), whereas the second group studied the occurrence of prefrontal theta-band activity during the decision-making process itself (Christie & Tata, 2009; Pinner & Cavanagh, 2017).

Examples of the first group are Massar and colleagues (2012 and 2014) and Gianotti and colleagues (2009). The former found that the higher the resting-state frontal theta-power (measured in the frontal midline in FZ, FCz, and CZ), the more risk-prone participants were (Massar et al., 2012, 2014). On the other hand, the latter found that it was not the midline theta-power but the frontal theta-band asymmetry in resting-state (measured as the difference between right and left prefrontal theta-power) that was correlated to increased risk-taking behavior (Gianotti et al., 2009).

The studies in the second group indicated a negative correlation between midline frontal theta-band activity measured immediately before making a risky choice (Christie & Tata, 2009; Pinner & Cavanagh, 2017). Christie and Tata (2009), however, argue that the midline increase in frontal theta-power observed during exposure to risky choices likely originates in the right anterior cingulate cortex (ACC) (Christie & Tata, 2009), indicating that the two hemispheres are not equally involved in this process.

To determine the functional relationship between frontal theta-power and risk-taking behavior using noninvasive brain stimulation techniques, such as transcranial alternating current stimulation (tACS) (Y. Z. Huang et al., 2005; Reinhart & Nguyen, 2019), is fundamental, as it allows us to experimentally manipulate oscillatory neural activity. tACS inputs an electric stimulus in a predefined frequency and sinusoidal shape over a specific brain area through electrodes placed on the scalp. This is assumed to induce or entrain brain oscillations in the same oscillatory pattern (Low Intensity Transcranial Electric Stimulation: Safety, Ethical, Legal Regulatory and Application Guidelines, 2017; Bland & Sale, 2019; Helfrich et al., 2014).

Only a few studies have used tACS to investigate the functional relevance of theta-band power in risk-taking behavior. Sela, Kilin, and Lavidor (2012) had participants perform the balloon analog risk task (BART) while stimulating either the right or left DLPFC (electrodes F4/CP6 and F3/CP5, respectively) with tACS at 6.5 Hz and 1 mA peak-to-peak intensity (Sela et al., 2012). They hypothesized that tACS applied to the left DLPFC reduces frontal theta-band asymmetry and, consequently, reduces risk-taking behavior, and right DLPFC tACS increases both frontal theta-band asymmetry and risk-taking behavior. Participants exhibited riskier behavior during left but not right or sham theta-band (6.5 Hz) DLPFC tACS, contradicting the authors' initial hypotheses (Sela et al., 2012).

In a recent study by Dantas and colleagues (2021), participants performed the Maastricht Gambling Task (MGT) while receiving tACS at 1.5 mA intensity at theta-band (6.5 Hz), gamma-band (40 Hz), or sham over the left DLPFC. Stimulation was delivered using a high-definition (HD) tACS setup over F3 [28]. Participants showed less risk-taking behavior after left theta-band tACS, a finding that is in line with the hypothesis that an increase in left theta-band power reduces risk-taking behavior. However, no significant changes in theta or gamma power that outlasted the tACS itself were observed (Dantas et al., 2021a). [28–31] Since the analysis of data from simultaneous EEG-tACS studies is challenging to analyze, electrophysiological effects of a specific stimulation protocol are best studied after the stimulation ended. However, to be able to do so, effects need to outlast the stimulation. Still, most studies that used both theta and gamma tACS at low intensities did not successfully detect electrophysiological aftereffects (Dantas et al., 2021b; Heise et al., 2019; Effects of Weak Transcranial Alternating Current Stimulation

on Brain Activity-a Review of Known Mechanisms from Animal Studies, 2013; Strüber et al., 2015). A recent noteworthy exception is Aktürk and colleagues (2022), where the aftereffects of theta-band tACS were detected after stimulation at individual theta frequency (Aktürk et al., 2022).

Wischnewski and Compen (2022) also explored the role of theta-band activity in risk-taking behavior. To that end, the group used a modified version of a sequential gambling task while applying tACS at 5 Hz and 1 mA peak-to-peak intensity, targeting the prefrontal cortex bilaterally. The group used Intra- and interhemispheric settings targeting the prefrontal cortex, each using four electrodes (5 × 3 cm). tACS was delivered during task execution, and both behavioral and EEG effects were evaluated. Their results indicated an increased perception of uncertainty but no significant changes in risk-taking behavior. However, their EEG results revealed increased theta-band asymmetry after intrahemispheric tACS and non-significant changes after interhemispheric stimulation (Wischnewski & Compen, 2022a).

These inconsistent results, observed when comparing these studies that indicate behavioral results in opposite directions or null behavioral results, can be due to a methodological choice common in tACS studies: the use of intensities between 1 mA and 1.5 mA (Bland & Sale, 2019). However, recent studies have questioned the effects of low-intensity transcranial electric stimulation (tES) in general, including both transcranial direct current stimulation (tDCS) and tACS (Alekseichuk et al., 2022; Low Intensity Transcranial Electric Stimulation: Safety, Ethical, Legal Regulatory and Application Guidelines, 2017; Widge, 2018). Despite a considerable number of studies finding behavioral and electrophysiological effects after electric stimulation, these effects are often inconsistent (Low Intensity Transcranial Electric Stimulation: Safety, Ethical, Legal Regulatory and Application Guidelines, 2017; Asamoah et al., 2019; Bland & Sale, 2019). Recent studies have indicated that it is only possible to create a cortical electric field and to obtain consistent effects with the use of higher intensities in electric brain stimulation (Low Intensity Transcranial Electric Stimulation: Safety, Ethical, Legal Regulatory and Application Guidelines, 2017; Y. Huang et al., 2017; Widge, 2018). This might explain the inconsistent results observed across studies with similar stimulation settings. Vöröslakos and colleagues (2018), for example, showed that only intensities higher than 4.5 mA significantly biased cortical alpha frequencies, with reliable electrophysiological effects observed only with intensities above 7 mA (Vöröslakos et al., 2018).

In our study, we used an experimental design that built on previous work to address two main research objectives. The first was to confirm the functional relationship between frontal theta-band power and risk-taking behavior, given the lack of consistency in the results of previous studies. To this end, we partially replicated the experimental design

of Dantas and colleagues (2021), using the MGT in a sham-controlled, within-subject design with theta-band (6.5 Hz) tACS over DLPFC. In doing so, we adopted a design that found significant behavioral effects of theta-band tACS, and we used a task known to elicit risk-taking behavior following the economic definition of risk.

The second research objective was to clarify the role of theta-power hemispheric asymmetry as an electrophysiological mechanism through which the prefrontal cortex regulates risk-taking behavior. We stimulated both the right and left DLPFC, aiming to explore the differential effects of right and left theta-band tACS in modulating risk-taking behavior. Finally, to investigate whether higher tACS intensities generate stronger (after) effects, we used two stimulation intensities (1.5 mA and 3 mA) over both stimulation sites (Figure 1). This design allowed us to study the potential different effects in terms of behavioral and EEG responses between the different stimulation protocols.

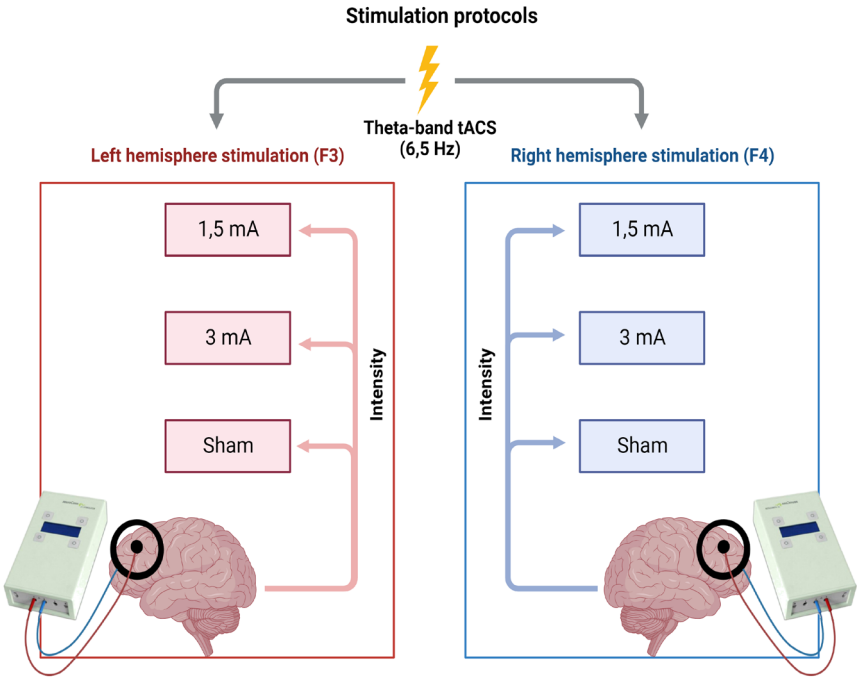


Figure 3.1 – Stimulation protocols. The left side depicts the protocols (1.5 mA, 3 mA, and sham stimulation) used over the left DLPFC (electrode position F3 of the international 10-20 EEG system); the right side depicts the protocols used over the right DLPFC (electrode position F4 of the international 10-20 EEG system).

3.2 MATERIALS AND METHODS

3.2.1 Participants

We recruited 39 healthy, right-handed participants: 30 participants (15 female, 1 non-binary, mean age 22.3 years, range 18–32 years, SD = 3.2) concluded the experiment. Four participants reported discomfort during the stimulation in the first session and did not take part in the second session. Five participants were excluded from the study because they were unable to attend the second experimental session within the requested interval of 15 days.

The participants had normal or corrected-to-normal vision and gave written informed consent after being introduced to the experiment and were screened for tACS safety (Low Intensity Transcranial Electric Stimulation: Safety, Ethical, Legal Regulatory and Application Guidelines, 2017). The study was approved by the Ethics Review Committee Psychology and Neuroscience (ERCPN) of Maastricht University, the Netherlands (ERCPN 188_07_02_2018).

3.2.2 Procedure

Participants were invited to the lab for two sessions that followed a similar procedure. The only differences between the sessions were the stimulation site, which was counterbalanced (right for session 1, left for session 2, or vice-versa) and the payment of participants' compensation by the end of session 2. During both sessions, upon arrival, participants received a full explanation of the study, filled in a pre-experimental test, and signed an informed consent form. Then, the EEG and tACS setups were prepared.
In each session, participants received three different conditions, in a counterbalanced fashion, with different stimulation protocols, namely stimulation with an intensity of 1.5 mA, 3 mA, and sham stimulation. During stimulation, participants performed the MGT. Each stimulation block was preceded by and ended with a short five-minute interval, during which we recorded three minutes of resting-state activity using EEG. The subsequent blocks followed the same protocol until the three stimulation conditions were completed. Figure 2 illustrates the detailed timeline of a session.

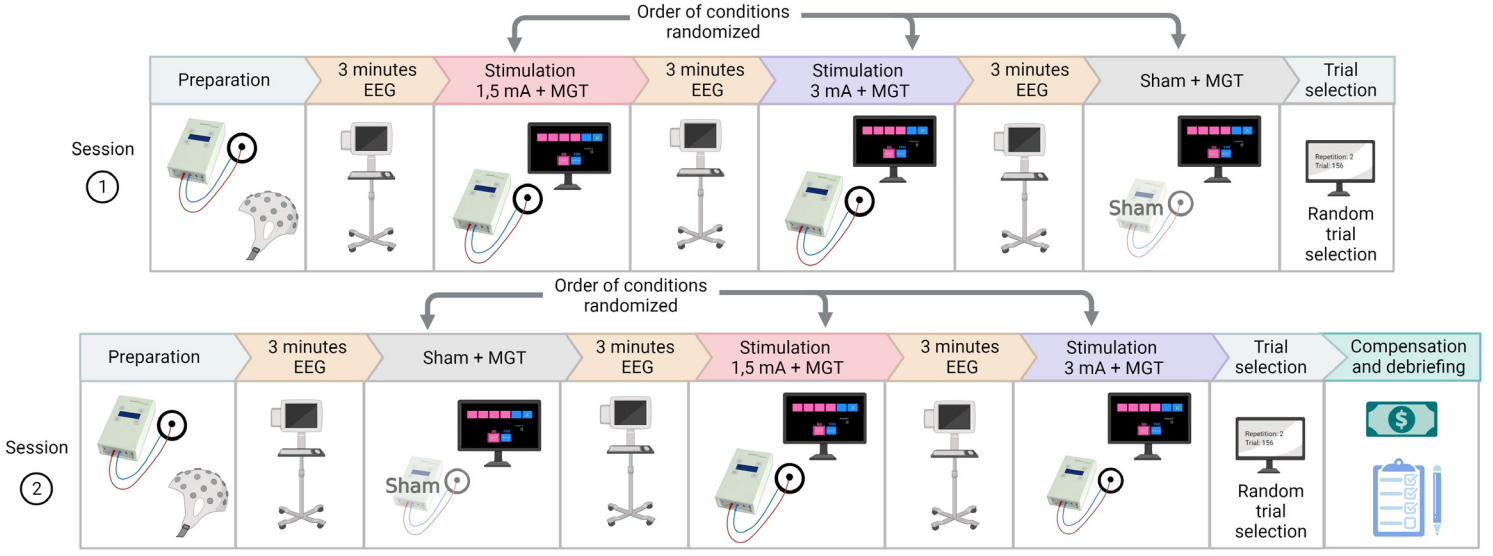


FIGURE 3.2 – EXPERIMENTAL DESIGN. THE FIGURE DEPICTS THE EXPERIMENTAL DESIGN, WHICH INCLUDES TWO SESSIONS. DURING EACH SESSION, PARTICIPANTS RECEIVED THREE DIFFERENT STIMULATION PROTOCOLS IN RANDOMIZED ORDER. THESE PROTOCOLS COULD BE EITHER THETA-BAND STIMULATION WITH (1) 1.5 MA INTENSITY, (2) 3 MA INTENSITY, OR SHAM. THE STIMULATION WAS EITHER DELIVERED OVER THE RIGHT (F4) OR LEFT (F3) DLPFC. STIMULATION WAS APPLIED DURING TASK EXECUTION (ONLINE) FOR APPROXIMATELY 20 MINUTES. BY THE END OF SESSION 2, PARTICIPANTS WERE DEBRIEFED AND COMPENSATED ACCORDINGLY.

3.2.3 The Maastricht Gambling Task (MGT)

As in Dantas et al. (2021), we used MGT to elicit and evaluate risk-taking behavior [41]. The MGT builds on the Cambridge Gambling task but avoids confounds, such as loss aversion, memory, learning, and wealth effects (Dantas et al., 2021a). In each trial of the task, six boxes were presented, and the distribution ranged from 1/6 pink boxes to 5/6 pink boxes, with the remaining boxes being blue. A token represented by a yellow cross (X) was hidden behind a random box out of the six. Participants had to guess the color of the box (blue or pink) hiding the token. The probability of the token being hidden behind a specific color was calculated by the color distribution of the boxes. One out of five different payoffs was randomly determined for each color as the reward for correct guess (5, 25, 50, 75, and 100 points). Participants received the corresponding reward if the correct color was guessed and did not receive anything otherwise. The task had 250 trials with a duration of approximately 20 minutes, in which 125 unique trials with all possible combinations of probabilities and payoffs were presented twice randomly. In each session, participants played the task three times, once during each stimulation condition.

Using this task, it is possible to evaluate different behavioral-dependent variables. The analyses focused on the level of risk taken by participants, which were calculated by considering both their choices of values and probabilities in each trial (a detailed calculation follows in the statistical analyses section). In addition to the level of risk, we evaluated participants' average choices of values, probability scores, and response times.

3.2.4 Compensation

One trial was selected at the end of each session for compensation. This was implemented in the following way: each participant could freely select one task repetition between 1 and 3 and then use an online random number generator to randomly select a trial. Each point gained in the task was converted to €0.1 in their final payment. Participants were informed about their earnings from each session right after the respective session; all payments were made after the whole experiment was concluded (session 2). After session 2, participants received both a fixed show-up fee (€7.5 or an academic credit named SONA point per hour) and the choice-dependent earnings from both sessions. Participants were compensated with vouchers that could be spent online or at local retailers; the average compensation was €40 (minimum: €5 (+5 SONA points); maximum: €60).

3.2.5 Transcranial alternating current stimulation (tACS)

Partly replicating the stimulation protocol used by Dantas and colleagues (2021), we targeted the left DLPFC (F3, based on the international 10-20 EEG system) and right DLPFC (F4, based on the international 10-20 EEG system) using an HD tACS setup composed of a small circular electrode (diameter: 2.1 cm; thickness: 2 mm) and a large rubber ring tACS electrode (outer diameter: 11 cm; inner diameter: 9 cm; thickness: 2 mm) (neuroConn, Ilmenau, Germany) fixed using conductive gel (Ten20 conductive Neurodiagnostic electrode paste, WEAVER and company, Aurora, CO, USA) and keeping the electrode impedance below 15 kΩ (Dantas et al., 2021c). HD tACS was applied in a single-blinded fashion using a neuroConn DC-stimulator (neuroConn, Ilmenau, Germany) set at 6.5 Hz frequency (theta-range stimulation) and two different intensities: 1.5 mA (as used in Dantas et al. 2021) and 3.0 mA.

The stimulation, which lasted on average for 20 minutes, was delivered during the task. During sham tACS, the stimulation was ramped up for 30 seconds and ramped down immediately after. Breaks of around five minutes (including three minutes of EEG recording) were taken between different stimulation protocols. The simulations of the different protocols were modeled using SimNIBS (Thielscher et al., 2015) and are shown in Figure 3.

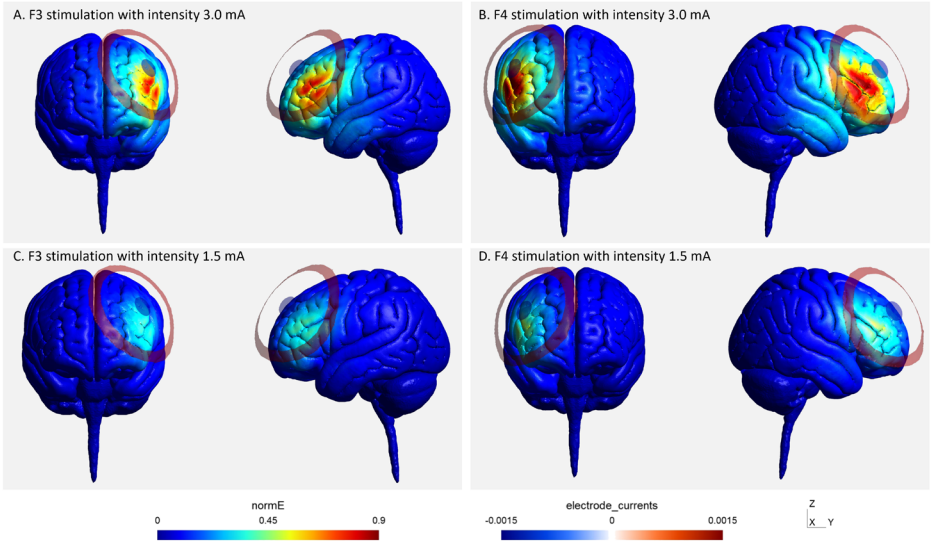


Figure 3.3 – SimNIBS HD tACS simulation. Simulations using 3.0 mA (A and B) and 1.5 mA (C and D) intensities. A and C show the front and left views of the stimulation made at F3. B and D show the front and right views of the stimulation made at F4. The colors stand for the normalized electric field (0–0.9), red areas indicate higher .

3.2.6 Electroencephalography (EEG)

To record prefrontal theta-band power, EEG electrodes were positioned on F1, F5, F2, F6, FZ, and FpZ (according to the 10-20 international EEG system). We recorded EEG immediately before and immediately after each of the three blocks of task and stimulation. Each EEG measurement lasted three minutes, and participants were asked to avoid any movement and stay relaxed with their eyes closed.

The BrainAmp Standard EEG amplifier and BrainVision Recorder software (BrainProducts GmbH, Munich, Germany) were used for data recording (DC: 200 Hz; sampling rate: 500 Hz). The electrode impedance was kept below 15 kΩ. The data were preprocessed (offline) using the FieldTrip toolbox (Oostenveld et al., 2011; Popov et al., 2018) and custom MATLAB scripts, during which the EEG recordings were low-pass filtered in the analog domain (cutoff frequency: 250 Hz) and digitized (sampling rate: 1000 Hz). A notch filter (50 Hz) was used to remove electrical noise and demean the data over the full dataset. The data were segmented into 90 trials of two seconds each. To exclude trials with high variance and excessive noise, variance analyses and visual inspection were performed.

The EEG data were preprocessed using a fast Fourier transformation with hanning tapers and output frequencies between 1 Hz and 20 Hz with FieldTrip (Oostenveld et al., 2011). Afterwards, we used custom MATLAB (*MATLAB R2018b*, 2018) scripts to average the data's power spectra for the pre-stimulation and each one of the measurements after the three stimulation protocols per session. We defined the theta-band to be between 5 Hz and 8 Hz, with 1.5 Hz above and 1.5 Hz below the stimulation frequency (6.5 Hz). The theta power was then analyzed per channel by comparing the data obtained after the different stimulation protocols with the pre-stimulation measurement.

3.2.7 Statistical Analyses

The data collected and codes used are available at https://data.mendeley.com/datasets/3ys3kw9mf6, thus ensuring the transparency of our findings and facilitating their reproducibility. The behavioral data were preprocessed using custom MATLAB scripts (Mathworks Inc., Massachusetts, USA). We analyzed four behavioral-dependent variables—risk, probability scores, value, and response time—and the EEG data. The statistical analyses were conducted using custom R scripts (R Core team, 2015).

3.2.7.1 RISK

To analyze risk, we first calculated each participant's level of risk in the chosen option per trial. During each MGT trial, participants were asked to choose a color, blue or pink, where X represents the payoff associated with the chosen color. Each color has a probability p of hiding a token. By guessing the color that hides the token correctly,

participant can win a payoff x, which can be equal to X if the participant guesses the color correctly or zero otherwise. This means that this specific trial would have an expected payoff of *xp* or $EX=xp$. To calculate participants' risk-taking, we calculated the trial's level of variation (Tobler et al., 2007), where the variance of payoffs from choosing color X in trial *i* is given by the following equation:

$$VarXi=\sum px-E(X)2. \quad (1)$$

From the variance, we calculated the trial's standard deviation as the square root of the trial's variation. The resulting score is our measure of risk-taking (e.g., Myerson, 2005) behavior and the main dependent variable, which, from now on, is referred to as "Risk."

$$Risk=SD=VarX \quad (2)$$

As each unique trial was presented twice during a complete MGT, we averaged the results of both repetitions for each participant in each MGT trial. These results were analyzed at the group level by fitting a linear mixed model (LMM) to predict risk-taking behavior (Risk), with session (sessions 1 and 2), side (stimulation site left and right DLPFC), condition (sham, 1.5 mA, and 3 mA) and their interaction (side*condition) as factors (formula: Risk ~ session + side + condition + side*condition, estimated using REML and nlminb optimizer), and using a first-order autoregressive covariance structure (AR1). The remaining possible interactions were excluded from the model, as they were not significant and did not improve the model's fit. The model included participant per trial as a random effect accounting for the individual differences in participant's responses to the different trials presented during the task execution.

The post hoc analyses also included the number of stimulation exposures (StimExp, 0, 1, or 2) and session (1 or 2) as factors in a LMM (estimated using REML and nlminb optimizer) to predict Risk (formula: Risk ~ session + side + condition + StimExp + session * condition + session * StimExp + side * condition) and used a first-order autoregressive covariance structure (AR1). Again, the model included participant per trial as a random effect. The analyses presented normally distributed residuals and showed no heteroscedasticity, and no observations were removed as outliers.

3.2.7.2 PROBABILITY SCORES

Replicating the analyses used by Dantas and colleagues (2021), we calculated probability scores (Prob) indicating the probability of winning associated with the color chosen by the participants in each trial of the MGT. This approach, similar to what was used in several previous studies (Boggio, Zaghi, et al., 2010; Fecteau, Pascual-leone, et al., 2007; Knoch et al., 2006), considered a choice risky if the winning probability was

below 50% and safe if it was above 50%. Aiming to conduct a more detailed analysis of a participant's choices of probabilities, we classified them into a scale ranging from -2 to 2, where options with 1/6 probabilities received a score of 2 and options with probabilities of 2/6 received a score of 1 and so on (Dantas et al., 2021b). The choices of options with a higher probability received a negative score, while choices of lower probabilities received a positive score, as used in previous studies (Fecteau, Knoch, et al., 2007; Fecteau, Pascual-Leone, et al., 2007; Minati et al., 2012; Rogers et al., 1999). These probability scores can be seen in 3.A.2.

The statistical analyses were done by fitting a LMM (estimated using REML and nlminb optimizer) to predict the effects of session, side, condition, and the interaction between side and condition on participants' probability scores (formula: Prob ~ session + side + condition + side*condition) and using a first-order autoregressive covariance structure (AR1). The remaining interactions were excluded for not being significant and not improving the model's fit. Again, participant per trial was used as a random effect. The analyses presented normally distributed residuals and showed no heteroscedasticity. No observations were removed as outliers.

3.2.7.3 VALUE

Participants' choices of values (Value) were calculated as the average payoffs of the options they chose in the MGT. Since the color chosen was associated with a payoff in each trial, this choice was computed independently of the trial's outcome. The average value data were analyzed using an LMM (estimated using REML and the nlminb optimizer). We fitted the model to predict the effects of session, side, condition, and the interaction side*condition on Value (formula: Value ~ session + side + condition + side*condition). The model included participant per trial as a random effect. Again, the analyses presented normally distributed residuals and showed no heteroscedasticity. There were no outliers.

3.2.7.4 RESPONSE TIME

Response time (RT) was calculated as the time difference between the trial onset and the participants' finger press on the keyboard. Unlike the other dependent variables analyzed, the data on participants' response time included outliers. We used custom R scripts to remove observations outside 1.5 times the interquartile range above the upper quartile and below the lower quartile (R Bloggers, 2011). A total of 1598 observations (of different participants) were removed, leaving 20152 observations.

Afterwards, we fitted an LMM (estimated using REML and nlminb optimizer) to predict RT. Session, side, condition, and its interactions were used as factors (formula: RT ~ session + side + condition + session * side + session * condition + condition * side +

session * side * condition). Participant per trial was included as a random effect. The final analyses presented normally distributed residuals and showed no heteroscedasticity.

3.2.7.5 EEG DATA

For the EEG analyses, we fitted a LMM (estimated using REML and nlminb optimizer) to predict the theta power in each of the electrodes (F1, F2, F5, F6, FZ, and FpZ), with side (left and right), stimulation condition (sham, 1.5 mA, and 3 mA), and their interaction (side*condition) as factors (formula: theta-power ~ condition + side + condition * side) and used a compound symmetry covariance structure. The model included participant per trial as a random effect.

Considering the findings in the literature regarding the correlation between frontal theta-band asymmetry and risk-taking behavior (Dantas et al., 2021b; Gianotti et al., 2009; Sela et al., 2012), we ran further analyses including the levels of frontal theta-band asymmetry (AsymPre) into our model (formula: Risk ~ AsymPre + side + condition + AsymPre * side + AsymPre * condition + side * condition). Again, we included participant per trial as a random effect. In this step, we investigated whether the resting-state frontal theta-band asymmetry, measured before task and stimulation, could help predict risk-taking behavior. We estimated participants' frontal theta-band asymmetry by calculating the difference in theta power measured by averaging the right hemisphere (F2 and F6) minus the left hemisphere (F1 and F5) (Gianotti et al., 2009).

To further investigate the relationship between resting-state and frontal theta-power, we also included the average theta-power estimated in the right (AVRIGHTPRE, averaging F2PRE and F6PRE), left (AVLEFTPRE, averaging F1PRE and F5PRE), and midline (AVMIDLINEPRE, averaging FZPRE and FpZPRE) before the stimulation or task as factors in a mixed model to predict Risk (formula: Risk ~ AVLEFTPRE + AVRIGHTPRE + AVMIDLINEPRE + SESSION + side + condition + AVLEFTPRE * AVRIGHTPRE + condition * side + AVLEFTPRE * condition + AVRIGHTPRE *condition + AVMIDLINEPRE * condition). The remaining possible interactions were excluded from the model, as they were not significant and did not improve the model's fit. The model included participant per trial as a random effect. No covariance structure was used.

The final step of our analyses is a series of Pearson correlation analyses including Risk and the EEG measurements before stimulation and task, aiming to achieve a better understanding of the relationship between frontal theta-power and risk-taking behavior.

3.3 RESULTS

3.3.1 Behavioral Results

In this section, we present the main behavioral results of our experiment. The detailed statistical methodology can be found in the Statistical Analyses section.

3.3.1.1 MAIN RESULTS: RISK

When analyzing the effects of both stimulation intensities over the left hemisphere on risk-taking behavior, the LMM analysis showed a statistically significant and positive conditional effect of both 1.5 (beta = 0.23, t(21714) = 2.31, p = 0.021) and 3 mA (beta = 0.35, t(21714) = 3.51, p < .001) theta-band tACS compared to sham. Thus, risk-taking behavior increased after both 1.5 mA and 3 mA tACS over the left DLPFC (F3).

To evaluate the effect of both stimulation intensities over the right hemisphere on risk-taking behavior, we analyzed the interaction between side (right) and intensity (sham, 1.5 mA, and 3 mA), again compared to sham. The LMM analysis showed a nearly significant and negative conditional effect of 1.5 mA tACS (beta =-0.27, t(21714) =-1.91, p = 0.056) and a significant negative conditional effect of the interaction between 3 mA stimulation and the right side (beta =-0.50, t(21714) =-3.27, p = 0.001), compared to baseline (sham). Hence, risk-taking behavior was significantly reduced only after the 3 mA theta-band tACS over the right DLPFC (F4).

We did not find significant effects of session (beta =-0.08, t(21714) =-0.76, p = 0.450) or stimulation side, comparing sham over left DLPFC to sham over right DLPFC (beta = 0.10, t(21714) = 0.76, p = 0.448). This means that participants had no significant differences in risk-taking behavior between the sessions. Further, there was no difference in their behavior due to the simple placement of the stimulation setting over the right or left hemispheres (without active stimulation).

As we saw a significant increase in risk-taking behavior after left 1.5 mA (and 3 mA) stimulation, we ran post hoc analyses by adding the amount of exposure to stimulation as a factor. These analyses accounted for the possibility of spillover effects of stimulation, considering that participants were stimulated twice (plus sham) within one session. The full report of these post hoc analyses is available in supplementary material 3.A.3. Of note, we observed a significant reduction of risk-taking behavior as the amount of exposure to stimulation increased (beta =-0.36, t(21710) =-3.61, p < .001), and a replication of the findings of Dantas and colleagues (2021), with a significant reduction in risk-taking behavior after left 1.5 mA stimulation (beta =-0.50, t(21710) =-3.31, p < .001).

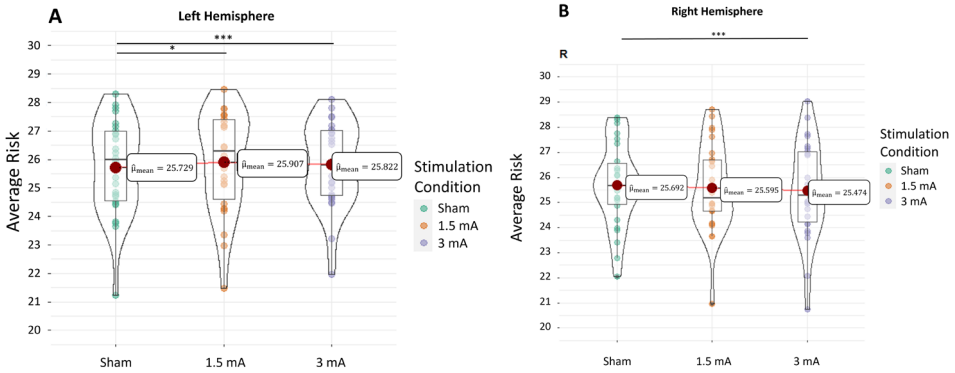


*Figure 3.4 – Average risk-taking behavior by stimulation condition and hemisphere. The average risk-taking was estimated by the average standard deviation of each participant's choice across stimulation conditions (Sham in green, 1.5 mA in purple, and 3 mA in orange) over the left DLPFC (left hemisphere) and the right DLPFC (right hemisphere). The figure depicts the individual average risk-taking behavior (dots), the group average by stimulation condition (bars), and the mean by stimulation condition (dark red marks). * p < .05; ** p < .01; *** p < .001.*

3.3.1.2 PROBABILITY SCORES

The analyses of probability scores showed a significant negative effect of session, indicating that participants chose significantly lower probabilities during session 2 (beta = -0.04, t(21714) = -3.87, p < .001) compared to session 1. Although there was a nearly significant positive effect of the 1.5 mA stimulation over the left hemisphere (beta = 0.02, t(21714) = 1.83, p = 0.067), there were no significant effects of any of the stimulation conditions.

3.3.1.3 VALUE

Regarding participants' average choice of value, there were significant effects of both stimulation protocols over the right and left hemispheres. Stimulation over the left hemisphere led to a significant increase in the average choices of value. This effect was found for both intensity levels: 1.5 mA (beta = 0.49, t(21714) = 2.23, p = 0.026) and 3 mA (beta = 0.78, t(21714) = 3.44, p < .001).

The stimulation over the right hemisphere led to a significant reduction in the average value chosen only at 3 mA (beta =-1.11, t(21714) =-3.24, p = 0.001), and not at 1.5 mA stimulation (beta =-0.55, t(21714) =-1.74, p = 0.082). There were no significant effects of either session (beta =-0.23, t(21714) =-0.95, p = 0.342) or side (beta = 0.23, t(21714) = 0.75, p = 0.455) on participants' choice of value.

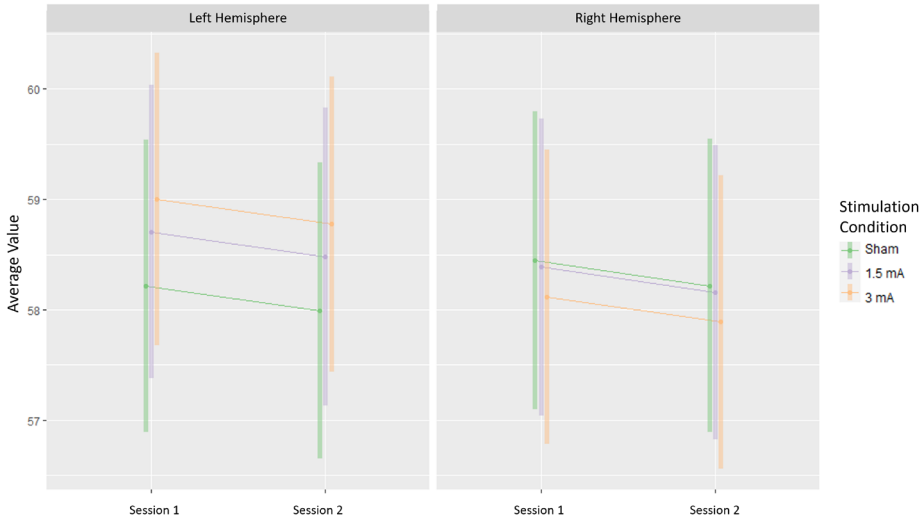


Figure 3.5 – Average value choices by stimulation condition and hemisphere. The figure depicts the average choices of payoff or the value per session (x axis), the stimulation condition (lines), and the hemisphere stimulated (left and right).

3.3.1.4 RESPONSE TIME

Participants' response time was significantly lower in session 2 compared to session 1 (beta = -0.18, t(20111) = -2.74, p = 0.006). During session 1, both 1.5 mA (beta = -0.03, t(20111) = -4.20, p < .001) and 3 mA (beta = -0.02, t(20111) = -2.31, p = 0.021) stimulation over the left hemisphere led to a significant reduction in RT. tACS over the right hemisphere in session 1 led to increases in RT, with similar effects during 1.5 mA (side right * intensity 1.5 Ma, beta = 0.09, 95% CI [0.07, 0.12], t(20111) = 7.05, p < .001) and 3 mA (side right * intensity 3 Ma, beta = 0.09, 95% CI [0.07, 0.12], t(20111) = 7.05, p < .001) stimulation.

The interactions of the different stimulation conditions with the sessions were mainly significant. There was a significant positive effect of the 3 mA stimulation over the left hemisphere (session 2*intensity 3 mA, beta = 0.03, t(20111) = 2.19, p = 0.028), with non-significant changes in response time observed during 1.5 mA over the left hemisphere in session 2 (beta = 0.02, t(20111) = 1.39, p = 0.165). The stimulation over the right hemisphere during session 2 yielded significant negative effects during both 1.5 mA (side right * intensity 1.5 mA * session 2, beta = -0.09, t(20111) = -5.06, p < .001) and 3 mA stimulation (side right * intensity 3 mA * session 2, beta = -0.10, t(20111) = -5.79, p < .001).

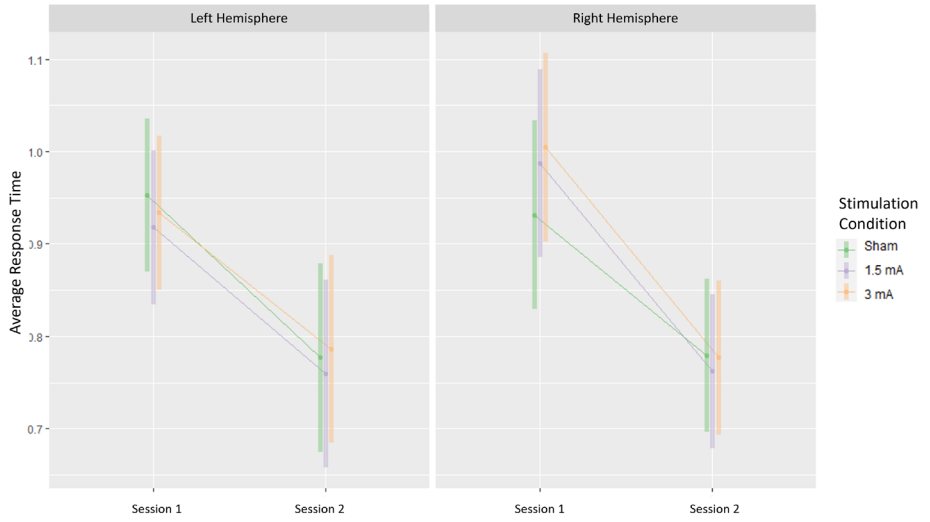


Figure 3.6 – Average response time by stimulation condition and hemisphere. The figure depicts the average response time per session (x axis), the stimulation condition (lines), and the hemisphere stimulated (left and right).

3.3.2 EEG Results

3.3.2.1 THETA-BAND ENTRAINMENT

To evaluate the potential entrainment effects, we compared theta-power levels before the task (resting-state: eyes closed) with theta-power levels immediately after the task and stimulation (resting-state: eyes closed). The estimated theta power was averaged for the left hemisphere (left, F1, and F5), right hemisphere (right, F2, and F6), and midline (midline, FZ, and FpZ). The analyses showed a significant or a nearly significant increase in theta power after left but not right tACS. This increase was not only limited to the left hemisphere but was also observed in the right hemisphere and midline. The results by side after left DLFPC tACS are depicted in Table 1, and the results after right DLPFC stimulation are detailed in Table 2 (the detailed results per electrode are available in supplementary material 3.A.4).

Table 2 –Theta power measured after left DLPFC stimulation. Results compared to measurements in the resting-state before stimulation and task.

Stimulation over the left DLPFC						
Average by side	**Condition**	**Estimates**	**std. Error**	**CI**	**p**	**df**
Left	SHAM	0.25	0.07	0.11 – 0.38	**0.001**	198
Left	1.5 mA	0.14	0.07	0.00 – 0.28	**0.045**	198
Left	3 mA	0.18	0.07	0.04 – 0.32	**0.01**	198
Right	SHAM	0.25	0.06	0.12 – 0.37	**<0.001**	198
Right	1.5 mA	0.15	0.06	0.02 – 0.27	**0.02**	198
Right	3 mA	0.19	0.06	0.07 – 0.31	**0.002**	198
Midline	SHAM	0.22	0.06	0.10 – 0.34	**<0.001**	198
Midline	1.5 mA	0.14	0.06	0.01 – 0.26	**0.029**	198
Midline	3 mA	0.17	0.06	0.05 – 0.29	**0.007**	198

Table 2:Theta power measured after the right DLPFC stimulation. Results compared to measurements in the resting-state before stimulation and task.

Stimulation over the right DLPFC						
Average by side	**Condition**	**Estimates**	**std. Error**	**CI**	**p**	**df**
Left	SHAM	-0.12	0.1	-0.32 – 0.08	0.243	198
Left	1.5 mA	-0.02	0.1	-0.22 – 0.19	0.882	198
Left	3 mA	-0.01	0.1	-0.21 – 0.19	0.928	198
Right	SHAM	-0.13	0.09	-0.30 – 0.05	0.152	198
Right	1.5 mA	0	0.09	-0.18 – 0.17	0.957	198
Right	3 mA	-0.01	0.09	-0.19 – 0.17	0.92	198
Midline	SHAM	-0.09	0.09	-0.27 – 0.09	0.309	198
Midline	1.5 mA	0.02	0.09	-0.16 – 0.20	0.856	198
Midline	3 mA	0.04	0.09	-0.14 – 0.22	0.671	198

3.3.2.2 THETA-POWER AND RISK-TAKING BEHAVIOR

We first assessed whether resting-state frontal theta-band asymmetry significantly affected individual risk-taking behavior. The levels of theta-band asymmetry measured during resting-state (before stimulation or task) did not significantly affect the levels of risk-taking behavior (beta = -4.05, t(28) = -1.70, p = 0.101). Nevertheless, there was a significant effect of the interaction between resting-state frontal theta asymmetry and 1.5 mA stimulation over the left (but not right) hemisphere (beta = 1.43, t(21712) = 2.55, p = 0.011), indicating a significant increase in risk-taking behavior.

Exploring this relationship in more detail, we added the average theta power measured over the right (AVRIGHTPRE, F2, and F6), left (AVLEFTPRE, F1, and F5), and midline electrodes (AVMIDLINEPRE, FZ, and FpZ) into the model to estimate the effects of such factors on risk-taking behavior. The results of this analysis showed a reduction in risk-taking behavior from session 1 to session 2 (beta = -0.31, t(21708) = -4.79, p <

.001). We also found a negative effect of the interaction between resting-state theta-power measured on the right and left hemispheres, meaning that this interaction led to reductions in risk-taking behavior and is statistically significant and negative (beta = -1.12, t(25) =-3.24, p = 0.002). This indicates that participants' resting-state theta-power significantly affects their risk-taking behavior. Again, we observed a significant effect of the interaction between the right side and stimulation at 3 (beta =-0.38, t(21708) =-2.48, p = 0.013). Furthermore, we observed a significant effect of the interaction between the theta-power measured before the stimulation in the right hemisphere and 1.5 mA stimulation, which led to increased risk-taking behavior (beta = 1.99, t(21708) = 2.02, p = 0.044), indicating that the stimulation effects are state-dependent. Supplementary material 3.A.5 presents the full results of this analysis.

To study the correlation between risk-taking behavior and the levels of baseline theta-power (before task and execution), we performed a correlation analysis between the average resting-state frontal theta-power (measured in the left, middle, and right hemispheres) and participants' risk-taking behavior. These correlation analyses show significant negative correlations between risk-taking behavior and the average frontal theta-power in the left (r =-0.03, t(21748) =-4.57, p < 0.001) and right (r =-0.04, t(21748) =-5.23, p < 0.001) hemispheres. We also evaluated the correlation between resting-state frontal theta-band frontal asymmetry (right–left average theta-power) and risk-taking behavior, which was again negative and significant (r =-0.02, t(21748) =-3.47, p = 0.024). However, the correlation coefficients indicate that the correlation between frontal left and right resting-state theta-power is stronger than the correlation obtained between resting-state frontal asymmetry and risk-taking behavior. Overall, our results indicate a significant negative correlation between resting-state frontal theta-power measured before task/stimulation and participants' risk-taking behavior.

3.4 DISCUSSION

Several EEG studies have shown a correlation between frontal theta-band power and risk-taking behavior (Gianotti et al., 2009; Knoch et al., 2006; Massar et al., 2012, 2014; Schiller et al., 2014; Schmidt et al., 2018, 2019). Although the functional relevance of this theta-band power in risk-taking behavior has been studied, evidence from studies that experimentally modulated this oscillatory frequency band using NIBS is sparse and inconsistent. To investigate the functional relationship between frontal theta-band activity and risk-taking behavior, we utilized a within-subject design with single-blinded sham control and combined EEG-HD tACS application (6.5 Hz) to the left and right DLPFC during the execution of the MGT (Dantas et al., 2021b). EEG was recorded before and immediately after task execution and stimulation. Our design also included two stimulation intensities: 1.5 mA and 3 mA [25,37].

3.4.1 Behavioral Results

As initially hypothesized, the behavioral results confirm the functional relevance of frontal theta-band activity and the modulation of risk-taking behavior. We found increased risk-taking behavior after left theta-band tACS (1.5 mA and 3 mA) and reduced risk-taking behavior after high intensity (3 mA) but not low intensity (1. 5 mA) after right DLPFC theta-band tACS. These findings indicate that frontal theta-band activity plays a functional role in decision-making under risk, that it plays an important part in the electrophysiological mechanism involved in the processing and modulation of this type of behavior (Gianotti et al., 2009; Massar et al., 2012, 2014; Studer et al., 2013).

When looking at participants' choices of probabilities, we did not find any effects of tACS, which is in line with the findings of Dantas and colleagues (2021). However, our results show a significant shift toward choosing lower probabilities from Session 1 to Session 2. This shift toward choosing options with lower probabilities can signal an increase in risk proneness over time due to a higher familiarization with the task (Chuang & Schechter, 2015; Dion & Miller, 1971). However, this increase was not reflected in participants' risk-taking behavior. Further studies are needed to investigate this effect of time on probability choices.

Participants' average choices of values, on the other hand, were significantly higher during the left hemisphere tACS (high and low intensity) compared to sham. This effect was in the same direction as the effects observed in risk-taking behavior. Again, in line with these effects, tACS to the right DLPFC led to a significant reduction in average value choices. However, the reduction in average value choices was observed only during high-intensity tACS. Considering our use of the standard deviation of the chosen option as a measure of risk (which accounts for both probabilities and values), the observed results indicate that the changes in risk-taking behavior were mainly driven by the changes in the average value sensitivity. These results are in line with previous studies, indicating that a lower sensitivity to value is associated with reduced risk-taking behavior (Boggio, Campanhã, et al., 2010; Dantas et al., 2021b; Fecteau, Knoch, et al., 2007; Gilmore et al., 2018; Levasseur-Moreau & Fecteau, 2012).

The effects of tACS on response times were session-dependent. In session 1, left DLPFC tACS (1.5 mA or 3 mA) led to significant decreases in response time, while right DLPFC stimulation (1.5 or 3 mA) led to increases in response time. In session 2, response times were generally faster, and the direction of the stimulation effects was the opposite of what was observed in session 1. During session 2, left hemisphere stimulation (3 mA) resulted in increases in response time, while right hemisphere stimulation (1.5 mA or 3 mA) led to reductions. These findings indicate that, at baseline, theta-band tACS over the right hemisphere increases response time. However, when the task is repeated in

session 2 and the participant has faster responses, this same protocol will potentialize these "natural" responses, leading to steeper decreases in response times. The opposite logic seems to apply to left hemisphere stimulation. This proposed mechanism can, however, only be speculated, and more research is necessary to better understand the effect of frontal theta-band tACS on response time during risky decision-making.

3.4.2 EEG Results

The electrophysiological data were analyzed to evaluate the possible oscillatory entrainment of theta-band tACS. The comparison between the frontal theta-power recorded during three minutes immediately before and after the stimulation and task showed a significant increase in theta-power after sham stimulation. These findings indicate that theta-power increases as a response to the decision-making task, which is in line with the EEG literature on risk-taking behavior, according to which frontal theta-band activity increases when exposed to risky choice environments (Christie & Tata, 2009; Pinner & Cavanagh, 2017; Schmidt et al., 2018).

When comparing the active stimulation protocols, after left DLPFC tACS, at 1.5 mA or 3 mA, we observed a general increase in left, right, and midline theta-power. No significant electrophysiological aftereffects were observed after the right DLPFC tACS.

STIMULATION INTENSITY

Recent studies have questioned the cortical reach of low-intensity transcranial electric stimulation (tES). They have indicated that the low intensities commonly used in studies, such as 1 mA or 1.5 mA, are not sufficient to reach the cortex, considering the electric resistance created by the scalp [25,35,36]. We therefore tested the effect of a lower and a higher-intensity tACS on risk-taking.

According to our findings, lower-intensity tACS may in some cases not be enough to consistently induce behavioral effects (Sela et al., 2012; Wischnewski & Compen, 2022a). For example, while both 1.5 mA and 3 mA left prefrontal cortex stimulation significantly increased risk-taking behavior and frontal theta-power (compared to sham), we did not find significant changes in risk-taking behavior during right hemisphere stimulation at 1.5 mA intensity. These null results are in line with Sela and colleagues (2012), where no behavioral changes were observed after 1 mA right DLPFC peak-to-peak stimulation. Nevertheless, the stimulation of the right DLPFC with 3 mA tACS in our study led to a significant reduction in risk-taking behavior. Hence, it might be necessary to use higher tACS intensities to robustly find behavioral responses (Low Intensity Transcranial Electric Stimulation: Safety, Ethical, Legal Regulatory and Application Guidelines, 2017; Asamoah et al., 2019; Bland & Sale, 2019; Widge, 2018). These results indicate that a possible reason for inconsistent results in behavioral responses can be the use of low-intensity

stimulation protocols (Alekseichuk et al., 2022; Effects of Weak Transcranial Alternating Current Stimulation on Brain Activity-a Review of Known Mechanisms from Animal Studies, 2013; Schutter, 2016).

While electrophysiological theta-band tACS aftereffects are often not found (Bland & Sale, 2019; Dantas et al., 2021b), recent studies have detected significant changes in theta-power with the use of intrahemispheric montage (Wischnewski & Compen, 2022b) or by applying tACS at individual theta-power (Aktürk et al., 2022; D. W. Zhang et al., 2022). In our study, left hemisphere tACS led to significant increases in theta-power, with higher (albeit not significantly different) estimated increases after 3 mA stimulation than after 1.5 mA tACS.

There were no significant changes in theta-power after right tACS, although we saw a decrease in risk taking behavior after 3 mA right DLPFC stimulation. While one might argue that a higher tACS intensity may be required for significant electrophysiological aftereffects in general, the question remains as to why this seems to be the case after right, but not left, hemispheric stimulation. Thus, further studies investigating the effect of different stimulation intensities on different stimulation sites are needed.

3.4.3 Interhemispheric stimulation

We were able to show behavioral effects after right and left theta-band tACS, with a significant increase in risk-taking behavior after left DLPFC tACS (both 1.5 and 3 mA) and a significant reduction in risk-taking behavior after right stimulation (3 mA only). These changes in risk-taking behavior confirm that different hemispheres have different roles in this electrophysiological mechanism, since the stimulation of each hemisphere induced behavioral changes in opposite directions, which is in line with previous findings (Gianotti et al., 2009; Goel et al., 2007; Li et al., 2019; Schiller et al., 2014).

However, although side of stimulation seems to play a key role in the modulation of risk-taking behavior, the results indicate that the relationship between frontal theta-power in each hemisphere and the modulation of risk-taking behavior is not simply derived from the levels of frontal theta-band asymmetry, as suggested by Gianotti and colleagues (2009) (Gianotti et al., 2009).

Consistent with Gianotti and colleagues (2009), we observed a significant negative correlation between risk-taking behavior and frontal theta-band asymmetry, which indicates that higher frontal theta-band asymmetry was correlated with lower levels of risk-taking behavior. However, our results revealed that the negative correlations between frontal theta-power and risk-taking behavior were also significant and stronger than the correlation observed between frontal asymmetry and risk-taking behavior.

These findings indicate that frontal theta-power during resting-state is also a strong indicator of individual risk proneness, and that this is independent of right–left theta power asymmetry.

Moreover, resting-state frontal asymmetry did not significantly affect risk-taking behavior when included as a factor in our analyses, while the interaction between theta-power measured on the right and left hemisphere had a significant negative effect on risk-taking behavior. These findings indicate that the frontal theta-power significantly affects risk-taking behavior, and that the relative difference between hemispheres (asymmetry) does not.

3.4.4 State-dependent Effects

As previously mentioned, we found significant effects of resting-state theta-power on risk-taking behavior. Specifically, when adding the average left, right, and midline resting-state theta-power to our LMM to evaluate the effects of such factors on risk-taking behavior, we saw that the interaction between average theta-power in the right and left hemispheres led to significant negative effect on risk-taking behavior. This means that the higher theta power in both the right and left DLPFC the lower risk-taking behavior, in our experimental conditions.

The same analyses showed significant effects of right DLPFC 3 mA stimulation, which again reduced participants' risk-taking behavior. However, the left hemisphere stimulation effect was dependent on participants' resting-state frontal theta-power. We only observed significant results when the left hemisphere stimulation (at 1.5 mA) interacted with the resting-state theta-power measured in the right hemisphere, which yielded significant increases in risk-taking behavior. We also added resting-state frontal theta-band asymmetry (left–right theta-power) as a factor to our LMM, and this factor did not significantly affect participants' risk-taking behavior. However, again, the interaction between frontal theta-band asymmetry and left 1.5 mA tACS yielded significant increases in risk-taking behavior.

These findings suggest that the effects of theta-band tACS are potentially state-dependent, implying that although the involvement of theta-band activity in the modulation of risk-taking behavior is clear, the direction of the results observed after theta-band tACS in risk-taking behavior potentially depends on the participants' baseline frontal theta-power. Nevertheless, since our experimental design does not include a full EEG set, it is not possible to reliably attribute these measurements to specific brain areas.

The post hoc behavioral analyses provided further evidence of state dependence. Despite aligning with Sela and colleagues (2012), where left DLPFC theta-band tACS

increased risk-taking behavior, the current results differed from those reported by Dantas and colleagues (2021). Further analyses revealed that longer exposure to stimulation resulted in reduced risk-taking behavior. Additionally, left hemisphere stimulation at 1.5 mA led to significant reductions in risk-taking behavior (in line with Dantas et al., 2021), while non-significant effects were observed at 3 mA tACS when controlling for the amount of stimulation exposure. However, the behavioral effects of right hemisphere stimulation were not affected by adding these factors in the model.

While our design aimed at controlling for spillover effects by having short breaks between the different stimulation conditions, it is possible that the sequence of stimulation protocols and/or the repetition of the task could account for the observed differences in effect direction. Therefore, further research is needed to disentangle the effects of the task and stimulation.

Overall, our findings confirm the relevance of frontal theta-band activity in risk-taking behavior [20,68]. Our results further indicate that, based on EEG data, it is possible to estimate an individual's risk proneness, which is a relatively simple method independent of a specific task. More importantly, we contribute to the field of decision neuroscience and advance our knowledge of the underlying neural processes of risk-taking behavior. Our study adds to the current literature by highlighting the importance of a specific oscillatory pattern in the processing of a complex behavior such as decision-making under risk.

3.5 CONCLUSION

This study aimed to investigate the relationship between frontal theta-band activity power and risk-taking behavior using tACS at 6.5 Hz. A single-blinded, sham-controlled, within-subject design was used, and risk-taking behavior was measured using the MGT. Stimulation was applied over the left and right DLPFC at 1.5 mA and 3 mA. The results showed that left hemisphere stimulation led to an increase in risk-taking behavior compared to sham, which was also reflected as significant overall increases in frontal theta-power. Right hemisphere stimulation led to a reduction in risk-taking behavior only at a higher intensity of 3 mA; no EEG aftereffects were found. The effect of the stimulation was modulated by the resting-state theta-power as well as the amount of exposure to the stimulation. These findings suggest that lateralized oscillatory patterns play a crucial role in processing complex behaviors such as decision-making under risk and could potentially be utilized in clinical settings to diagnose and intervene in cases involving patients with abnormal risk-taking behaviors.

Competing Interests

The authors have no known competing financial interests or personal relationships that

could have influenced the research reported in this paper.

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3.6 REFERENCES

Aktürk, T., de Graaf, T. A., Güntekin, B., Hanoğlu, L., & Sack, A. T. (2022). Enhancing memory capacity by experimentally slowing theta frequency oscillations using combined EEG-tACS. Scientific Reports, 12(1), 14199. https://doi.org/10.1038/s41598-022-18665-z

Alekseichuk, I., Wischnewski, M., & Opitz, A. (2022). A minimum effective dose for (transcranial) alternating current stimulation. Brain Stimulation, 15(5), 1221–1222. https://doi.org/10.1016/J.BRS.2022.08.018

Low intensity transcranial electric stimulation: Safety, ethical, legal regulatory and application guidelines, 128 Clinical Neurophysiology 1774 (2017). https://doi.org/10.1016/j.clinph.2017.06.001

Asamoah, B., Khatoun, A., & Mc Laughlin, M. (2019). tACS motor system effects can be caused by transcutaneous stimulation of peripheral nerves. Nature Communications, 10(1), 1–16. https://doi.org/10.1038/s41467-018-08183-w

Başar, E., Başar-Eroglu, C., Karakaş, S., & Schürmann, M. (2001). Gamma, alpha, delta, and theta oscillations govern cognitive processes. International Journal of Psychophysiology, 39(2–3), 241–248. https://doi.org/10.1016/S0167-8760(00)00145-8

Bland, N. S., & Sale, M. v. (2019). Current challenges: the ups and downs of tACS. In Experimental Brain Research (Vol. 237, Issue 12, pp. 3071–3088). Springer. https://doi.org/10.1007/s00221-019-05666-0

Boggio, P. S., Campanhã, C., Valasek, C. A., Fecteau, S., Pascual-Leone, A., & Fregni, F. (2010). Modulation of decision-making in a gambling task in older adults with transcranial direct current stimulation. European Journal of Neuroscience, 31(3), 593–597. https://doi.org/10.1111/j.1460-9568.2010.07080.x

Boggio, P. S., Zaghi, S., Beatriz, A., Fecteau, S., Pascual-leone, A., & Fregni, F. (2010). Modulation of risk-taking in marijuana users by transcranial direct current stimulation (tDCS) of the dorsolateral prefrontal cortex (DLPFC). Drug and Alcohol Dependence, 112(3), 220–225. https://doi.org/10.1016/j.drugalcdep.2010.06.019

Cavanagh, J. F., & Frank, M. J. (2014a). Frontal theta as a mechanism for cognitive control. Trends in Cognitive Sciences, 18(8), 414–421. https://doi.org/10.1016/j.tics.2014.04.012

Cavanagh, J. F., & Frank, M. J. (2014b). Frontal theta as a mechanism for cognitive control. Trends in Cognitive Sciences, 18(8), 414–421. https://doi.org/10.1016/j.tics.2014.04.012

Christie, G. J., & Tata, M. S. (2009). Right frontal cortex generates reward-related theta-band oscillatory activity. NeuroImage, 48(2), 415–422. https://doi.org/10.1016/j.neuroimage.2009.06.076

Chuang, Y., & Schechter, L. (2015). Stability of experimental and survey measures of risk, time, and social preferences: A review and some new results. Journal of Development Economics, 117, 151–170. https://doi.org/10.1016/j.jdeveco.2015.07.008

Cohen, M. X., & Donner, T. H. (2013). Midfrontal conflict-related theta-band power reflects neural oscillations that predict behavior. Journal of Neurophysiology, 110(12), 2752–2763. https://doi.org/10.1152/JN.00479.2013/ASSET/IMAGES/LARGE/Z9K0241322250006.JPEG

Dantas, A. M., Sack, A. T., Bruggen, E., Jiao, P., & Schuhmann, T. (2021a). Reduced risk-taking behavior during frontal oscillatory theta-band neurostimulation. Brain Research, 1759, 147365. https://doi.org/10.1016/j.brainres.2021.147365

Dantas, A. M., Sack, A. T., Bruggen, E., Jiao, P., & Schuhmann, T. (2021b). Reduced risk-taking behavior during frontal oscillatory theta-band neurostimulation. Brain Research, 1759, 147365. https://doi.org/10.1016/j.brainres.2021.147365

Dantas, A. M., Sack, A. T., Bruggen, E., Jiao, P., & Schuhmann, T. (2021c). Reduced risk-taking behavior during frontal oscillatory theta-band neurostimulation. Brain Research, 1759, 147365. https://doi.org/10.1016/J.BRAINRES.2021.147365

Dion, K. L., & Miller, N. (1971). An analysis of the familiarization explanation of the risky-shift. Journal of Experimental Social Psychology, 7(5), 524–533. https://doi.org/10.1016/0022-1031(71)90014-X

Dippel, G., Chmielewski, W., Mückschel, M., & Beste, C. (2016). Response mode-dependent differences in neurofunctional networks during response inhibition: an EEG-beamforming study. Brain Structure and Function, 221(8), 4091–4101. https://doi.org/10.1007/s00429-015-1148-y

Dippel, G., Mückschel, M., Ziemssen, T., & Beste, C. (2017). Demands on response inhibition processes determine modulations of theta-band activity in superior frontal areas and correlations with pupillometry – Implications for the norepinephrine system during inhibitory control. NeuroImage, 157, 575–585. https://doi.org/10.1016/J.NEUROIMAGE.2017.06.037

Drichoutis, A. C., & Lusk, J. L. (2016). What can multiple price lists really tell us about risk preferences? Journal of Risk and Uncertainty, 53(2–3), 89–106. https://doi.org/10.1007/s11166-016-9248-5

Fecteau, S., Knoch, D., Fregni, F., Sultani, N., Boggio, P., & Pascual-leone, A. (2007). Diminishing Risk-Taking Behavior by Modulating Activity in the Prefrontal Cortex : A Direct Current Stimulation Study. 27(46), 12500–12505. https://doi.org/10.1523/JNEUROSCI.3283-07.2007

Fecteau, S., Pascual-leone, A., Zald, D. H., Liguori, P., The, H., Boggio, P. S., Fregni, F., & Ht, C. (2007). Activation of Prefrontal Cortex by Transcranial Direct Current Stimulation Reduces Appetite for Risk during Ambiguous Decision Making. 27(23), 6212–6218. https://doi.org/10.1523/JNEUROSCI.0314-07.2007

Fecteau, S., Pascual-Leone, A., Zald, D. H., Liguori, P., Théoret, H., Boggio, P. S., Fregni, F., The, H., Boggio, P. S., Fregni, F., & Ht, C. (2007). Activation of Prefrontal Cortex by Transcranial Direct Current Stimulation Reduces Appetite for Risk during Ambiguous Decision Making. Journal of Neuroscience, 27(23), 6212–6218. https://doi.org/10.1523/JNEUROSCI.0314-07.2007

Gianotti, L. R. R., Knoch, D., Faber, P. L., Lehmann, D., Pascual-Marqui, R. D., Diezi, C., Schoch, C., Eisenegger, C., & Fehr, E. (2009). Tonic activity level in the right prefrontal cortex predicts individuals' risk taking. Psychological Science, 20(1), 33–38. https://doi.org/10.1111/j.1467-9280.2008.02260.x

Gilmore, C. S., Dickmann, P. J., Nelson, B. G., Lamberty, G. J., & Lim, K. O. (2018). Transcranial Direct Current Stimulation (tDCS) paired with a decision-making task reduces risk-taking in a clinically impulsive sample. Brain Stimulation, 11(2), 302–309. https://doi.org/10.1016/j.brs.2017.11.011

Goel, V., Tierney, M., Sheesley, L., Bartolo, A., Vartanian, O., & Grafman, J. (2007). Hemispheric Specialization in Human Prefrontal Cortex for Resolving Certain and Uncertain Inferences. Cerebral Cortex, 17(10), 2245–2250. https://doi.org/10.1093/CERCOR/BHL132

Heise, K. F., Monteiro, T. S., Leunissen, I., Mantini, D., & Swinnen, S. P. (2019). Distinct online and offline effects of alpha and beta transcranial alternating current stimulation (tACS) on continuous bimanual performance and task-set switching. Scientific Reports, 9(1). https://doi.org/10.1038/s41598-019-39900-0

Helfrich, R. F., Schneider, T. R., Rach, S., Trautmann-Lengsfeld, S. A., Engel, A. K., & Herrmann, C. S. (2014). Entrainment of Brain Oscillations by Transcranial Alternating Current Stimulation. Current Biology, 24(3), 333–339.

Huang, Y., Liu, A. A., Lafon, B., Friedman, D., Dayan, M., Wang, X., Bikson, M., Doyle, W. K., Devinsky, O., & Parra, L.

C. (2017). Measurements and models of electric fields in the in vivo human brain during transcranial electric stimulation. ELife, 6. https://doi.org/10.7554/eLife.18834

Huang, Y. Z., Edwards, M. J., Rounis, E., Bhatia, K. P., & Rothwell, J. C. (2005). Theta burst stimulation of the human motor cortex. Neuron, 45(2), 201–206. https://doi.org/10.1016/j.neuron.2004.12.033

Klírová, M., Voráčková, V., Horáček, J., Mohr, P., Jonáš, J., Dudysová, D. U., Kostýlková, L., Fayette, D., Krejčová, L., Baumann, S., Laskov, O., & Novák, T. (2021). Modulating Inhibitory Control Processes Using Individualized High Definition Theta Transcranial Alternating Current Stimulation (HD θ-tACS) of the Anterior Cingulate and Medial Prefrontal Cortex. Frontiers in Systems Neuroscience, 0, 25. https://doi.org/10.3389/FNSYS.2021.611507

Knoch, D., Gianotti, L. R. R., Pascual-leone, A., Treyer, V., Regard, M., Hohmann, M., & Brugger, P. (2006). Disruption of Right Prefrontal Cortex by Low-Frequency Repetitive Transcranial Magnetic Stimulation Induces. 26(24), 6469–6472. https://doi.org/10.1523/JNEUROSCI.0804-06.2006

Koul, A., Soriano, M., Avenanti, A., Cavallo, A., & Becchio, C. (2019). Investigating the causal role of frontal and parietal cortices in intention understanding: a cTBS study. Brain Stimulation, 12(2), 485. https://doi.org/10.1016/j.brs.2018.12.585

Levasseur-Moreau, J., & Fecteau, S. (2012). Translational application of neuromodulation of decision-making. In Brain Stimulation (Vol. 5, Issue 2, pp. 77–83). Elsevier. https://doi.org/10.1016/j.brs.2012.03.009

Li, Y., Chen, R., Zhang, S., Turel, O., Bechara, A., Feng, T., Chen, H., & He, Q. (2019). Hemispheric mPFC asymmetry in decision making under ambiguity and risk: An fNIRS study. Behavioural Brain Research, 359, 657–663. https://doi.org/10.1016/J.BBR.2018.09.021

Massar, S. A. A., Kenemans, J. L., & Schutter, D. J. L. G. (2014). Resting-state EEG theta activity and risk learning: Sensitivity to reward or punishment? International Journal of Psychophysiology, 91(3), 172–177. https://doi.org/10.1016/j.ijpsycho.2013.10.013

Massar, S. A. A., Rossi, V., Schutter, D. J. L. G., & Kenemans, J. L. (2012). Baseline EEG theta/beta ratio and punishment sensitivity as biomarkers for feedback-related negativity (FRN) and risk-taking. Clinical Neurophysiology, 123(10), 1958–1965. https://doi.org/10.1016/j.clinph.2012.03.005

MATLAB R2018b (9.7.0.1190202 (R2018b)). (2018). The MathWorks Inc.

McFerren, A., Riddle, J., Walker, C. P., Buse, J. B., & Frohlich, F. (2021). Causal role of frontal-midline theta in cognitive effort: a pilot study. Https://Doi.Org/10.1152/Jn.00068.2021. https://doi.org/10.1152/JN.00068.2021

Minati, L., Campanhã, C., Critchley, H. D., & Boggio, P. S. (2012). Effects of transcranial direct-current stimulation (tDCS) of the dorsolateral prefrontal cortex (DLPFC) during a mixed-gambling risky decision-making task. Cognitive Neuroscience, 3(2), 80–88. https://doi.org/10.1080/17588928.2011.628382

Oostenveld, R., Fries, P., Maris, E., & Schoffelen, J.-M. (2011). FieldTrip: Open Source Software for Advanced Analysis of MEG, EEG, and Invasive Electrophysiological Data. Computational Intelligence and Neuroscience, 2011, 1–9. https://doi.org/10.1155/2011/156869

Pinner, J. F. L., & Cavanagh, J. F. (2017). Frontal theta accounts for individual differences in the cost of conflict on decision making. Brain Research, 1672, 73–80. https://doi.org/10.1016/j.brainres.2017.07.026

Popov, T., Oostenveld, R., & Schoffelen, J. M. (2018). FieldTrip made easy: An analysis protocol for group analysis of the auditory steady state brain response in time, frequency, and space. Frontiers in Neuroscience, 12(OCT), 711. https://doi.org/10.3389/fnins.2018.00711

R Bloggers, R. (2011). boxplot outlier | R-statistics blog. https://www.r-statistics.com/tag/boxplot-outlier/

R Core team. (2015). R Core Team. In R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing , Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org/. (Vol. 55, pp. 275–286). https://www.r-project.org/

Effects of weak transcranial alternating current stimulation on brain activity-a review of known mechanisms from animal studies, 7 Frontiers in Human Neuroscience 687 (2013). https://doi.org/10.3389/fnhum.2013.00687

Reinhart, R. M. G., & Nguyen, J. A. (2019). Working memory revived in older adults by synchronizing rhythmic brain circuits. Nature Neuroscience, 1. https://doi.org/10.1038/s41593-019-0371-x

Rogers, R. D. R., Everitt, B. J., Baldacchino, A., Blackshaw, A. J., Swainson, R., Wynne, K., Baker, N. B., Hunter, J., Carthy, T., Booker, E., London, M., Deakin, J. F. W., Sahakian, B. J., & Robbins, T. W. (1999). Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan-depleted normal volunteersEvidence for monoaminergic mechanisms. …, 20(4), 322–339. https://doi.org/10.1016/S0893-133X(98)00091-8

Schiller, B., Gianotti, L. R. R., Nash, K., & Knoch, D. (2014). Individual differences in inhibitory control - Relationship between baseline activation in lateral PFC and an electrophysiological index of response inhibition. Cerebral Cortex, 24(9), 2430–2435. https://doi.org/10.1093/cercor/bht095

Schmidt, B., Kanis, H., Holroyd, C. B., Miltner, W. H. R., & Hewig, J. (2018). Anxious gambling: Anxiety is associated with higher frontal midline theta predicting less risky decisions. Psychophysiology, 55(10), e13210. https://doi.org/10.1111/psyp.13210

Schmidt, B., Kessler, L., Holroyd, C. B., & Miltner, W. H. R. (2019). Wearing a bike helmet leads to less cognitive control, revealed by lower frontal midline theta power and risk indifference. Psychophysiology, 56(12). https://doi.org/10.1111/psyp.13458

Schutter, D. J. L. G. (2016). Cutaneous retinal activation and neural entrainment in transcranial alternating current stimulation: A systematic review. NeuroImage, 140, 83–88. https://doi.org/10.1016/j.neuroimage.2015.09.067

Sela, T., Kilim, A., & Lavidor, M. (2012). Transcranial alternating current stimulation increases risk-taking behavior in the Balloon Analog Risk Task. Frontiers in Neuroscience, 6(FEB), 1–11. https://doi.org/10.3389/fnins.2012.00022

Strüber, D., Rach, S., Neuling, T., & Herrmann, C. S. (2015). On the possible role of stimulation duration for after-effects of transcranial alternating current stimulation. Frontiers in Cellular Neuroscience, 9(AUGUST), 311. https://doi.org/10.3389/fncel.2015.00311

Studer, B., Pedroni, A., & Rieskamp, J. (2013). Predicting Risk-Taking Behavior from Prefrontal Resting-State Activity and Personality. PLoS ONE, 8(10), e76861. https://doi.org/10.1371/journal.pone.0076861

Thielscher, A., Antunes, A., & Saturnino, G. B. (2015). Field modeling for transcranial magnetic stimulation: A useful tool to understand the physiological effects of TMS? Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS, 2015-November, 222–225. https://doi.org/10.1109/EMBC.2015.7318340

Tobler, P. N., O'Doherty, J. P., Dolan, R. J., & Schultz, W. (2007). Reward value coding distinct from risk attitude-related uncertainty coding in human reward systems. Journal of Neurophysiology, 97(2), 1621–1632. https://doi.org/10.1152/jn.00745.2006

Vöröslakos, M., Takeuchi, Y., Brinyiczki, K., Zombori, T., Oliva, A., Fernández-Ruiz, A., Kozák, G., Kincses, Z. T., Iványi, B., Buzsáki, G., & Berényi, A. (2018). Direct effects of transcranial electric stimulation on brain circuits in rats and humans. Nature Communications 2018 9:1, 9(1), 1–17. https://doi.org/10.1038/s41467-018-02928-3

Widge, A. S. (2018). Cross-Species Neuromodulation from High-Intensity Transcranial Electrical Stimulation. Trends in Cognitive Sciences, 22(5), 372–374. https://doi.org/10.1016/J.TICS.2018.03.006

Wischnewski, M., & Compen, B. (2022a). Effects of theta transcranial alternating current stimulation (tACS) on exploration and exploitation during uncertain decision-making. Behavioural Brain Research, 426, 113840. https://doi.org/10.1016/j.bbr.2022.113840

Wischnewski, M., & Compen, B. (2022b). Effects of theta transcranial alternating current stimulation (tACS) on exploration and exploitation during uncertain decision-making. Behavioural Brain Research, 426, 113840. https://doi.org/10.1016/j.bbr.2022.113840

Wischnewski, M., Zerr, P., & Schutter, D. J. L. G. (2016). Effects of Theta Transcranial Alternating Current Stimulation Over the Frontal Cortex on Reversal Learning. Brain Stimulation, 9(5), 705–711. https://doi.org/10.1016/j.brs.2016.04.011

Womelsdorf, T., Johnston, K., Vinck, M., & Everling, S. (2010). Theta-activity in anterior cingulate cortex predicts task rules and their adjustments following errors. Proceedings of the National Academy of Sciences of the United States of America, 107(11), 5248–5253. https://doi.org/10.1073/pnas.0906194107

Zhang, D., & Gu, R. (2018). Behavioral preference in sequential decision-making and its association with anxiety. Human Brain Mapping, 39(6), 2482–2499. https://doi.org/10.1002/hbm.24016

Zhang, D. W., Moraidis, A., & Klingberg, T. (2022). Individually tuned theta HD-tACS improves spatial performance. Brain Stimulation, 15(6), 1439–1447. https://doi.org/10.1016/J.BRS.2022.10.009

3.A SUPPLEMENTARY MATERIAL

3.A.1 EEG AND STIMULATION SETTING

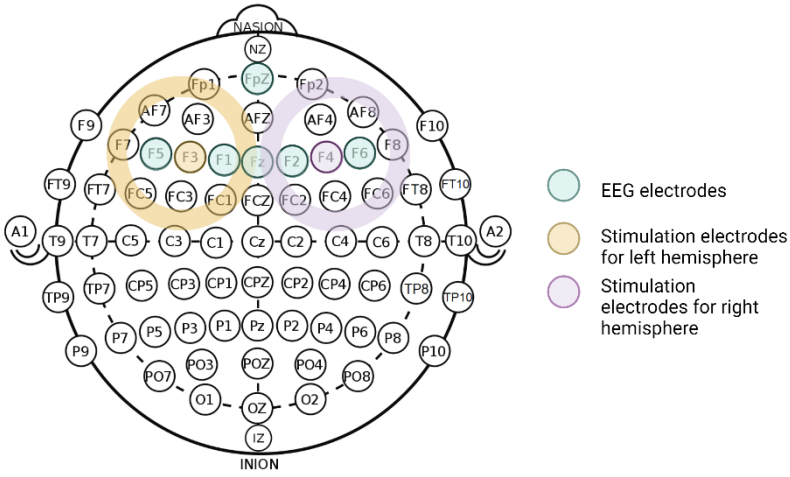

FIGURE 3.A.1 – EEG AND STIMULATION SETTINGS.

The EEG settings were kept constant across sessions, with FpZ, FZ, F1, F2, F5 and F6 electrodes (blue) placed around the stimulation sites. In each session participants received either stimulation over the left hemisphere (yellow) or over the right hemisphere (purple).

3.A.2 PROBABILITY SCORES: HIGHER SCORES INDICATE THAT PARTICIPANTS CHOSE THE TRIALS WITH LOWER PROBABILITIES, WHILE LOWER SCORES INDICATE THAT PARTICIPANTS CHOSE HIGHER PROBABILITIES

PINK	BLUE	CHOICE	PROBABILITY
5	1	BLUE	2
1	5	PINK	2
4	2	BLUE	1
2	4	PINK	1
3	3	PINK	0
3	3	BLUE	0
4	2	PINK	-1
2	4	BLUE	-1
5	1	PINK	-2
1	5	BLUE	-2

3.A.3 Post hoc analyses on the effects of repeated stimulation on risk-taking behavior

Our results indicate a significant reduction of risk-taking behavior from session 1 to session 2 (beta =-0.56, t(21710) =-2.52, p = 0.012). A significant increase in risk-taking behavior was observed due to left hemisphere stimulation in the first session both with intensity 1.5 mA (beta = 0.55, t(21710) = 4.28, p < .001) and 3 mA (beta = 0.52, t(21710) = 4.11, p < .001).

Our results show a significant negative effect of the amount of exposure to stimulation (beta =-0.36, t(21710) =-3.61, p < .001), indicating a reduction on risk-taking behavior as the amount of exposure to stimulation increases. We also observed a significant positive effect of the interaction between exposure to stimulation and session (beta = 0.30, t(21710) = 2.21, p = 0.027).

In these analyses, the interaction between left 1.5mA stimulation and session 2 led to a significant reduction in risk-taking behavior (beta =-0.50, t(21710) =-3.31, p < .001), replicating the findings of Dantas et al. (2021). The 3 mA stimulation did not yield a significant effect (beta =-0.10, t(21710) =-0.59, p = 0.556). As observed in our initial analyses, there was a significant reduction in risk-taking behavior during right side 3mA stimulation (beta =-0.59, t(21710) =-3.71, p < .001), while the effects of the right side 1.5mA stimulation were still not significant (beta =-0.25, t(21710) =-1.79, p = 0.074).

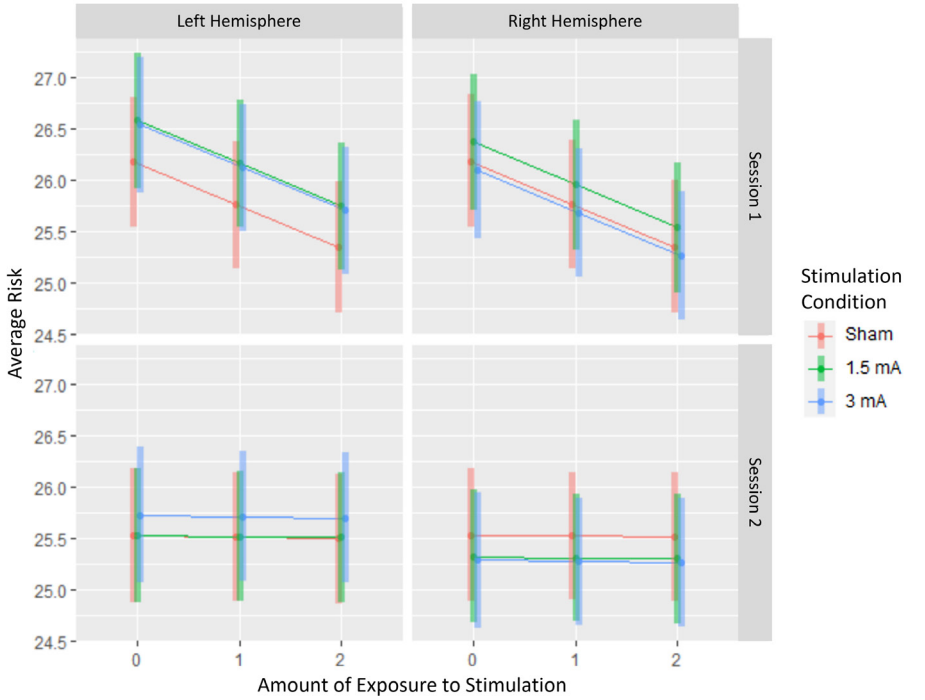

Figure 3.A.2 – Average risk-taking behavior by stimulation condition and amount of exposure to stimulation. Results are presented by session (vertical) and side (horizontal). The horizontal axis indicates the number of exposures to stimulation from zero to two.

3.A.4 EEG analyses. Theta power changes per electrode measured

Elect.	Elect. Side	Stim. Side	Condition	Estimates	std. Error	CI	p	df
F1	left	left	RESTING-STATE (Baseline)	-0,34	0,14	-0,62 –-0,06	**0,016**	198
F1	left	left	SHAM	0,25	0,07	0,10 – 0,39	**0,001**	198
F1	left	left	1,5 mA	0,15	0,07	0,00 – 0,30	**0,047**	198
F1	left	left	3 mA	0,18	0,07	0,04 – 0,33	**0,013**	198
F1	left	right	RESTING-STATE	-0,05	0,08	-0,20 – 0,10	0,519	198
F1	left	right	SHAM	-0,1	0,11	-0,31 – 0,11	0,345	198
F1	left	right	1,5 mA	0	0,11	-0,22 – 0,21	0,981	198
F1	left	right	3 mA	0	0,11	-0,21 – 0,21	0,996	198
F5	left	left	RESTING-STATE (Baseline)	0,13	0,14	-0,15 – 0,41	0,353	198
F5	left	left	SHAM	0,24	0,07	0,11 – 0,38	**0,001**	198
F5	left	left	1,5 mA	0,13	0,07	-0,01 – 0,27	**0,065**	198
F5	left	left	3 mA	0,17	0,07	0,04 – 0,31	**0,013**	198

CONTINUED.

Elect.	Elect. Side	Stim. Side	Condition	Estimates	std. Error	CI	p	df
F5	left	right	RESTING-STATE	0,03	0,07	-0,11 – 0,17	0,678	198
F5	left	right	SHAM	-0,14	0,1	-0,34 – 0,06	0,171	198
F5	left	right	1,5 mA	-0,03	0,1	-0,23 – 0,17	0,786	198
F5	left	right	3 mA	-0,02	0,1	-0,21 – 0,18	0,881	198
F2	right	left	RESTING-STATE (Baseline)	-0,4	0,14	-0,67 –-0,12	**0,005**	198
F2	right	left	SHAM	0,25	0,06	0,13 – 0,38	**<0,001**	198
F2	right	left	1,5 mA	0,15	0,06	0,02 – 0,27	**0,025**	198
F2	right	left	3 mA	0,18	0,06	0,05 – 0,30	**0,006**	198
F2	right	right	RESTING-STATE	0,06	0,07	-0,07 – 0,19	0,352	198
F2	right	right	SHAM	-0,16	0,09	-0,34 – 0,03	0,093	198
F2	right	right	1,5 mA	-0,01	0,09	-0,20 – 0,17	0,883	198
F2	right	right	3 mA	-0,02	0,09	-0,20 – 0,16	0,822	198
F6	right	left	RESTING-STATE (Baseline)	0,15	0,14	-0,12 – 0,42	0,272	198
F6	right	left	SHAM	0,24	0,07	0,11 – 0,37	**<0,001**	198
F6	right	left	1,5 mA	0,14	0,07	0,01 – 0,27	**0,035**	198
F6	right	left	3 mA	0,2	0,06	0,07 – 0,32	**0,003**	198
F6	right	right	RESTING-STATE	-0,11	0,07	-0,24 – 0,02	0,104	198
F6	right	right	SHAM	-0,1	0,09	-0,29 – 0,08	0,265	198
F6	right	right	1,5 mA	0	0,1	-0,18 – 0,19	0,96	198
F6	right	right	3 mA	0,01	0,09	-0,17 – 0,20	0,879	198
FpZ	midline	left	RESTING-STATE (Baseline)	0,32	0,14	0,05 – 0,60	**0,022**	198
FpZ	midline	left	SHAM	0,22	0,07	0,09 – 0,35	**0,001**	198
FpZ	midline	left	1,5 mA	0,14	0,07	0,01 – 0,27	**0,039**	198
FpZ	midline	left	3 mA	0,18	0,07	0,05 – 0,31	**0,007**	198
FpZ	midline	right	RESTING-STATE	-0,03	0,07	-0,16 – 0,11	0,703	198
FpZ	midline	right	SHAM	-0,11	0,1	-0,30 – 0,08	0,254	198
FpZ	midline	right	1,5 mA	-0,02	0,1	-0,21 – 0,17	0,839	198
FpZ	midline	right	3 mA	0,02	0,1	-0,17 – 0,21	0,857	198
FZ	midline	left	RESTING-STATE (Baseline)	-0,44	0,13	-0,70 –-0,18	**0,001**	198
FZ	midline	left	SHAM	0,22	0,07	0,09 – 0,35	**0,001**	198
FZ	midline	left	1,5 mA	0,12	0,07	-0,01 – 0,26	0,072	198
FZ	midline	left	3 mA	0,14	0,07	0,01 – 0,27	**0,033**	198
FZ	midline	right	RESTING-STATE	-0,03	0,07	-0,17 – 0,12	0,714	198
FZ	midline	right	SHAM	-0,08	0,1	-0,27 – 0,11	0,426	198
FZ	midline	right	1,5 mA	0,05	0,1	-0,15 – 0,25	0,604	198
FZ	midline	right	3 mA	0,07	0,1	-0,12 – 0,26	0,477	198

3.A.5 Effects of resting-state theta power on Risk.

Predictors	Estimates	std. Error	CI	p	df
(Intercept)	26.24	0.36	25.53 – 26.94	<0.001	21730
AVLEFTPRE	2.95	2.20	-1.36 – 7.26	0.180	21730
AVRIGHTPRE	-2.89	3.16	-9.08 – 3.30	0.360	21730
AVMIDLINEPRE	-0.46	3.28	-6.88 – 5.97	0.889	21730
Session [2]	-0.31	0.06	-0.44 –-0.18	<0.001	21730
Side [Right]	-0.04	0.11	-0.26 – 0.18	0.711	21730
1.5mA	0.14	0.12	-0.10 – 0.39	0.237	21730
3 mA	0.16	0.12	-0.08 – 0.39	0.188	21730
AVLEFTPRE × AVRIGHTPRE	-1.12	0.37	-1.84 –-0.39	0.002	21730
SIDE [R] : 1.5mA	-0.18	0.16	-0.49 – 0.12	0.238	21730
SIDE [R] : 3 mA	-0.38	0.15	-0.69 –-0.08	0.013	21730
AVLEFTPRE : 1.5mA	-0.56	0.69	-1.91 – 0.80	0.420	21730
AVLEFTPRE : 3 mA	-0.52	0.68	-1.85 – 0.81	0.444	21730
AVRIGHTPRE : 1.5mA	1.98	0.98	0.06 – 3.91	0.044	21730
AVRIGHTPRE : 3 mA	0.47	0.98	-1.45 – 2.38	0.634	21730
AVMIDLINEPRE : 1.5mA	-1.73	1.03	-3.76 – 0.29	0.093	21730
AVMIDLINEPRE : 3 mA	0.26	1.01	-1.73 – 2.25	0.798	21730

THE CONTROLLER

PART II

PREFRONTAL CORTEX AND RISK-TAKING BEHAVIOR

4

THE FUNCTIONAL RELEVANCE OF RIGHT DLPFC AND VMPFC IN RISK-TAKING BEHAVIOR

BASED ON: DANTAS, A. M., SACK, A. T., BRUGGEN, E., JIAO, P., & SCHUHMANN, T. (2023). THE FUNCTIONAL RELEVANCE

ABSTRACT

The prefrontal cortex can be partialized in various anatomical and functional sub regions. Among those regions, both right dorsolateral prefrontal cortex (rDLPFC) and ventromedial prefrontal cortex (VMPFC) have been associated with risk-taking behavior based on neuroimaging studies. Noninvasive brain stimulation (NIBS) studies aiming at demonstrating the functional relevance of neural activity in these areas almost exclusively focused on the rDLPFC, where its experimental stimulation with a (generally) inhibitory protocol lead to a measurable increase in risk-taking behavior due to reduced cognitive control. The functional relevance of VMPFC in risk-taking behavior has not yet been addressed using NIBS, although multiple neuroimaging studies correlate this area's activity with valuation.

Here, we used NIBS to investigate the functional relevance of both, the rDLPFC and VMPFC in risk-taking behavior. We hypothesized that, compared to sham stimulation, VMPFC suppression leads to a reduction in risk-taking behavior by reducing the appeal to higher value options and consequently the attractiveness of riskier options, whereas rDLPFC suppression leads to an increase in risk taking, replicating previous findings.

We applied continuous theta burst stimulation (cTBS), a generally inhibitory protocol, to stimulate either VMPFC or DLPFC before the execution of the computerized Maastricht Gambling Task (MGT) in a within-subject design with 30 participants. The MGT allowed the analysis of potential brain region-specific effects of cTBS on risk-taking behavior such as participants' choices of average values, probabilities, and response time.

cTBS applied to either rDLPFC or VMPFC both led to an increase in risk-taking behavior and in the average value chosen as compared to sham transcranial magnetic stimulation. No effect on the choice of probabilities was found. A significant increase in response time was observed exclusively after suppressing rDLPFC. We speculate that these similar behavioral consequences following cTBS over DLPFC and VMPFC are likely due to the strong anatomical and functional interconnection between both brain regions.

Keywords: Risk-taking behavior, TMS, cTBS, rDLPFC, VMPFC

4.1 INTRODUCTION

The prefrontal cortex plays a fundamental role in high order cognitive processes, including attention, inhibitory control, decision-making and risk-taking behavior (Boggio et al., 2010; Kito et al., 2012; Rao et al., 2008). This region is partialized into different sub regions based on their cytoarchitecture, anatomical position or function (Carlén, 2017). Numerous imaging studies explored the relevance of these prefrontal sub regions, more specifically the dorsolateral prefrontal cortex (DLPFC) and ventromedial prefrontal cortex (VMPFC), in risk-taking behavior (Kuhnen & Knutson, 2005; Rao et al., 2008). There is currently an almost exclusive focus on the DLPFC when it comes to studying the functional relevance of prefrontal brain regions in risk-taking behavior. In contrast, systematic investigations of the functional relevance of VMPFC using NIBS, have not taken place, although neuroimaging studies repeatedly indicated that also this prefrontal area is activated during the execution and modulation of risk-taking behavior (Rudorf & Hare, 2014).

The DLPFC has been reported to be involved in self-control and executive control which directly links to risk taking behavior (Hutcherson et al., 2012). A number of studies using different techniques of noninvasive brain stimulation (NIBS) have successfully demonstrated that applying a (generally) inhibitory protocol to the DLPFC leads to increases in risk taking behavior, likely by the inhibition of self-control (Boggio et al., 2010; Fecteau, Pascual-Leone, et al., 2007; Koul et al., 2019; Rao et al., 2008). A relevant example is the work of Knoch and colleagues (2006) where the experimental deactivation of the right DLPFC (rDLPFC) using 1 Hz repeated transcranial magnetic stimulation (TMS) caused significant increases in risk-taking behavior, whereas this was not the case after left DLPFC (lDLPFC) stimulation (Knoch et al., 2006).

Neuroimaging literature frequently linked VMPFC activation with valuation (Bartra et al., 2013; Chib et al., 2009; Lim et al., 2011), the calculation of each option's maximum expected utility (or expected value of reward). Valuation is a key component in the processing of risk. When faced with a risky choice, one integrates the available information and evaluates the presented options in terms of risk-benefit before choosing (Rudorf & Hare, 2014). This complex process, according to the economics literature, includes a calculation of an option's level of risk by considering both its probabilities of winning and its payoff (so the option's expected value) compared to the same aspects of the deferred option (Myerson, 2005). The greater the spread, thus the standard deviation, between winning and losing with the chosen option, the greater the risk of that option (Myerson, 2005).

Within this conceptualization of risk-taking behavior, the VMPFC's activation has been taken as a proxy for the value encoding component of decision-making under risk (Bartra et al., 2013; Chib et al., 2009). This assumption derives from previous studies correlating

increases in VMPFC activity to the attribution of higher subjective value of presented options (Chib et al., 2009; D'Argembeau, 2013; Hiser & Koenigs, 2018). According to these findings, we may speculate that the suppression of VMPFC activity would cause a significant reduction in the subjective valuation of presented options and therefore reduce the attractiveness of riskier options with higher benefits.

However, to our knowledge no previous studies targeted the VMPFC with NIBS while directly studying risk-taking behavior. One reason may be the challenging anatomical position of VMPFC as compared to DLPFC, requiring TMS coils capable of stimulation slightly deeper regions in the brain. Only recent developments allowed the stimulation of deeper areas such as the VMPFC using double cone coil TMS technology (Roth et al., 2002). With the use of a double cone coil, Cho and colleagues (2015) were able to target the VMPFC and demonstrated that after a protocol of 10Hz repetitive TMS (rTMS), healthy participants displayed lower discounting rates in an intertemporal choices task (Cho et al., 2015). In a study including healthy participants with pathological gambling, neither 10Hz rTMS to the VMPFC, nor continuous Theta Burst Stimulation (CTBS, an inhibitory protocol) to the DLPFC reduced participants' delay discounting (Zack et al., 2016). Nevertheless, significant reductions in bet size, game speed and subjective reinforcement were observed after DLPFC suppression only (Zack et al., 2016). Although these studies do not explore the stimulation's effect on risk-taking behavior directly, they did successfully investigate related phenomena and represent an important contribution to a better understanding of the functional relevance of VMPFC in decision-making (Cho et al., 2015; Zack et al., 2016).

Here we aimed at investigating the functional relevance of the rDLPFC and VMPFC in risk-taking behavior, with two main objectives. The first being the replication of Knoch et al.'s finding that inhibiting the DLPFC (i.e., self-control) increases risk taking behavior (Knoch et al., 2006), but with a cTBS rather than 1 Hz rTMS protocol.

The second objective is to evaluate the effects of suppressing the VMPFC with an inhibitory cTBS protocol on risk-taking behavior. To that end, we used the Maastricht Gambling Task (MGT) (Dantas et al., 2021), which is a computerized task that elicits and measures risk-taking behavior. This task allows us to analyze potential brain region-specific effects of cTBS on risk-taking behavior, as well as additional measures of participants' choices under risk.

Risk-taking behavior is measured by the standard deviation of the chosen option, a measure of risk often used in the economics and finance literature, taking into account of the varying payoffs and probabilities. Additional measures of participants' choice pattern under risk include (1) expected value (sometimes called "bet decision" (Yazdi et

al., 2019) or "betting behavior" (Clark et al., 2017)) and probability spread of the chosen option, and (2) response time.

We hypothesized that stimulating the rDLPFC with a generally inhibitory protocol leads to an increase in risk-taking behavior, due to a reduction in executive control, as previously found by Knoch and colleagues (2006). This effect should not be restricted to a specific aspect of risk-taking behavior since both the choice of probabilities and the average value choice would be in theory affected by a reduction in executive control.

We also hypothesized that stimulating the VMPFC with a generally inhibitory protocol leads to a reduction in average values chosen due to a lower subjective value of the presented options. This reduction of subjective value would therefore lower appeal to choose riskier options with higher payoff (Berkman, 2018; Hiser & Koenigs, 2018; Rudorf & Hare, 2014). Since our estimation of risk-taking behavior takes into account both the payoff values and the probabilities of each option offered, a significant reduction in average value would lead to a reduction in risk-taking behavior. Based on this rationale, the choice of probabilities would therefore not be affected by the VMPFC suppression.

4.2 METHODS

4.2.1 Sample

We calculated our sample size using GPower (Universität Düsseldorf: G*Power, n.d.) using as reference the effect size obtained by Knoch and colleagues (2006) ($F(2,24) = 4.92$)), which led to an aimed sample size of 30 participants. Thirty healthy, right-handed participants (18 female, mean age 25.4 years, range 19–44 years, SD= 6.04) participated in this study. All participants were members of the academic community of Maastricht University, had normal or corrected-to-normal vision and gave written informed consent after being introduced to the experiment. As part of the recruitment, participants were screened for TMS safety (Safety, Ethical Considerations, and Application Guidelines for the Use of Transcranial Magnetic Stimulation in Clinical Practice and Research, 2009). The study was approved by the Ethics Review Committee Psychology and Neuroscience (ERCPN) of Maastricht University, The Netherlands (ERCPN 188_07_02_2018). Participants were compensated based on the choices they made and luck in the risk-taking task in the form of vouchers with monetary value in the local commerce. Three participants reported discomfort during the stimulation and one of them reported headache after participation in session 1 and were therefore not invited to the following sessions. Their results were excluded from the analyses. We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

4.2.2 Task

To elicit and evaluate participants' risk-taking behavior and estimate their valuation and choice of probabilities, we used the Maastricht Gambling Task (MGT). This task is based on the Cambridge gambling Task (CGT) (Rogers et al., 1999), but controls for loss aversion, memory and wealth effects (Dantas et al., 2021). In the MGT, participants are asked to indicate the color of the box they believe that hides a token represented by a yellow X. They see six boxes which can be either pink or blue. The task presents independent trials in which the boxes distribution and payback offered to each option varies. The task consists of 2 repetitions of 125 unique trials, with all possible combinations of probabilities (1/6 pink and 5/6 blue to 5/6 pink and 1/6 blue) and rewards (5, 25, 50, 75 and 100 points). If the participant guesses the color that hides the token correctly, she wins the value assigned to that color. Otherwise, the participant gains zero points. Participants played the complete task twice in each session (before and after stimulation). Please refer to Dantas et al. (2021) for more details of the task.

For compensation, a random trial was selected by the participant and out of that outcome, each point gained in the task was converted to €0.1 in their final compensation to be paid by the end of the experiment. From the task we obtain four main dependent variables: risk, average value, probability scores and response time (exact calculations are presented in the Statistical analyses, section 4.2.5).

4.2.3 Procedure

In each session participants were asked to first fill in a pre-experimental check and sign a consent form confirming the absence of COVID-19 symptoms and recognizing being aware of the specific measures taken to guarantee safety from contamination, following Maastricht University's guidelines. They were then assigned to a randomized condition determining the order of stimulation.

Afterwards, the stimulations sites were determined according to the international 10-20 EEG system. To stimulate we located the coil above FpZ (VMPFC) and F4 (rDLPFC) F4. Sham stimulation was delivered either over FpZ or F4 (50% of the times in each location also in a randomized fashion). In the first session, the resting motor threshold (rMT) was determined.

Participants then received a task explanation and instructions, followed by 10 practice trials. In the sequence, they played five rounds of 50 trials each of the MGT. They then received the stimulation in the location determined according to the protocol assigned for that day and immediately after, they played the MGT for a second time.

After playing the game twice, participants were asked to select a random number using

an online random number generator and the selected number represented the trial that would be paid by the end of the experiment. We then reported the payoff obtained in that session and the participants were dismissed.

The same procedure was repeated in every session, during which participants received either VMPFC, rDLPFC or sham stimulation. By the end of the third session participants were compensated with €7.5 per hour of participation and the total gained with one random trial of the task per experimental session. After this, participants were debriefed.

4.2.4 Stimulation

In each session participants received either VMPFC, rDLPFC or sham stimulation immediately before the second repetition of the MGT. The stimulation position was determined using the international 10/20 EEG system, with FpZ as location for the VMPFC stimulation and F4 for rDLPFC stimulation. The sham stimulation position was randomly assigned and could be over FpZ or F4, with the coil flipped by 180 degrees, meaning that no actual stimulation occurred in this condition.

Choosing an ideal control condition for TMS studies is difficult and which of the control conditions is the best to use is still under debate (Duecker & Sack, 2015; Loo et al., 2000). We chose to use a sham condition, during which we flipped the coil 180 degrees. Hereby, participants are exposed to the same clicking sound, however they do not receive actual stimulation.

We used a continuous theta burst stimulation protocol (cTBS), composed by a continuous 40 s train of 600 pulses, with short bursts (3 stimuli) of 50 Hz rTMS repeated at theta range (5 Hz) using a MagVenture x100 stimulator (MagVenture A/S, Farum, Denmark).

To be able to reach the VMPFC we used a double cone coil (MagVenture Cool D-B80 MagVenture A/S, Farum, Denmark), which allows deeper stimulation (Cho et al., 2015). The coil was placed tangentially to the scalp with the handle pointing backwards, parallel to the midline.

Magnetic stimulation was applied at 100% individual resting motor threshold (mean stimulation intensity = 36.6% (+/- 6.1 SD) of maximum stimulator output). The individual resting motor threshold was defined as the lowest stimulation intensity needed to elicit a visible contraction of the left abductor pollicis brevis (APB) in five out of ten pulses after stimulating the right motor cortex.

The simulation of the magnetic field for the stimulation protocol can be seen in Fig 1, using SimNibs (Thielscher et al., 2015). We also ran a simulation to exclude a possible

overlap between the stimulated areas in both active conditions, using a threshold of 1V/m (Figure 1 C).

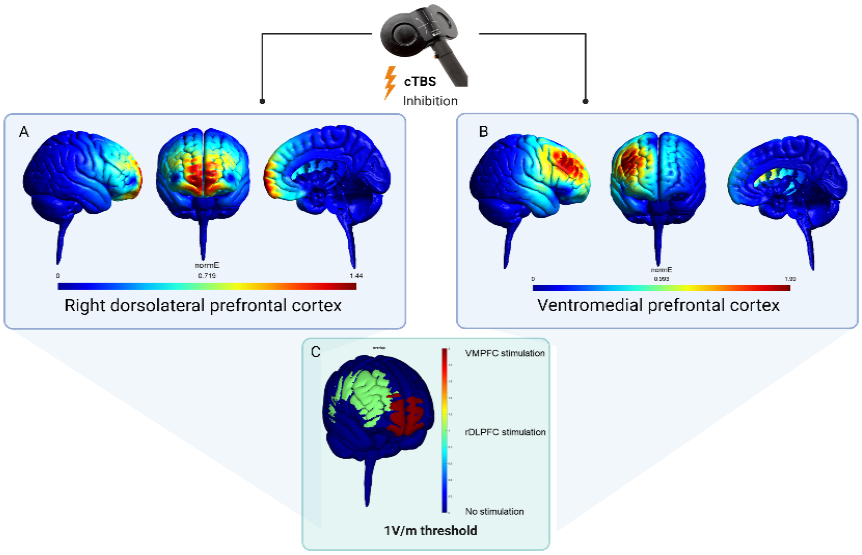

Figure 4.1 – SimNibs simulations of the induced electric field for the active stimulation protocols. Simulation of the induced electric field using SIMNIBS (Thielscher et al., 2015) of VMPFC stimulation (A), rDLPFC stimulation (B) and a simulation of a possible overlap between the two stimulation protocols at a 1 V/m threshold (C), also produced using SIMNIBS (Thielscher et al., 2015).

4.2.5 Statistical analyses

We focused on the four dependent variables obtained from the MGT (risk, value, probability scores and response time). To analyze risk, we estimated the standard deviation chosen in each trial, which takes into consideration both the probability of the chosen alternative and its payoff (Burke & Tobler, 2011; Dantas et al., 2021; Tobler et al., 2007). For each trial, participants can choose to bet on the color X (X= blue or pink), with probability p, a payoff of x and expected payoff E(X) of xp. The risk of this trial is therefore estimated by calculating the variance of payoffs from choosing color X in the trial i.

$$VarXi=\sum px-E(X)2 \quad (1)$$

The standard deviation is then calculated as the square root of the given variance, where:

$$Risk=SD=VarX \quad (2)$$

Considering that this measure of risk is composed of distinct factors, we also look into the average values and probabilities chosen by participants. Average value is calculated by averaging the participants' choices of value across task repetitions. To estimate participants' choices of probabilities, similarly to what was done in previous studies (Fecteau, Knoch, et al., 2007; Knoch et al., 2006; Rogers et al., 1999), we attributed scores to the probabilities chosen. Probabilities below 50% (considered in previous studies as risky (Rogers et al., 1999)) received positive scores and probabilities above 50% receive negative scores. The probabilities chosen were then transformed into a scale ranging from-2 to 2, where-2 indicates a probability of 5/6 and 2 indicates a probability of 1/6.

Finally, response times were measured per trial in seconds, from the moment when the trial was displayed in the screen until the participants' responses. All dependent measures were obtained from the MGT and preprocessed for analyses using customized MATLAB scripts (MATLAB R2018b, 2018). Since participants responded to the exact same trial twice each time they played the game, we averaged these responses to consolidate our dataset, considering they presented 94% consistency across these repetitions. In total we have 750 observations per participant (125 unique trials * 2 blocks * 3 sessions), with a total of 22500 observations.

The statistical analyses were done using customized R scripts (R Core team, 2015). We started the analyses by removing outliers, using custom R scripts to remove observations outside 1.5 times the interquartile range above the upper quartile and bellow the lower quartile (R Bloggers, 2011). No observations were excluded from the analyses of risk, valuation, or probability scores. 760 observations (of different participants) were excluded from the response time analyses as outliers, leaving 21740 observations.

We then ran a series of linear mixed model analyses. All models included block (block1 (before stimulation) or block2 (after stimulation)), stimulation (sham, VMPFC and rDLPFC) and their interaction (block*stimulation) as factors. The variables were dummy-coded, whereby block 1, was coded as 0 (baseline) and block 2was coded as 1. Sham was coded as 0 and hence presented the baseline to which a dummy variable for VMPFC and a dummy variable for rDLPFC were compared (please refer to the Appendices, section 4.A.1).

Given the within subject experimental design, we used participant as a random factor. Each participant was exposed to 125 unique trials with different choice scenarios. Each of these trials was coded in a variable named "Trial code". We used the combination of the participant and trial code as random intercept in our model, which captures individuals' baseline and accounts for individual differences to unique trials. Our model assumes that changes from this baseline are due to the factors included in the model as

fixed effects and hence no random slope is included.

The effects of stimulation on risk, valuation and probability scores were estimated by fitting a linear mixed model estimated using reduced maximum likelihood (REML) and compound symmetry (CS) covariance structure. The analysis of the effects on response time used a first order autoregressive (AR1) covariance structure. To ensure transparency and reproducibility, all data and codes used for its analyses and task are available at https://data.mendeley.com/datasets/vwzz3dt3pf. No part of the study procedures or analyses was pre-registered prior to the research being conducted.

4.3 RESULTS

4.3.1 Risk-taking behavior

Our results show a significant effect of the interaction block*stimulation, indicating an increase in risk-taking behavior after the suppression of both rDLPFC and VMPFC compared to sham, with a significant positive effect of block2*rDLPFC (beta = 0.46, t(23214) = 3.37, p < .001) and block2*VMPFC (beta = 0.35, t(23214) = 2.52, p = .01) on risk-taking behavior. Although the rDLPFC suppression effect has a higher beta compared to the effects observed after VMPFC inhibition, the contrast between these two conditions is not significantly different (block2*rDLPFC, beta = 0.12, t(15466) = .85, p = .394) (Figure 2).

There was also a significant negative effect of block, indicating that overall, participants reduced their risk-taking behavior from the first (baseline, dummy coded as zero) to the second repetition of the task (beta =-0.21, t(23214) =-2.21, p = 0.012) conditional on stimulation being Sham. There were no significant main effects of either rDLPFC (beta = -0.16, t(23214) =-1.67, p = 0.095) nor VMPFC (beta =-0.18, t(23214) =-1.90, p = 0.057) compared to sham in the first block.

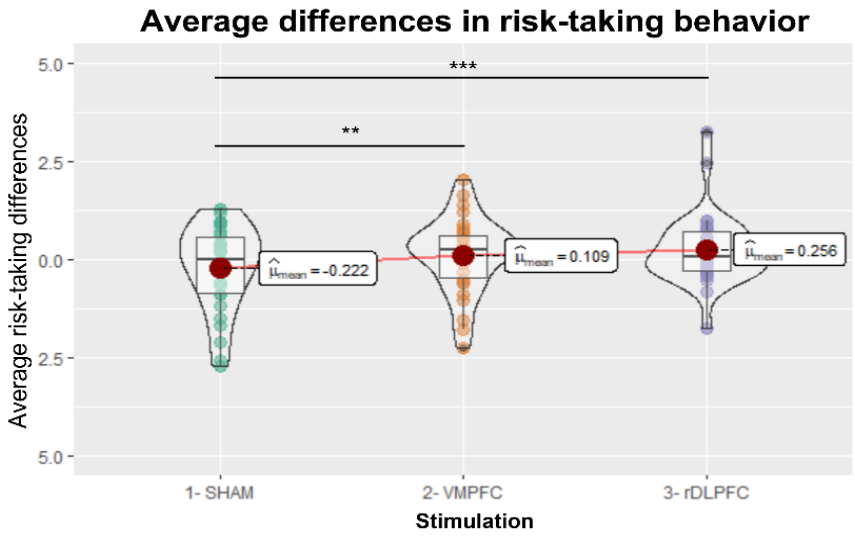

*FIGURE 4.2 - AVERAGE DIFFERENCES IN RISK-TAKING BEHAVIOR (N=30). AVERAGE DIFFERENCES IN RISK-TAKING ESTIMATED BY THE AVERAGE STANDARD DEVIATION OF EACH PARTICIPANT'S CHOICE ACROSS STIMULATION CONDITIONS (SHAM IN GREEN, VMPFC IN ORANGE, AND RDLPFC IN PURPLE) AND CONTRASTING THE RESULTS OBTAINED AFTER STIMULATION FROM BEFORE IT (BLOCK 2 – BLOCK 1). DARK RED MARKS INDICATE THE MEAN RISK PER CONDITION. *P<0.05; **P<0.01; ***P<0.001.*

4.3.2 Valuation

With respect to participants' average value chosen, the interaction of block2 with both active stimulation protocols, rDLPFC suppression (block2*rDLPFC, beta = 0.98, t(23214) = 3.16, p = .002) and VMPFC suppression (block2*VMPFC, beta = 0.71, t(23214) = 2.29, p = .022) was positive and significant. This means that the average value chosen by participants after rDLPFC and VMPFC stimulation were significantly higher than after sham stimulation. The contrast between VMPFC and rDLPFC inhibition protocols is not significantly different (block2*rDLPFC, beta = 0.27, t(15466) = .89, p = .374).

We also found a marginally significant negative effect of block with a reduction of average value from block 1 (baseline, dummy coded as zero) to block 2 (beta = -0.43, t(23214) =-1.98, p = 0.048) conditional on stimulation being Sham. Hence we observed a reduction in average value chosen between the first and second repetition of the task in the sham condition.

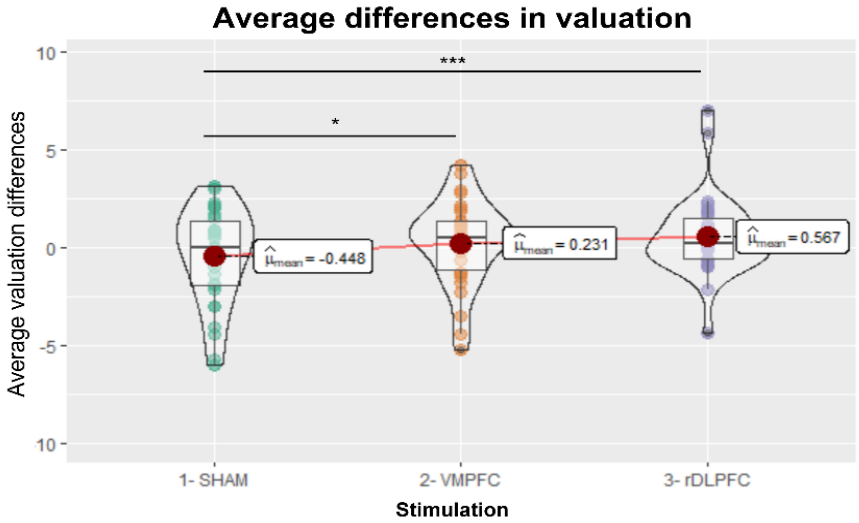

*Figure 4.3 - Average differences in valuation (n=30). Average differences in valuation estimated by the average value chosen by participants across stimulation conditions (Sham in green, VMPFC in orange, and rDLPFC in purple) and contrasting the results obtained after stimulation from before it (Block 2 – Block 1). Dark red marks indicate the mean risk per condition. *p<0.05; **p<0.01; ***p<0.001.*

4.3.3 Probability choices

When analyzing the average probability choices obtained before and after the stimulation protocols, we found no significant effects of either the interaction of block2 with the rDLPFC (p = .99) or the VMPFC stimulation (p = .95), meaning that there was no significant effect of the stimulation protocols.

4.3.4 Response time

The analyses of participants' response times indicated that participants were overall significantly faster in the second repetition of the task with a significant negative effect of block, comparing block1 to block2 (beta =-0.06, t(21704) =-12.32, p < .001). We also found a significant positive effect of the interaction between block2 and the rDLPFC stimulation (beta = 0.01, t(21704) = 2.17, p = .03). Albeit not significant, the interaction between block2 and VMPFC stimulation led to a decrease in response time (beta = -0.009, t(21704) =-1.32, p = 0.188). These results indicate that rDLPFC stimulation (but not VMPFC or the sham stimulation) led to a significant increase in response time.

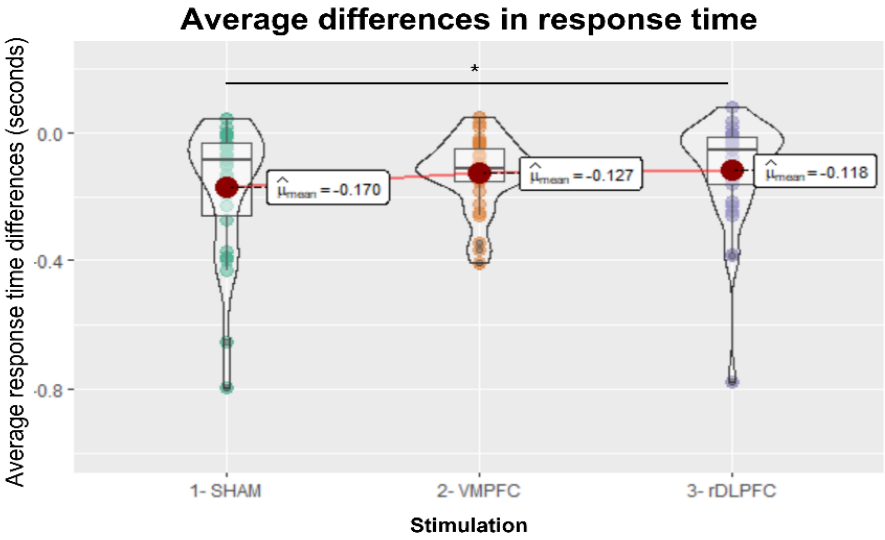

*Figure 4.4 - Average differences in response time (N=30). Average differences in response time estimated across stimulation conditions (Sham in green, VMPFC in orange, and rDLPFC in purple) and contrasting the results obtained after stimulation from before it (Block 2 – Block 1). Dark red marks indicate the mean risk per condition. *P<0.05; **P<0.01; ***P<0.001.*

4.4 DISCUSSION

Here, we aimed at using cTBS to investigate the functional relevance of two important prefrontal brain regions, the rDLPFC and the VMPFC, in risk-taking behavior, during the execution of the computerized MGT. Regarding the rDLPFC stimulation, we aimed at replicating the findings of Knoch and colleagues (2006) by stimulating this area with an inhibitory protocol expecting to significantly increase risk-taking behavior. However, rather than using a 10Hz rTMS protocol (Knoch et al., 2006), a cTBS protocol was adopted to reach such suppression with a shorter stimulation time. Our results show a successful replication of their findings, with a significant increase of risk-taking behavior after the cTBS-induced rDLPFC suppression.

Our second objective was to investigate the functional relevance of the VMPFC in risk-taking behavior. Recent TMS coil developments allow greater stimulation depth with the use of double-cone coils, making stimulation of deeper-lying areas, such as the VMPFC possible (Cho et al., 2015). We hypothesized that, compared to sham stimulation, VMPFC suppression would lead to a reduction in risk-taking behavior by reducing the appeal to riskier options with higher pay off. Contrary to our initial hypothesis, our results indicate that VMPFC suppression also leads to a significant increase in risk-taking behavior,

although a greater effect size was observed after rDLPFC suppression.

The MGT allowed us to analyze potential brain region-specific effects of cTBS on risk-taking behavior such as participants' average probability choices, average values, and response time after both rDLPFC and VMPFC stimulation. Our results indicate a significant increase in average value choices after both protocols, while no significant changes in probability choices were observed after either.

It is interesting to observe that the effects of both stimulation protocols on risk-taking behavior were driven by participants' valuation processing, and no significant effects were observed in their probability choices. This means that, considering that risk-taking behavior is estimated by calculating the standard deviation of the participant's choice, which takes into account both the option probability and payoff (see formulas 1 and 2 in the statistical analyses, section 4.2.5) (Myerson, 2005), a significant change in risk-taking behavior would be driven by one of these factors or an interaction between them. Hence, once there is no significant change in the probability scores, the significant increase in risk-taking behavior observed must be attributed to the significant increase in average value choices.

The finding that both VMPFC and rDLPFC suppression led to an increase in the average value choices and hence risk-taking behavior, with a stronger effect for the rDLPFC suppression, indicates that the VMPFC may not the only area responsible for valuation processing. A more feasible explanation, according to our findings, would be a network processing involving both the VMPFC and the DLPFC to evaluate options and modulate risk-taking behavior.

The similar results regarding risk-taking behavior and average choice of values obtained after the stimulation of the rDLPFC and VMPFC are also maybe not that surprising. These two areas are known to have a strong association considering their strong anatomical connectivity (Ghashghaei & Barbas, 2002). At least in the conditions of our study, it does not seem to be possible to fully dissociate the activity of the rDLPFC and VMPFC regarding risk-taking behavior and value choices using a repetitive inhibitory cTBS protocol. Our findings are in line with the results of Rudorf and Hare (2014), who demonstrated an interplay between the rDLPFC and the VMPFC during valuation in different contexts. According to the authors, varying choice contexts require more executive control for proper adjustment (Rudorf & Hare, 2014). An example of such variation is presented during the MGT, in which each trial brings different probabilities and payoffs with varying risk levels which can be more or less challenging, demanding adjustment and therefore more executive control.

Our findings are also in line with the assumption of Fecteau and colleagues (2007) that the DLPFC suppression would also affect the VMPFC and vice-versa due to their strong connectivity (Fecteau, Knoch, et al., 2007). The strong functional interplay between these two areas has been reported in several studies, for example, in the context of depression treatment (Dunlop et al., 2017), emotional regulation in bipolar disorder (Ladouceur et al., 2011) and during self-control in healthy participants. For example, Hare, Camerer and Rangel (2009) demonstrated the correlation between self-control during a choice task and the functional connectivity between DLPFC and VMPFC using fMRI (Hare et al., 2009).

Another possible explanation for the similar results obtained after both rDLPFC and VMPFC stimulation would be an overlap of stimulated areas. TMS is known as the NIBS method that offers greater focality. Nevertheless, considering our objective of reaching the VMPFC with our stimulation protocol, we opted for a double cone coil, which grants greater depth of stimulation (MagVenture, n.d.-b). However, this coil design offers lower focality compared to a traditional figure-of-eight coil (MagVenture, n.d.-a). To check for the possibility of stimulation overlap, we ran a simulation of the stimulated areas, with SimNibs (Thielscher et al., 2015), using a threshold of 1 V/m. The results, presented in Fig 1 show no significant overlap, meaning that this is an unlikely explanation.

Interestingly, and confirming the independent stimulation of each area, we found a region exclusive significant increase in response time after rDLPFC suppression but not after VMPFC or sham stimulation, excluding the overlap hypothesis. Albeit not significant, the VMPFC stimulation led to a decrease in response time. These findings represent behavioral evidence for the independent stimulation of these two areas since the increase of response time observed after rDLPFC stimulation is exclusive to this condition. This increase in response time might be attributed to varied factors. Higher response times are frequently associated with longer deliberation times, while shorter response times are commonly correlated with impulsivity and anxiety (Rubinstein, 2013). Considering the role of the DLPFC on executive control, we cannot attribute the observed increase in response time after the suppression of the rDLPFC to increased deliberation. However, it is possible that the temporary disruption of the rDLPFC, leads to the recruitment of other brain areas such as the left DLPFC or even the VMPFC itself, yielding higher response times. Nevertheless, this mechanism can only be speculated at this point and still needs to be explored for example by using a combination of NIBS and neuroimaging techniques.

Potential clinical applications emerge from these findings. Abnormal risk-taking behavior is a symptom and a diagnostic criterion in a variety of neural and psychological disorders including gambling disorder, addiction, binge eating, bipolar disorder, attention-deficit/

hyperactivity disorder (ADHD), and frontotemporal dementia (Dekkers et al., 2020; Giorgetta et al., 2012; Manoochehri & Huey, 2012; Pettorruso Giovanni Martinotti et al., 2020; Pettorruso et al., 2021; Reddy et al., 2013). Therefore, clarifying the underlying neural mechanisms of risk-taking behavior allows the development of more efficient treatment techniques. Using prefrontal TMS as therapeutic tool in the treatment or symptom management of patients with abnormal risk-taking is in line with previous findings (Pettorruso et al., 2021).

Decision-making under risk strongly affects people's health and wellbeing. In a clinical context, risk taking might even play a vital role, for example in suicidal ideation. TMS been applied in various clinical studies where the rates of suicidal ideation among participants with major depression disorder could significantly be reduced through prefrontal TMS (Croarkin et al., 2018; Cui et al., 2022; Weissman et al., 2018). Yet, these hypothesis and clinical applications still have to be explored in further studies.

As discussed, we found an increase in risk-taking behavior after both rDLPFC and VMPFC stimulation. A possible explanation for this could be that the results we see are caused by unspecific side effects of brain stimulation such as pain and/or unpleasantness. What in our perspective, however, speaks against this interpretation is the fact that we used a so-called TMS offline design, meaning that brain stimulation was applied outside the execution of the behavioral task. It is therefore rather unlikely that any potential unpleasant sensation during stimulation would affect task performance measures several minutes after stimulation has terminated. In addition, although risk taking behavior indeed increased after both, DLPFC and VMPFC stimulation, we also found differential effects between both brain regions with regard to response times, with an increase in response time only after rDLPFC stimulation and not after VMPFC stimulation. Therefore, we can conclude that the observed results are indeed due to strong interconnection between both VMPFC and rDLPFC that interact actively during the modulation of risk-taking behavior.

4.5 CONCLUSION

In conclusion, we here demonstrate a functional role of both, the rDLPFC and VMPFC in risk-taking behavior. We showed an increase in risk-taking behavior after right DLPFC cTBS, which replicates previous findings (Knoch et al., 2006). We also showed that cTBS applied over VMPFC also leads to increases in risk-taking behavior. Our results indicate that the increase in risky choices after stimulating both areas are likely due to increases in average valuation, contradicting theories that attribute valuation processing solely to the VMPFC. The study contributes to a better understanding of the underlying neural mechanisms of risk-taking behavior and the functional relevance of the VMPFC within this network, and expands the knowledge on the interconnection between rDLPFC and VMPFC.

Competing Interests statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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4.6 REFERENCES

Bartra, O., McGuire, J. T., & Kable, J. W. (2013). The valuation system: A coordinate-based meta-analysis of BOLD fMRI experiments examining neural correlates of subjective value. NeuroImage, 76, 412–427. https://doi.org/10.1016/j.neuroimage.2013.02.063

Berkman, E. T. (2018). The neuroscience of goals and behavior change. Consulting Psychology Journal, 70(1), 28–44. https://doi.org/10.1037/cpb0000094

Boggio, P. S., Zaghi, S., Villani, A. B., Fecteau, S., Pascual-Leone, A., & Fregni, F. (2010). Modulation of risk-taking in marijuana users by transcranial direct current stimulation (tDCS) of the dorsolateral prefrontal cortex (DLPFC). Drug and Alcohol Dependence, 112(3), 220–225. https://doi.org/10.1016/j.drugalcdep.2010.06.019

Burke, C. J., & Tobler, P. N. (2011). Coding of reward probability and risk by single neurons in animals. Frontiers in Neuroscience, 0(OCT), 121. https://doi.org/10.3389/fnins.2011.00121

Carlén, M. (2017). What constitutes the prefrontal cortex? Science, 358(6362), 478–482. https://doi.org/10.1126/SCIENCE.AAN8868/SUPPL_FILE/AAN8868S5.MP4

Chib, V. S., Rangel, A., Shimojo, S., & O'Doherty, J. P. (2009). Evidence for a common representation of decision values for dissimilar goods in human ventromedial prefrontal cortex. Journal of Neuroscience, 29(39), 12315–12320. https://doi.org/10.1523/JNEUROSCI.2575-09.2009

Cho, S. S., Koshimori, Y., Aminian, K., Obeso, I., Rusjan, P., Lang, A. E., Daskalakis, Z. J., Houle, S., & Strafella, A. P. (2015). Investing in the future: Stimulation of the medial prefrontal cortex reduces discounting of delayed rewards. Neuropsychopharmacology, 40(3), 546–553. https://doi.org/10.1038/npp.2014.211

Clark, L., Bechara, A., Damasio, H., Aitken, M. R. F., & Sahakian, B. J. (2017). Differential effects of insular and ventromedial prefrontal cortex lesions on risky decision-making. November. https://doi.org/10.1093/brain/awn066

Croarkin, P. E., Nakonezny, P. A., Deng, Z. de, Romanowicz, M., Voort, J. L. V., Camsari, D. D., Schak, K. M., Port, J. D., & Lewis, C. P. (2018). High-frequency repetitive TMS for suicidal ideation in adolescents with depression. Journal of Affective Disorders, 239, 282–290. https://doi.org/10.1016/J.JAD.2018.06.048

Cui, Y., Fang, H., Bao, C., Geng, W., Yu, F., & Li, X. (2022). Efficacy of Transcranial Magnetic Stimulation for Reducing Suicidal Ideation in Depression: A Meta-Analysis. Frontiers in Psychiatry, 12, 764183. https://doi.org/10.3389/FPSYT.2021.764183/FULL

Dantas, A. M., Sack, A. T., Bruggen, E., Jiao, P., & Schuhmann, T. (2021). Reduced risk-taking behavior during frontal oscillatory theta-band neurostimulation. Brain Research, 1759, 147365. https://doi.org/10.1016/j.brainres.2021.147365

D'Argembeau, A. (2013). On the role of the ventromedial prefrontal cortex in self-processing: The valuation hypothesis. Frontiers in Human Neuroscience, JUN. https://doi.org/10.3389/fnhum.2013.00372

Dekkers, T. J., Popma, A., Sonuga-Barke, E. J. S., Oldenhof, H., Bexkens, A., Jansen, B. R. J., & Huizenga, H. M. (2020). Risk Taking by Adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD): a Behavioral and Psychophysiological Investigation of Peer Influence. Journal of Abnormal Child Psychology, 48(9), 1129–1141. https://doi.org/10.1007/S10802-020-00666-Z/FIGURES/2

Duecker, F., & Sack, A. T. (2015). Rethinking the role of sham TMS. Frontiers in Psychology, 6(FEB), 210. https://doi.org/10.3389/FPSYG.2015.00210/BIBTEX

Dunlop, K., Hanlon, C. A., & Downar, J. (2017). Noninvasive brain stimulation treatments for addiction and

major depression. Annals of the New York Academy of Sciences, 1394(1), 31–54. https://doi.org/10.1111/nyas.12985

Fecteau, S., Knoch, D., Fregni, F., Sultani, N., Boggio, P., & Pascual-leone, A. (2007). Diminishing Risk-Taking Behavior by Modulating Activity in the Prefrontal Cortex : A Direct Current Stimulation Study. 27(46), 12500–12505. https://doi.org/10.1523/JNEUROSCI.3283-07.2007

Fecteau, S., Pascual-Leone, A., Zald, D. H., Liguori, P., Théoret, H., Boggio, P. S., Fregni, F., The, H., Boggio, P. S., Fregni, F., & Ht, C. (2007). Activation of Prefrontal Cortex by Transcranial Direct Current Stimulation Reduces Appetite for Risk during Ambiguous Decision Making. Journal of Neuroscience, 27(23), 6212–6218. https://doi.org/10.1523/JNEUROSCI.0314-07.2007

Ghashghaei, H. T., & Barbas, H. (2002). Pathways for emotion: Interactions of prefrontal and anterior temporal pathways in the amygdala of the rhesus monkey. Neuroscience, 115(4), 1261–1279. https://doi.org/10.1016/S0306-4522(02)00446-3

Giorgetta, C., Grecucci, A., Zuanon, S., Perini, L., Balestrieri, M., Bonini, N., Sanfey, A. G., & Brambilla, P. (2012). Reduced risk-taking behavior as a trait feature of anxiety. Emotion, 12(6), 1373–1383. https://doi.org/10.1037/A0029119

Hare, T. A., Camerer, C. F., & Rangel, A. (2009). Self-control in decision-Making involves modulation of the vmPFC valuation system. Science, 324(5927), 646–648. https://doi.org/10.1126/science.1168450

Hiser, J., & Koenigs, M. (2018). The Multifaceted Role of the Ventromedial Prefrontal Cortex in Emotion, Decision Making, Social Cognition, and Psychopathology. In Biological Psychiatry (Vol. 83, Issue 8, pp. 638–647). Elsevier USA. https://doi.org/10.1016/j.biopsych.2017.10.030

Hutcherson, C. A., Plassmann, H., Gross, J. J., & Rangel, A. (2012). Cognitive regulation during decision making shifts behavioral control between ventromedial and dorsolateral prefrontal value systems. Journal of Neuroscience, 32(39), 13543–13554. https://doi.org/10.1523/JNEUROSCI.6387-11.2012

Kito, S., Hasegawa, T., & Koga, Y. (2012). Cerebral blood flow in the ventromedial prefrontal cortex correlates with treatment response to low-frequency right prefrontal repetitive transcranial magnetic stimulation in the treatment of depression. Psychiatry and Clinical Neurosciences, 66(2), 138–145. https://doi.org/10.1111/j.1440-1819.2011.02312.x

Knoch, D., Gianotti, L. R. R., Pascual-leone, A., Treyer, V., Regard, M., Hohmann, M., & Brugger, P. (2006). Disruption of Right Prefrontal Cortex by Low-Frequency Repetitive Transcranial Magnetic Stimulation Induces. 26(24), 6469–6472. https://doi.org/10.1523/JNEUROSCI.0804-06.2006

Koul, A., Soriano, M., Avenanti, A., Cavallo, A., & Becchio, C. (2019). Investigating the causal role of frontal and parietal cortices in intention understanding: a cTBS study. Brain Stimulation, 12(2), 485. https://doi.org/10.1016/j.brs.2018.12.585

Kuhnen, C. M., & Knutson, B. (2005). The neural basis of financial risk taking. Neuron, 47(5), 763–770. https://doi.org/10.1016/j.neuron.2005.08.008

Ladouceur, C. D., Farchione, T., Diwadkar, V., Pruitt, P., Radwan, J., Axelson, D. A., Birmaher, B., & Phillips, M. L. (2011). Differential patterns of abnormal activity and connectivity in the amygdalaprefrontal circuitry in bipolar-I and bipolar-NOS youth. Journal of the American Academy of Child and Adolescent Psychiatry, 50(12), 1275-1289.e2. https://doi.org/10.1016/j.jaac.2011.09.023

Lim, S.-L., O'Doherty, J. P., & Rangel, A. (2011). The Decision Value Computations in the vmPFC and Striatum Use

a Relative Value Code That is Guided by Visual Attention. Journal of Neuroscience, 31(37), 13214–13223. https://doi.org/10.1523/JNEUROSCI.1246-11.2011

Loo, C. K., Taylor, J. L., Gandevia, S. C., McDarmont, B. N., Mitchell, P. B., & Sachdev, P. S. (2000). Transcranial magnetic stimulation (TMS) in controlled treatment studies: are some "sham" forms active? Biological Psychiatry, 47(4), 325–331. https://doi.org/10.1016/S0006-3223(99)00285-1

MagVenture. (n.d.-a). MagVenture C-B70.

MagVenture. (n.d.-b). MagVenture Cool D-B80.

Manoochehri, M., & Huey, E. D. (2012). Diagnosis and management of behavioral issues in frontotemporal dementia. Current Neurology and Neuroscience Reports, 12(5), 528–536. https://doi.org/10.1007/S11910-012-0302-7/TABLES/1

MATLAB R2018b (9.7.0.1190202 (R2018b)). (2018). The MathWorks Inc.

Myerson, R. B. (2005). Probability Models for Economic Decisions. Technometrics, 48(1), 159–159. https://doi.org/10.1198/tech.2006.s374

Pettorruso Giovanni Martinotti, M., Montemitro Luisa De Risio Primavera Alessandra Spagnolo Luigi Gallimberti Fabrizio Fanella Antonello Bonci, C., di Giannantonio Brainswitch Study Group, M., Pettorruso, M., Cassiani, B., di Natale, C., Fraticelli, S., Lorusso, M., Melone, A., Miuli, A., Mo-roni, V., Neri, F., Petrucci, I., Ruggiero, G., San-torelli, M., Chiara Spano, M., Stigliano, G., Tambelli, A., & Tourjansky, G. (2020). Multiple Sessions of High-Frequency Repetitive Transcranial Magnetic Stimulation as a Potential Treatment for Gambling Addiction: A 3-Month, Feasibility Study. European Addiction Research, 26(1), 52–56. https://doi.org/10.1159/000504169

Pettorruso, M., Miuli, A., di Natale, C., Montemitro, C., Zoratto, F., de Risio, L., d'Andrea, G., Dannon, P. N., Martinotti, G., & di Giannantonio, M. (2021). Non-invasive brain stimulation targets and approaches to modulate gambling-related decisions: A systematic review. Addictive Behaviors, 112. https://doi.org/10.1016/J.ADDBEH.2020.106657

R Bloggers, R. (2011). boxplot outlier | R-statistics blog.

R Core team. (2015). R Core Team. In R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing , Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org/. (Vol. 55, pp. 275–286).

Rao, H., Korczykowski, M., Pluta, J., Hoang, A., & Detre, J. A. (2008). Neural correlates of voluntary and involuntary risk taking in the human brain: An fMRI Study of the Balloon Analog Risk Task (BART). NeuroImage, 42(2), 902–910. https://doi.org/10.1016/j.neuroimage.2008.05.046

Reddy, L. F., Lee, J., Davis, M. C., Altshuler, L., Glahn, D. C., Miklowitz, D. J., & Green, M. F. (2013). Impulsivity and Risk Taking in Bipolar Disorder and Schizophrenia. Neuropsychopharmacology 2014 39:2, 39(2), 456–463. https://doi.org/10.1038/npp.2013.218

Rogers, R. D. R., Everitt, B. J., Baldacchino, A., Blackshaw, A. J., Swainson, R., Wynne, K., Baker, N. B., Hunter, J., Carthy, T., Booker, E., London, M., Deakin, J. F. W., Sahakian, B. J., & Robbins, T. W. (1999). Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan-depleted normal volunteers. Evidence for monoaminergic mechanisms. …, 20(4), 322–339. https://doi.org/10.1016/S0893-133X(98)00091-8

Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in

clinical practice and research, 120 Clinical Neurophysiology (2009). /pmc/articles/PMC3260536/

Roth, Y., Zangen, A., & Hallett, M. (2002). A coil design for transcranial magnetic stimulation of deep brain regions. Journal of Clinical Neurophysiology, 19(4), 361–370. https://doi.org/10.1097/00004691-200208000-00008

Rubinstein, A. (2013). Response time and decision making: An experimental study. In Judgment and Decision Making (Vol. 8, Issue 5). http://arielrubinstein.tau.ac.il/papers/RT2012.pdf.

Rudorf, S., & Hare, T. A. (2014). Interactions between dorsolateral and ventromedial prefrontal cortex underlie context-dependent stimulus valuation in goal-directed choice. Journal of Neuroscience, 34(48), 15988–15996. https://doi.org/10.1523/JNEUROSCI.3192-14.2014

Thielscher, A., Antunes, A., & Saturnino, G. B. (2015). Field modeling for transcranial magnetic stimulation: A useful tool to understand the physiological effects of TMS? Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS, 2015-November, 222–225. https://doi.org/10.1109/EMBC.2015.7318340

Tobler, P. N., O'Doherty, J. P., Dolan, R. J., & Schultz, W. (2007). Reward value coding distinct from risk attitude-related uncertainty coding in human reward systems. Journal of Neurophysiology, 97(2), 1621–1632. https://doi.org/10.1152/jn.00745.2006

*Universität Düsseldorf: G*Power. (n.d.). Retrieved October 20, 2022, from https://www.psychologie.hhu.de/arbeitsgruppen/allgemeine-psychologie-und-arbeitspsychologie/gpower*

Weissman, C. R., Blumberger, D. M., Brown, P. E., Isserles, M., Rajji, T. K., Downar, J., Mulsant, B. H., Fitzgerald, P. B., & Daskalakis, Z. J. (2018). Bilateral Repetitive Transcranial Magnetic Stimulation Decreases Suicidal Ideation in Depression. The Journal of Clinical Psychiatry, 79(3), 5831. https://doi.org/10.4088/JCP.17M11692

Yazdi, K., Rumetshofer, T., Gnauer, M., Csillag, D., Rosenleitner, J., & Kleiser, R. (2019). Neurobiological processes during the Cambridge gambling task. Behavioural Brain Research, 356, 295–304. https://doi.org/10.1016/j.bbr.2018.08.017

Zack, M., Cho, S. S., Parlee, J., Jacobs, M., Li, C., Boileau, I., & Strafella, A. (2016). Effects of High Frequency Repeated Transcranial Magnetic Stimulation and Continuous Theta Burst Stimulation on Gambling Reinforcement, Delay Discounting, and Stroop Interference in Men with Pathological Gambling. Brain Stimulation, 9(6), 867–875. https://doi.org/10.1016/j.brs.2016.06.003

4.A SUPPLEMENTARY MATERIAL

4.A.1 Variables coding

Table 4.A.1 Block coding:

Block	Code
Before stimulation	0
After stimulation	1

Table 4.A.2 Stimulation condition coding:

Stimulation condition	Code
Sham	0
VMPFC	1
rDLPFC	2

4.A.2 Results tables

Table 4.A.3 – Risk-taking behavior

	Value	Std. Error	DF	t-value	p-value
(Intercept)	26,25	0,35	23214	75,31	0,000
Block2	-0,21	0,10	23214	-2,21	0,027
VMPFC	-0,18	0,10	23214	-1,90	0,057
rDLPFC	-0,16	0,10	23214	-1,67	0,095
Block2*VMPFC	0,35	0,14	23214	2,52	0,012
Block2*rDLPFC	0,46	0,14	23214	3,37	0,001

Table 4.A.4 - Average value choices

	Value	Std. Error	DF	t-value	p-value
(Intercept)	59,53	0,78	23214	76,36	0,000
Block2	-0,43	0,22	23214	-1,98	0,048
VMPFC	-0,36	0,22	23214	-1,64	0,101
rDLPFC	-0,31	0,22	23214	-1,40	0,163
Block2*VMPFC	0,71	0,31	23214	2,29	0,022
Block2*rDLPFC	0,98	0,31	23214	3,16	0,002

Table 4.A.5 - Probability choices

	Value	Std. Error	DF	t-value	p-value
(Intercept)	-0,92	0,03	23214	-33,00	0,000
Block2	0,01	0,01	23214	0,67	0,506
VMPFC	0,00	0,01	23214	-0,05	0,962
rDLPFC	0,00	0,01	23214	0,31	0,757
Block2*VMPFC	0,00	0,02	23214	-0,07	0,946
Block2*rDLPFC	0,00	0,02	23214	0,02	0,987

Table 4.A.6 - Response time

	Value	Std. Error	DF	t-value	p-value
(Intercept)	0,86	0,02	21704	35,43	0,000
Block2	-0,06	0,00	21704	-12,32	0,000
VMPFC	-0,03	0,01	21704	-5,03	0,000
rDLPFC	-0,02	0,01	21704	-3,30	0,001
Block2*VMPFC	-0,01	0,01	21704	-1,32	0,188
Block2*rDLPFC	0,01	0,01	21704	2,17	0,030

THE SECRET RULERS

PART III

BACTERIA, AND A CERTAIN GUT FEELING

5

THE EFFECTS OF PROBIOTICS ON RISK AND TIME PREFERENCES

BASED ON: DANTAS, A. M., SACK, A. T., BRUGGEN, E., JIAO, P., & SCHUHMANN, T. (2022). THE EFFECTS OF PROBIOTICS ON RISK AND TIME PREFERENCES. SCIENTIFIC REPORTS 2022 12:1, 12(1), 1–10. HTTPS://DOI.ORG/10.1038/S41598-022-16251-X

ABSTRACT

Animal models, human neuroimaging and lesion studies revealed that the gut microbiota can influence the interaction between the central and the enteric nervous systems via the gut-brain axis (GBA) and can affect brain regions linked to basic emotional and cognitive processes. The role of the gut microbiota in decision-making in healthy humans thus far remains largely unknown. Our study establishes a functional relationship between the gut microbiota and healthy humans' decisions that involve risk and time. We conducted a between subjects' placebo-controlled double-blinded design, with two groups and two sessions separated by 28 days, during which participants received daily doses of probiotics or a placebo. We investigated whether the prolonged and controlled intake of probiotics affects risk-taking behavior and intertemporal choices using incentivized economic tasks.

We found a significant decrease in risk-taking behavior and an increase in future-oriented choices in the probiotics group as compared to the placebo group. These findings provide the first direct experimental evidence suggesting a potential functional role on the part of the microbiota-gut-brain axis in decision-making, creating a path for potential clinical applications and allowing for a better understanding of the underlying neural mechanisms of risk-taking behavior and intertemporal choices.

KEYWORDS: GUT-BRAIN, PROBIOTICS, RISK, INTERTEMPORAL CHOICE

5.1 INTRODUCTION

Our gut hosts a complex ecosystem of bacteria which plays a fundamental role on maintaining our health, nutrition, immune defenses and as more recently discovered, brain activity and behavior [1]. These gut microbiota form a complex system composed also by the central and enteric nervous systems, known as the microbiota-gut-brain-axis [2]. The proper ecological balance of the gut microbiota is known to affect brain development, cognitive performance [3], mood, reactivity to stress and socialization [4–6], and it even plays a role in certain psychopathologies [3,7–9]. Nevertheless, we still lack an understanding toward the effects of this system on decision-making. To address this, we conducted a double-blinded experiment in which we externally administered probiotics or placebo among healthy participants and established the causal relationship between probiotics intake and risky and intertemporal decision-making.

The study of the relationship between gut microbiota and decision making in animal studies has shown promising results. For instance, antibiotics-induced changes in the gut microbiota lead to increases in exploratory behavior [10], while germ-free mice exhibit anxiety-like behavior and increased risk-taking behavior, which reverts to normal levels with bacterial colonization [11]. Furthermore, it was revealed that the *Bifidobacteria infantis*, commonly present in healthy intestines, plays an important role in tryptophan metabolism, influencing serotonin production [12]. In a similar vein, research with germ-free mice revealed increased concentrations of cortical dopamine and the influence of the gut microbiota on the myelination of frontal brain areas [13]. All these factors play important roles in high-order cognitive processes, which also includes decision-making [14–17].

The results obtained in animal models have been successfully replicated in humans, demonstrating the relevance of the gut microbiota for brain development, important cognitive processes and behavior [5,18]. Studies with patients have demonstrated the clinical potential of GBA interventions [19] but fewer studies have explored the role of the GBA in healthy participants' cognition [3].

Amongst the studies with healthy participants, relevant findings were obtained with the use of brain functional magnetic resonance imaging (fMRI). For example, it was identified that the *Bifidobacterium* concentration is positively correlated with the increasing connectivity of the frontal nodes of the default mode network, while the prevalence of *Prevotella_9* and *Bacteroides* is negatively correlated [20]. It was also shown that participants who received probiotics, compared to a control group, had decreased functional connectivity between the frontal pole and frontal medial-cortex during resting-state fMRI [12], as well as a significant reduction in brain activity in sensory and affective regions, such as the insula, and increased activity in cortical regulatory regions, such as the DLPFC and MPFC, during a standardized emotional face recognition task

[28]. Both the DLPFC and ventromedial prefrontal cortex (VMPFC) play a fundamental role in decision-making [21] and are especially relevant to risk-taking behavior [22–26] and intertemporal choices [21,27,28], the focus of this study. Although these findings cited above point to a potential influence of the GBA in decision-making, this direct relationship is still unexplored. Therefore, we here investigate how changes in the gut microbiota can affect human decision-making in healthy participants and more specifically risk-taking behavior and intertemporal decision-making.

To that end, we used a double-blind protocol with 4 weeks of ingestion of either probiotics or placebo (two groups, gender balanced, between subjects' design) and incentivized tasks to measure risk-taking behavior and intertemporal choices. Specifically, we used the Maastricht Gambling Task (MGT) [24] to measure risk-taking behavior and the Maastricht Choice Game (MCG) to assess intertemporal choices. We hypothesized that by changing the gut microbiota composition with the probiotics protocol, we could affect risk-taking behavior and intertemporal choices. These changes would occur via the gut-brain axis leading to changes in brain activity. According to the results observed both in animal models and the effects of probiotics in brain activity [8,11,18,29], we expect a significant reduction both on risk-taking behavior and present bias. Hence, we hypothesized that the processing of risk and intertemporal decisions goes beyond the central nervous system's limits in our healthy participants. A graphic abstract of our study is depicted in Figure 5.1.

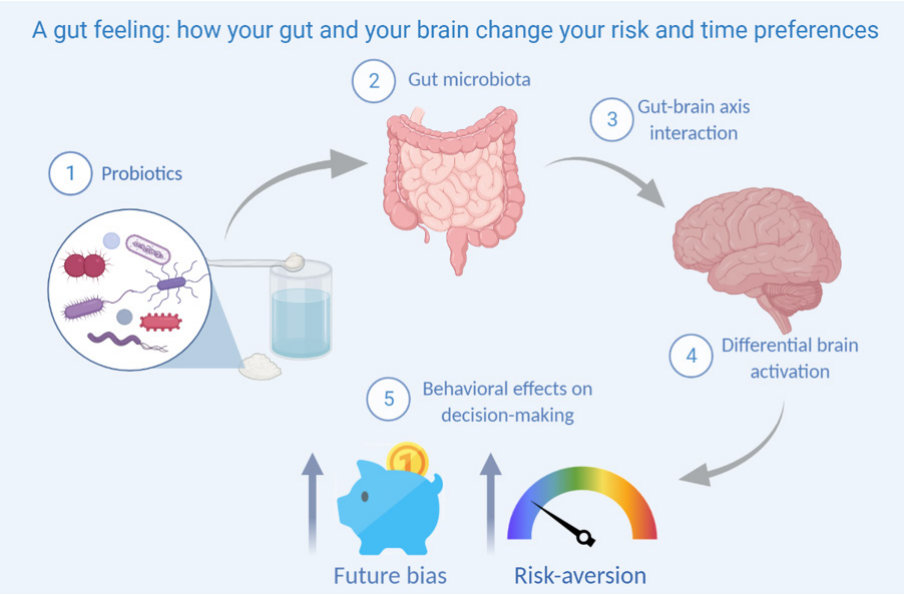

Figure 5.1 - Graphical abstract
Figure depicts a graphic abstract of the present study.

5.2 METHODS

We conducted a double-blind between-subjects study, with probiotics or placebo administration as a between-subjects factor. The study included two experimental sessions with a 28-day interval, during which participants took daily doses of either active probiotics or placebo (see section 5.2.5 for details). The study included a questionnaire to control for diet, arousal, self-control, and mood effects, as well as to provide alternative measures of time and risk preferences.

5.2.1 Sample

We recruited 72 participants using posters on campus and social media targeting the local community. Due to the COVID-19 lockdown in March of 2019, twelve participants discontinued the experiment, and three participants were excluded from the sample because they did not follow the probiotic intake protocol. Therefore, 57 healthy adults, with no reported psychological, psychiatric or gastric disease, right-handed, using a gender balanced sample (29 women) and with an average age of 23.4 years (SD=4) finished the experiment (29 in the probiotics group, 28 in the placebo group). All participants had normal or corrected-to-normal vision, reported to be well rested during the experimental session's days and gave written informed consent after being introduced to the experiment and screened for safety.

The safety screening followed the procedures recommended by the manufacturer (Winclove probiotics, The Netherlands) [11,30], excluding participants who had any sort of gastrointestinal disease or were using any medication during the experiment, with the exception of contraceptive pills. The study was approved by the local ethical committee, Maastricht University's Ethics Review Committee of Psychology and Neuroscience (ERCPN, approval code OZL_208_15_05_2019) and carried out in accordance with the standards set by the Declaration of Helsinki (Fortaleza Amendments).

Participants were asked to not consume more than two units of alcohol a day or any drugs on the day before, as well as during the experiment. Additionally, they were required to not take any antibiotics, medication or other probiotics throughout the entire experimental period. Participants were compensated for participation and rewarded according to task outcome.

5.2.2 Experimental design

Each participant underwent one of the assigned conditions of microbiota manipulation (probiotics or placebo). The conditions were assigned randomly, and the experiment was conducted in a double-blind fashion. Participation included two experimental sessions separated by 28 days (+/- 1), during which participants took daily doses of probiotics or placebo. Participants were reminded daily about probiotics ingestion via email to

improve compliance, and a follow-up questionnaire was used in Session 2 to check for proper probiotic/placebo intake. The experimental design is illustrated in Figure 5.2.

In each session, participants were invited to our laboratory, where they signed the written consent form and filled out a questionnaire via Qualtrics. They were instructed to not change their dietary patterns, not take any probiotics other than those provided to them as part of the experiment and not to take antibiotics during the 30 days of this experiment. Any deviations had to be reported, and participants who did not sufficiently comply with these requirements were excluded from the sample, with three participants being excluded from the sample for these reasons.

In the first session, participants first filled in a questionnaire to check for diet, arousal, self-control, and mood effects. We also used the Global Preference Survey [31] (GPS) to estimate risk and time preferences. The survey was adapted using the text from the English version, with values pertinent to the Dutch population (based on the Dutch version), considering that our international participant base is fluent in English and resides in the Netherlands. After filling in the questionnaire, participants were also asked to fill out the Brief Self-Control Scale [32] (BSCS), the Self-Assessment Manikin [33] (SAM) and a short diet assessment. This was done to later be able to control for self-control, mood and potential dietary changes, respectively.

Finally, participants completed the Maastricht Gambling Task (MGT) and the Maastricht Choice Game (MCG), computer tasks used to elicit and estimate risk--taking behavior and intertemporal choices, respectively. The task order was randomized to avoid any potential order effect. The explanation of each task was followed by ten practice trials before task execution. The tasks are described in more detail below.

After finishing the two tasks, we used an online random number generator, with which participants could select a random trial in each task that would be used to determine payments. Following the completion of the first session of the experiment, participants either received the first dose of probiotics or placebo and a box with the remaining 29 doses in individual sachets. They were instructed to take one dose daily for the next 28 days and reminded daily via mail to take their doses. The last dose was taken in Experimental Session 2.

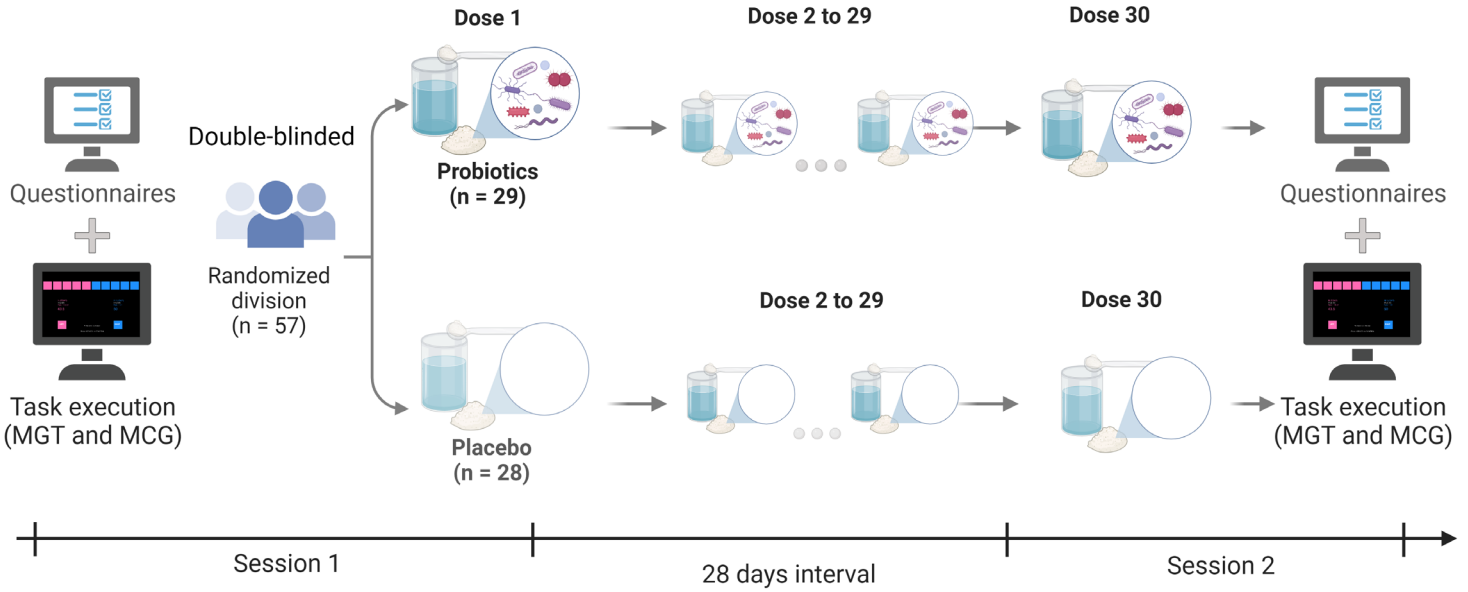

FIGURE 5.2 - EXPERIMENTAL DESIGN
FIGURE DEPICTS THE DOUBLE-BLINDED PLACEBO-CONTROLLED EXPERIMENTAL DESIGN, ALONG WITH THE MAIN PROCEDURES FOR BOTH EXPERIMENTAL SESSIONS AND THE PROBIOTICS/PLACEBO PROTOCOL FOLLOWED BY THE PARTICIPANTS DURING THE 30 DAYS OF THE EXPERI-MENT.

To minimize possible differences in responses due to differences in the period of the day in which the experiment was conducted, session 2 took place on the 30th (+/- 1) day of the experimental period, at the same period of the day. Before starting the procedures, participants ingested the last dose of either probiotics or placebo at the lab. Participants also completed a check, in which they stated whether they missed any doses during the interval. Participants who missed taking three or more doses were excluded from the sample. The second session followed the same procedure as Session 1, only the GPS was now not administered. At the end of Session 2, participants were debriefed.

After each session, payments to participants were administered in two parts. In the first part, participants randomly chose one trial of the MGT and one trial of the MCG for payment. As the MCG involves payments at different dates after the session (explained in detail in Section 5.2.4), bank transfers were made on the dates specified in a randomly chosen trial in MCG. We used this method so that all MCG payments could be done in the same way without participants having to come back to the lab. The second part of the payment, including their participation reward, at the rate of €7,5 per hour, plus rewards to the randomly chosen trial in MGT was made using vouchers with monetary value. This was done at the end of the experiment (end of session 2).

5.2.3 Maastricht Gambling Task (MGT)

The MGT is a computerized gambling task that is based on the Risk Task or Cambridge Gambling Task [34] and further developed by Dantas et al. (2021). Participants are presented with six colored boxes (see Figure 5.3A for an example screen) that can be either pink or blue. The number of pink boxes was randomized and could range from one to five (the remaining boxes are blue). Participants are informed that a token represented by a yellow X is hidden in one of the boxes. They need to guess the color of the box that hides the token. Unlike the original Risk Task, the MGT uses independent trials to control for memory effects. Moreover, to control for loss aversion, in the MGT participants do not lose points. The trials offer either positive points in case of a correct guess or zero points in the case of incorrect guess. Finally, to avoid any type of deception, all possible combinations of payoff and probabilities are presented to the participants and the token position is clearly randomized. Please see Dantas et al. (2021 present in Chapter 2, section 2.2.3 of this volume) for a complete description of the task.

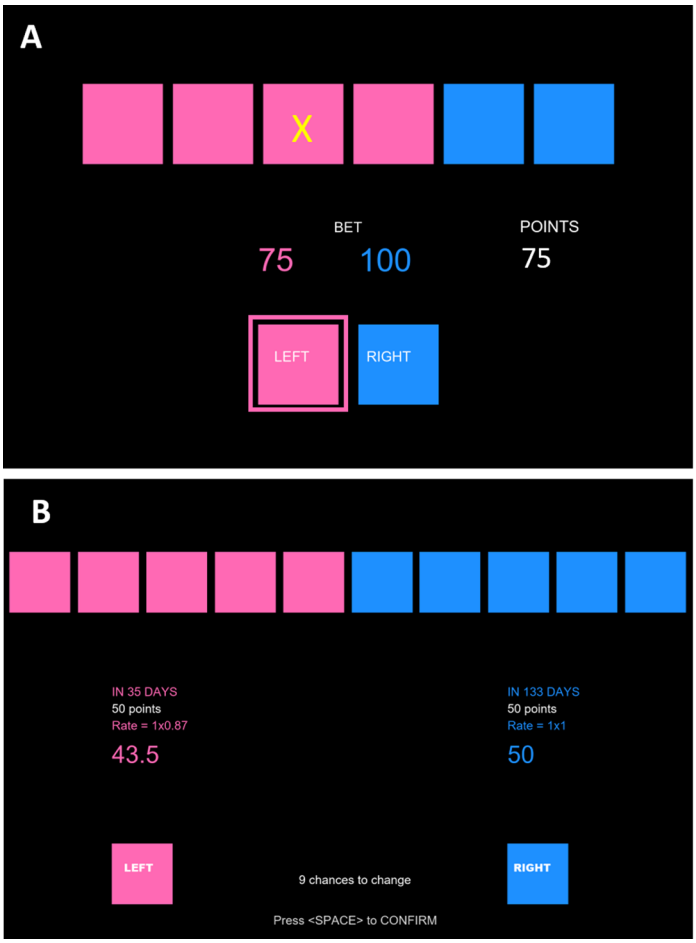

Figure 5.3 - Example screens of the tasks used.
Image A displays an example screen from the Maastricht Gambling Task (MGT), and image B shows an example screen from the Maastricht Choice Game (MCG).

5.2.4 Maastricht Choice Game (MCG)

We developed the MCG to elicit and estimate intertemporal choices based on the Convex Time Budget (CTB) method developed by Andreoni and Sprenger (2009) [35]. We used the CTB concept applied in a similar choice environment that is used in the MGT to maintain a relatively constant visual stimulation. In contrast to the MGT, and following the CTB method, each participant is initially endowed with 100 tokens and must spend this endowment entirely on two options.

Each option involves a payment at a specific date, an earlier date and a later date. The earlier options (t) could either be immediate (zero days) or in 35 days (after the end of the experiment). The later options offered either 35, 72 or 90 days (k) after the earlier options (therefore, the later option date is t+k). Any amount allocated to the later option (t+k) stays the same, but those allocated to the earlier option (t) were multiplied by one of twenty potential discount factors (0.50, 0.525, 0.55, 0.575, 0.60, 0.625, 0.65, 0.675, 0.70, 0.725, 0.75, 0.775, 0.80, 0.825, 0.85, 0.875, 0.90, 0.925, 0.95 and 0.99). Therefore, 120 unique combinations of discount rates and dates were generated. Each combination was displayed twice, so a total of 240 trials were presented in a random order. These were divided into five blocks of 48 trials.

Participants could freely allocate the endowment between boxes of two colors. Pink boxes represented the earlier option, and blue boxes represented the later option. Each box represented 10% of the total endowment (10 points). Participants were limited to a maximum of 15 attempts before a final decision is made in each trial. The number of tokens allocated to each option and the payoff for each date were displayed on the screen. An example screen is presented in Figure 5.3B.

Both MGT and MCG ruled out memory effects and wealth effects by using independent trials, in which the results of previous trials did not affect the following one.
To evaluate time preferences, we used the following model:

$$Maxxt\ Uxt = xt\alpha + \beta\delta k\ (xt+k)\alpha \quad (3)$$

Such a model states that the choice in a trial is the result of utility maximization according to equation (3). In the model, *t* represents the earlier date (0 or 35 days), and *k* represents the delay between the earlier and later dates (35, 70 or 95). Therefore, xt is the payoff at date *t,* and $xt+k$ is the payoff at date *t+k*. Parameter α captures risk attitude: $0<\alpha\leq 1$; $\alpha=1$ indicates risk neutrality. Our estimation of α here provides an additional check for the results in our MGT regarding risk attitude. In order to deal with corner solutions, in which participants allocate all points to either the earlier or the latter option, our estimation strategy adopts the two-limit Tobit maximum likelihood regression [35].

The parameters of major interest in this model for our research are each participant's present-bias ($\beta>0$) and time discount ($0<\delta\leq 1$). According to Andreoni and Sprenger (2012), $\beta<1$ indicates present-bias, while $\beta>1$ indicates future-bias. This parameter indicates how sharply a participant discounts between now and the immediate future. Finally, δ indicates a participant's time discounting, or how much each dollar of future reward would be worth in present terms.

The compensation for this task was provided via bank transfer according to the trial randomly selected by the participant for payment. For the randomly selected trial for payment determination, bank transfer was done on the dates specified in that trial according to the allocation decision made in that trial.

5.2.5 Probiotics

The probiotic Ecologic®Barrier (Ecologic®Barrier, Winclove probiotics, The Netherlands) is composed of Bifidobacterium bifidum W23, Bifidobacterium lactis W52, Lactobacillus acidophilus W37, Lactobacillus brevis W63, L. casei W56, Lactobacillus salivarius W24, and Lactococcus lactis (W19 and W58), distributed as sachets containing 2 g of freeze-dried powder of the PF and indicated for oral intake. Participants received the composition for 30 days [11,30]. For the same timeframe of 30 days, the control group received a bacteria-free placebo created by the same laboratory, which was based on corn starch and identical to the probiotic composition both visually and in flavor.

5.2.6 Statistical analyses

To facilitate transparency and reproducibility, our datasets and codes are available at DOI: 10.17632/nbz385mhny.2 . We analyzed the data from the MGT to estimate risk-taking behavior and the data from the MCG to estimate present-bias and time discounting.

All data were preprocessed using a custom MATLAB (The Mathworks Inc., Massachusetts, US). Our design included a between-subjects factor (group = placebo or probiotics) and a within-subject factor (time = session 1 and session 2). All trials (250 for the MGT and 240 for the MCG in each session) were analyzed per session and per participant. The control measures were analyzed with regressions using custom R scripts [36]. The intertemporal choice analyses included an extra step in preprocessing, in which the parameters α (risk attitude), β (present-bias) and δ (time discounting) were estimated by running a two-limit Tobit maximum likelihood regression [35]. These parameters were estimated for each session.

The statistical analyses included a series of linear mixed model analyses, which are robust considering the missing data and appropriate for our mixed design. We again used custom R scripts [36] to estimate the effects of the each factor and, more importantly, the interaction of time*group, which indicates the effects of the probiotics protocol versus the placebo protocol in Session 2. Our final models were fixed-effects models, with participant-specific and trial effects as the random effects. All the analyses presented normally distributed residuals and showed no heteroscedasticity.

Risk-taking behavior was analyzed by fitting a linear mixed model (formula = risk ~ group + time + group * time) estimated using REML. The follow-up analyses, including the

payments received by the participants between sessions, were again estimated using REML, including the payments received as part of the MCG compensation (payment) and the participation fee from Session 1 (participation) (formula = risk ~ group + time + payment + participation + group * time).

The results of the MCG were again analyzed using linear mixed models. The effects of the probiotics protocol versus placebo on present-bias was estimated using REML, with group and session as the main factors. More importantly, we focus on the group*time interaction to evaluate the effects of the probiotics intervention (formula = present bias ~ group + time + group*time). The analyses of time discount were estimated with the same method and using REML (formula = time discount ~ group + time + group*time).

5.3 RESULTS

In this section, we present the main behavioral results of our experiment.

5.3.1 Risk-taking behavior

The interaction effect of group*time, which tests our hypothesis by comparing the effects on both groups after the probiotics/placebo intervention, is negative and can be considered small and significant (beta =-0.42, SE = 0.16, t(14118) =-2.67, p = .008). This indicates that, despite the overall increase in risk-taking behavior over time, there was a significant reduction in risk-taking behavior in the probiotics group as compared to the placebo group in Session 2. More details can be observed in Figure 5.4.

As expected, the effect of group was not significant (p = 0.922), indicating no difference between groups in the first session. There was a small positive and significant effect on the part of time (beta = 0.42, SE = 0.11, t(14118) = 3.69, p < .001), indicating an increase in risk-taking behavior from Session 1 to Session 2 for both groups. To examine the observed increase in risk-taking behavior over time more closely, we ran an additional analysis. More specifically, we investigated whether the variation in the payout of the participant fee from the MCG task created a house money effect, or a payoff-based belief distortion [37,38], and consequently increased risk-taking behavior [39]. We therefore added the payments received by participant between Sessions 1 and 2 to the model. These payments included the participation fee for all participants and the immediate payment of the MCG for some of the participants (others received it 35 days later, in line with the incentivized MCG task). The inclusion of two regressors for the amount of the immediate payment from the MCG (payment) and the participation fee (participation) significantly improved the model's fit. The results yielded significant yet small effects on the part of the immediate payment (beta =-0.04, SE = 0.02, p < .05) and the participation fee (beta = 0.03, SE = 0.12, p < .01). Our main result is robust to the addition of the two payment factors into the model, still indicating a significant negative effect on the part of

the probiotics intervention, which can now be classified as a medium effect (beta =-0.50, SE = 0.16, p < .01). Additional analyses for the MGT are available in the supplemental material (S1).

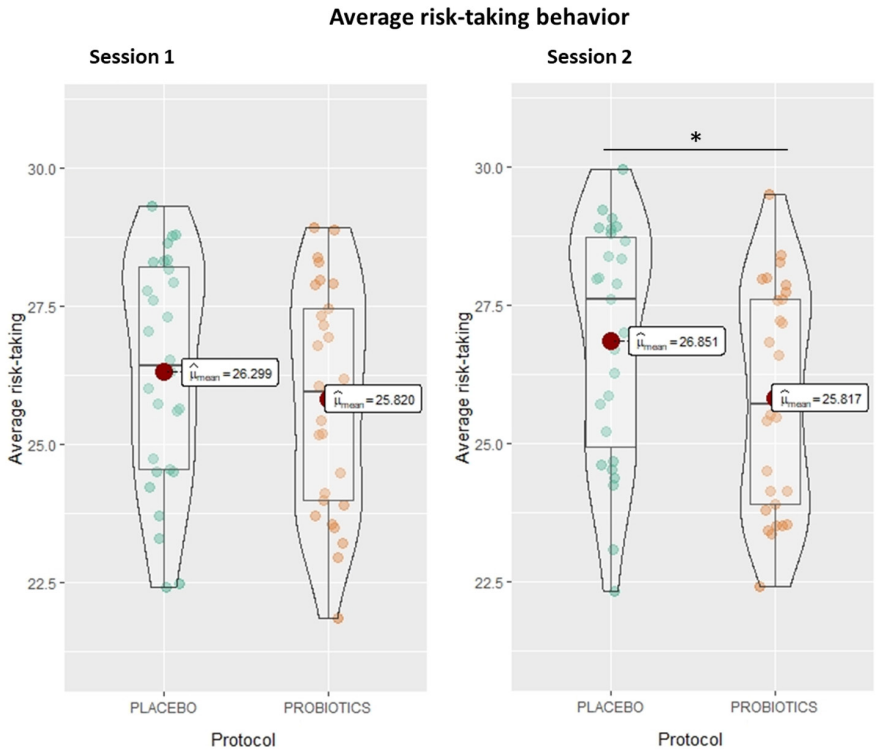

Figure 5.4 - Average Risk-taking Behavior (n = 57) Average risk-taking estimated by the average standard deviation of each participant's choice across sessions and protocols (placebo in green and probiotics in orange). The MGT allows risk scores from 1.8 to 50. The present analyses show participants' average risk-taking scores. Average risk-taking scores vary between 21.84 and 29.31.

5.3.2 Intertemporal choices

Regarding the probiotics interaction (group*time), we observed a significant large positive effect on β (t(13216) =12.028, p < .001). This means that the probiotics intervention leads to a significant increase in β, to a value above 1, which, according to Andreoni and Sprenger (2012), is characterized as a future bias, meaning that these participants were more likely to make future-oriented choices. It is important to highlight that participants already presented β values above 1, independent of the probiotics manipulation,

indicating future bias, which is expected when using the convex time budget method [35]. Our results demonstrated a small, albeit significant, positive effect of session (t(13261) = 1.99, p = .046), meaning that there was a small significant increase in β from Session 1 to Session 2 in both groups. As expected, no significant effect of group was observed (p = .506). Details can be seen in Figure 5.5.

Furthermore, we analyzed participants' time discounting. The effect of the probiotics protocol, analyzed via the interaction group*session, was negative and can be considered medium and significant (beta =-0.01, SE = 0.01, t(13261) =-4.911, p < .001). We did not find a significant main effect on the part of group, as expected (p = .24). There was a large and significant effect on the part of session (beta = 0.03, SE = 0.01, t(13261) = 20.785, p < .001). Additional analyses for the MCG are available in the supplemental material (S2).

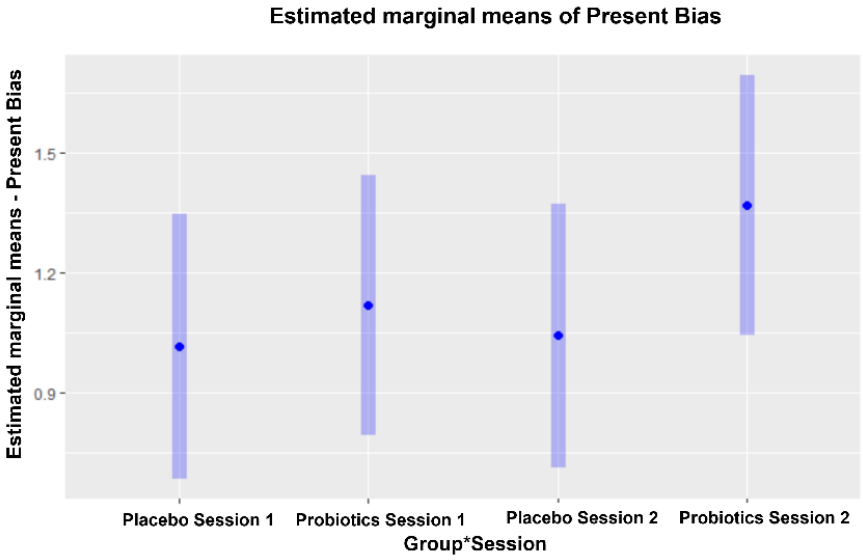

Figure 5.5 - Estimated marginal means of Present Bias (n = 57)
*Estimated marginal means of present bias calculated using a linear mixed model considering as factors Time (Session 1 and Session 2) and Protocol (Probiotics and Placebo) and its interaction (Time*Protocol). Trial and Time are taken as repeated measures and participant-specific and trial effects are used as the random effects. Participants' present bias (Beta) was estimated based on the model of convex budgets by Andreoni and Sprenger (2012) considering their responses during the MCG, with are averaged for each session. Dots represent participants' estimated marginal means for each session and treatment. Bars indicate the 95% confidence interval of the linear model employed for data analyses. Values above 1 are interpreted as indicating future bias.*

5.3.3 Control variables, time and risk preferences

We controlled for a series of variables, such as mood, self-control, arousal and diet. No significant effects on the part of the probiotics protocol (time*group) were observed on the mood scores (p = .17), self-control (p = .49), arousal (p = .72) or diet (p = .48). There were also no significant changes in diet when comparing the two time points estimated (p = .92).

We used the GPS [40] to estimate participant's time and risk preferences before the probiotics/placebo protocol, assuming a stability of this construct along time. These measurements were correlated to the task results aiming to find a correlation between risk preferences and risk-taking behavior (MGT results) and time preferences and intertemporal choices (MCG results).

Our results indicate a small significant correlation between risk-taking behavior estimated with the MGT and the GPS's qualitative (r(14123) = .03, p = .042) and quantitative estimation of risk preferences (r(14123) = .02, p = .045). GPS's qualitative measure of time preferences were negatively correlated with β (present bias) (r(13318) =-.04, p < .001) and no significant correlation with δ (time discounting). It's quantitative estimation, named patience, was positively correlated with participants' β (r(13318) = .04, p < .001) and δ a (r(13078) = .33, p < .001). The visualization of such correlations are available in the supplemental material (S1.4 and S2.3).

5.4 DISCUSSION

Given the crescent number of studies showing the fundamental relevance of the gut-brain axis as a bidirectional network in cognitive processes, here, we investigated the influence of the gut brain axis on decision-making in the face of risk and in the context of intertemporal choices [41]. To this end, we conducted a placebo-controlled double-blinded design with two sessions separated by 28 days, during which participants received daily doses of probiotics (or placebo). We investigated whether the prolonged and controlled intake of probiotics affected risk-taking behavior and intertemporal choices using incentivized tasks.

Our results confirmed the relationship between changes in the GBA and decision-making. Firstly, it was observed a significant reduction in risk-taking behavior after prolonged probiotic intake. Considering that there were no significant dietary or mood differences from Session 1 to Session 2 and the experimental conditions were identical, we can attribute the observed effects to the probiotic intake. Thus, participants who underwent the probiotics protocol were significantly less likely to choose risky options as compared to participants in the placebo group in Session 2, indicating a significant decrease in risk-taking behavior.

Secondly, our results showed that participants in the probiotics group exhibited a significantly higher future-bias and a significant reduction in time discounting as compared to the placebo group in Session 2. These results indicate that, after the prolonged use of probiotics, participants were significantly more likely to make future-oriented choices, investing more in delayed options than participants who received a placebo for the same period.

To further explore the robustness of our findings on risk-taking behavior, we control for additional factors. Since we observed that the placebo group exhibited a significant increase in risk taking in Session 2, we examined the results of the risk-taking behavior task more closely. We explored the potential reasons for this increase. We hypothesized that these increases in risk-taking behavior can be related to the fact that participants received the money between Session 1 to Session 2, potentially causing house money effect or payoff belief distortion [37,38]. The house money effect causes increases in risk-taking behavior in the presence of prior gains [37], and payoff-based belief distortion, increases participants optimism and risk-proneness after a gain [37,38].

This hypothesis was tested by adding the participation fee and immediate payments received between Session 1 and Session 2 as factors in our analysis. This way, we were able to show that the increase in risk-taking behavior in the placebo group was indeed an effect of the payments received by the participants between sessions; when we controlled for these payments in our model, the effect of time was no longer significant for either group. The effect of the interaction group*time, meaning the effects of the probiotics protocol on risk-taking after controlling for payments between sessions, not only remains significant but shows a larger effect size. Hence, we can affirm that the probiotics protocol led to a significant negative effect on risk-taking behavior. This means that, in the group that received probiotics, the significant increase in risk-taking behavior due to the payments between sessions seems to have been neutralized, considering that all other conditions were stable across groups and sessions.

In terms of intertemporal choices, we also observed an increase in future bias and time discounting from Session 1 to Session 2. These increases in both the placebo and probiotics groups are not unexpected and can be attributed to increased familiarity with the task and more confidence in the researchers, establishing a different reference point for their choices [11]. The probiotics intervention seems to have attenuated the effect on time discounting, which can be seen as a significant reduction in time discounting when comparing the probiotics and placebo groups in Session 2. Moreover, the group that underwent the probiotics protocol showed a larger significant increase in future bias than the placebo group, confirming the significant effect of probiotics on intertemporal choices.

Another interesting finding with respect to intertemporal choices is that participants were inherently future biased in both groups in Session 1, with an average β of 1.01, indicating future bias [35]. This contradicts the expectation based on the economics literature [47], which holds that most people are present- rather than future-biased. However, deviations from present-bias are not uncommon in empirical studies [48]. Moreover, our results are in line with Andreoni and Sprenger (2012), who also use a convex time budget, as we do in our task. It is important to stress that our task already presents significant delay intervals and a wide variety of discount rates, which should lead to realistic representations of participants' time preferences. One potential explanation for the future bias is that the payoffs offered to participant were not large enough, making it "easier" to wait for the payoffs[48,49].

Overall, our findings about the effect on probiotics on risk-taking corroborate the results obtained in previous studies. According to research using animal models, germ-free rodents exhibit increased risk-taking behavior, which is reversed to a normal levels after their gut microbiota are normalized via fecal transplantation or probiotic administration [11,42]. The administration of the same probiotic composition (Ecologic®Barrier, Winclove probiotics, The Netherlands), for six weeks in rats led to a significant reduction in risk-taking behavior [11]. Regarding studies with humans, although it was not the main point of their study, Bagga et al. (2018) also observed a significant reduction in risk-aversion after four weeks of probiotics, in line with our findings [42]. Yet, this study used a different probiotics composition (Ecologic®825, Winclove probiotics, The Netherlands) and a non-incentivized, self-reported measure of risk.

To our knowledge, no study to date has explored how the GBA affects intertemporal choices. Roman et al. (2018) conducted a comparable study but used a two-choice task, which is considered a measurement of impulsivity rather than intertemporal preferences because the delay time is only 5 seconds [43]. Nevertheless, their results point in a similar direction as ours since the prolonged consumption of probiotics (3 weeks with daily ingestion of a milk yogurt containing *Lactobacillus casei Shirota*) led to a significant reduction in impulsive choices [43].

Finally, it is important to highlight the potential practical impact of our current findings. Our results open doors for studies on the therapeutical use of probiotics in populations that present abnormal patterns of risk-taking behavior, such as patients with attention deficit and hyperactivity disorder (ADHD), addictions or depression [22,44,45]. Evidently, more studies in this direction are needed.

The communication between the gut and the brain during decision-making is also still unclear [3]. Two main pathways are potentially involved, namely the vagus nerve and

neurotransmitter production [3,41]. Nevertheless, we can only speculate, at this point, that the changes in gut microbiota affect decision-making through these pathways; the relative importance of each pathway in this neuronal network is still unclear [18].

It is important to highlight that our study mainly focused on behavioral responses before and after the probiotics (or placebo protocol), in which participants were asked to confirm their compliance with the protocol verbally and completed a pre experimental check. Although these choices were based on published studies that used similar methods [4,5,8,42], they also represent a limitation for our study, since no stool samples analyses were used to ensure differences in gut microbiota after the probiotics protocol and no additional measures were taken to evaluate possible metabolic changes due to the protocol. Therefore, we recommend the implementation of such steps in follow up studies.

In addition to potential clinical applications, the results that we observe for healthy participants calls for more research on the relationship between nutrition and decision-making. Various factors affect the gut microbiota, including genetics, health status, mode of birth, use of antibiotics, and stress levels [19]. However, diet is certainly one of the main factors to guarantee a balanced gut microbiota [46]. In our study, we used probiotics as a method to interfere with the microbiota-gut-brain axis by increasing microbiota diversity. Similar effects could potentially be achieved with a rich and healthy diet, healthier habits, and the lower use of unadvised antibiotics [7,47,48]. This is interesting in light of the fact that people with economic constraints often struggle to have access to nutritious diets [49], which would facilitate higher risk taking and more present-bias. For example, participants with poorer diets could be more likely to prefer immediate consumption over investing in a pension plan, potentially compromising their future financial wellbeing, with significant financial, social and economic impacts.

In resume, our findings suggest that the gut-brain axis may be a fundamental player in the neuronal mechanisms underlying decision-making. This means that our current neuroeconomical models used to predict risk-taking behavior and intertemporal choices, among potentially other types of complex decision-making, should not be limited to the CNS.

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5.5 REFERENCES

*Andreoni, J., & Sprenger, C. (2012). Estimating Time Preferences from Convex Budgets † By J ames A ndreoni and C harles S prenger *. 102(7), 3333–3356.*

Bagga, D., Aigner, C. S., Reichert, J. L., Cecchetto, C., Fischmeister, F. P. S., Holzer, P., Moissl-Eichinger, C., & Schöpf, V. (2019). Influence of 4-week multi-strain probiotic administration on resting-state functional connectivity in healthy volunteers. European Journal of Nutrition, 58(5), 1821–1827. https://doi.org/10.1007/s00394-018-1732-z

Bagga, D., Reichert, J. L., Koschutnig, K., Aigner, C. S., Holzer, P., Koskinen, K., Moissl-Eichinger, C., & Schöpf, V. (2018). Probiotics drive gut microbiome triggering emotional brain signatures. Gut Microbes, 9(6), 486–496. https://doi.org/10.1080/19490976.2018.1460015

Bercik, P., Denou, E., Collins, J., Jackson, W., Lu, J., Jury, J., Deng, Y., Blennerhassett, P., MacRi, J., McCoy, K. D., Verdu, E. F., & Collins, S. M. (2011). The intestinal microbiota affect central levels of brain-derived neurotropic factor and behavior in mice. Gastroenterology, 141(2), 599-609.e3. https://doi.org/10.1053/j.gastro.2011.04.052

Bercik, P., Park, A. J., Sinclair, D., Khoshdel, A., Lu, J., Huang, X., Deng, Y., Blennerhassett, P. A., Fahnestock, M., Moine, D., Berger, B., Huizinga, J. D., Kunze, W., Mclean, P. G., Bergonzelli, G. E., Collins, S. M., & Verdu, E. F. (2011). The anxiolytic effect of Bifidobacterium longum NCC3001 involves vagal pathways for gut-brain communication. Neurogastroenterology and Motility, 23(12), 1132–1139. https://doi.org/10.1111/j.1365-2982.2011.01796.x

Bradley, M. M., & Lang, P. J. (1994). Measuring emotion: The self-assessment manikin and the semantic differential. Journal of Behavior Therapy and Experimental Psychiatry, 25(1), 49–59. https://doi.org/10.1016/0005-7916(94)90063-9

Bravo, J. A., Forsythe, P., Chew, M. v, Escaravage, E., Savignac, H. M., Dinan, T. G., Bienenstock, J., & Cryan, J. F. (2011). Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. Proceedings of the National Academy of Sciences, 108(38), 16050–16055. https://doi.org/10.1073/pnas.1102999108

Carabotti, M., Scirocco, A., Maselli, M. A., & Severi, C. (2015). The gut-brain axis: Interactions between enteric microbiota, central and enteric nervous systems. Annals of Gastroenterology, 28(2).

Clark, L., Bechara, A., Damasio, H., Aitken, M. R. F., & Sahakian, B. J. (2017). Differential effects of insular and ventromedial prefrontal cortex lesions on risky decision-making. November. https://doi.org/10.1093/brain/awn066

Colzato, L. S., Steenbergen, L., de Kwaadsteniet, E. W., Sellaro, R., Liepelt, R., & Hommel, B. (2013). Tryptophan Promotes Interpersonal Trust. Psychological Science, 24(12), 2575–2577. https://doi.org/10.1177/0956797613500795

Cools, R., Barker, R. A., Sahakian, B. J., & Robbins, T. W. (2003). L-Dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease. Neuropsychologia, 41(11), 1431–1441. https://doi.org/10.1016/S0028-3932(03)00117-9

Cryan, J. F., & Dinan, T. G. (2012). Mind-altering microorganisms: The impact of the gut microbiota on brain and behaviour. In Nature Reviews Neuroscience (Vol. 13, Issue 10, pp. 701–712). Nature Publishing Group. https://doi.org/10.1038/nrn3346

Dantas, A. M., Sack, A. T., Bruggen, E., Jiao, P., & Schuhmann, T. (2021). Reduced risk-taking behavior during

frontal oscillatory theta-band neurostimulation. Brain Research, 1759, 147365. https://doi.org/10.1016/j.brainres.2021.147365

Davis, S. C., Yadav, J. S., Barrow, S. D., & Robertson, B. K. (2017). Gut microbiome diversity influenced more by the Westernized dietary regime than the body mass index as assessed using effect size statistic. MicrobiologyOpen, 6(4), 476. https://doi.org/10.1002/mbo3.476

Desbonnet, L., Garrett, L., Clarke, G., Bienenstock, J., & Dinan, T. G. (2008). The probiotic Bifidobacteria infantis: An assessment of potential antidepressant properties in the rat. Journal of Psychiatric Research, 43(2), 164–174. https://doi.org/10.1016/j.jpsychires.2008.03.009

Dinan, T. G., Stanton, C., & Cryan, J. F. (2013). Psychobiotics: A novel class of psychotropic. Biological Psychiatry, 74(10), 720–726. https://doi.org/10.1016/j.biopsych.2013.05.001

Dinan, T. G., Stilling, R. M., Stanton, C., & Cryan, J. F. (2015). Collective unconscious: How gut microbes shape human behavior. Journal of Psychiatric Research, 63, 1–9. https://doi.org/10.1016/j.jpsychires.2015.02.021

Falk, A., Becker, A., Dohmen, T., Enke, B., Huffman, D., & Sunde, U. (2018). Global Evidence on Economic Preferences. The Quarterly Journal of Economics, 133(4), 1645–1692. https://doi.org/10.1093/qje/qjy013*

Figner, B., Knoch, D., Johnson, E. J., Krosch, A. R., Lisanby, S. H., Fehr, E., & Weber, E. U. (2010). Lateral prefrontal cortex and self-control in intertemporal choice. Nature Neuroscience, 13(5), 538–539. https://doi.org/10.1038/nn.2516

Guillermo A Calvo, & Carmen M Reinhart. (2002). The Global Preferences Survey. Source: The Quarterly Journal of Economics, 117(2), 379–408. https://doi.org/10.1162/003355301556310

Hoban, A. E., Stilling, R. M., Ryan, F. J., Shanahan, F., Dinan, T. G., Claesson, M. J., Clarke, G., & Cryan, J. F. (2016). Regulation of prefrontal cortex myelination by the microbiota. Translational Psychiatry, 6(4), e774–e774. https://doi.org/10.1038/tp.2016.42

Jiao, P. (2020). Payoff-Based Belief Distortion. The Economic Journal, 130(629), 1416–1444. https://doi.org/10.1093/ej/ueaa019

Kohn, N., Szopinska-Tokov, J., Llera, A., Beckmann, C., Arias Vasquez, A., & Aarts, E. (2020). Multivariate associative patterns between the gut microbiota and large-scale brain network connectivity. In bioRxiv (p. 2020.08.25.266122). Cold Spring Harbor Laboratory. https://doi.org/10.1101/2020.08.25.266122

Kohno, M., Ghahremani, D. G., Morales, A. M., Robertson, C. L., Ishibashi, K., Morgan, A. T., Mandelkern, M. A., & London, E. D. (2015). Risk-taking behavior: Dopamine D2/D3 receptors, feedback, and frontolimbic activity. Cerebral Cortex, 25(1), 236–245. https://doi.org/10.1093/cercor/bht218

Koul, A., Soriano, M., Avenanti, A., Cavallo, A., & Becchio, C. (2019). Investigating the causal role of frontal and parietal cortices in intention understanding: a cTBS study. Brain Stimulation, 12(2), 485. https://doi.org/10.1016/j.brs.2018.12.585

Luna, R. A., & Foster, J. A. (2015). Gut brain axis: Diet microbiota interactions and implications for modulation of anxiety and depression. Current Opinion in Biotechnology, 32(Figure 1), 35–41. https://doi.org/10.1016/j.copbio.2014.10.007

Mani, A., Mullainathan, S., Shafir, E., & Zhao, J. (2013). Poverty impedes cognitive function. Science, 341(6149), 976–980. https://doi.org/10.1126/science.1238041

Messaoudi, M., Lalonde, R., Violle, N., Javelot, H., Desor, D., Nejdi, A., Bisson, J. F., Rougeot, C., Pichelin, M., Cazaubiel, M., & Cazaubiel, J. M. (2011). Assessment of psychotropic-like properties of a probiotic formulation

(Lactobacillus helveticus R0052 and Bifidobacterium longum R0175) in rats and human subjects. British Journal of Nutrition, 105(5), 755–764. https://doi.org/10.1017/S0007114510004319

Messaoudi, M., Violle, N., Bisson, J. F., Desor, D., Javelot, H., & Rougeot, C. (2011). Beneficial psychological effects of a probiotic formulation (Lactobacillus helveticus R0052 and Bifidobacterium longum R0175) in healthy human volunteers. Gut Microbes, 2(4). https://doi.org/10.4161/gmic.2.4.16108

O'Mahony, S. M., Clarke, G., Borre, Y. E., Dinan, T. G., & Cryan, J. F. (2015). Serotonin, tryptophan metabolism and the brain-gut-microbiome axis. Behavioural Brain Research, 277, 32–48. https://doi.org/10.1016/j.bbr.2014.07.027

Oriach, C. S., Robertson, R. C., Stanton, C., Cryan, J. F., & Dinan, T. G. (2016). Food for thought: The role of nutrition in the microbiota-gut-brain axis. Clinical Nutrition Experimental, 6, 25–38. https://doi.org/10.1016/j.yclnex.2016.01.003

Papalini, S., Michels, F., Kohn, N., Wegman, J., van Hemert, S., Roelofs, K., Arias-Vasquez, A., & Aarts, E. (2019). Stress matters: Randomized controlled trial on the effect of probiotics on neurocognition. Neurobiology of Stress, 10, 100141. https://doi.org/10.1016/J.YNSTR.2018.100141

Pollak, Y., Dekkers, T. J., Shoham, R., & Huizenga, H. M. (2019). Risk-Taking Behavior in Attention Deficit/Hyperactivity Disorder (ADHD): a Review of Potential Underlying Mechanisms and of Interventions. In Current Psychiatry Reports (Vol. 21, Issue 5, pp. 1–11). Current Medicine Group LLC 1. https://doi.org/10.1007/s11920-019-1019-y

R Core team. (2015). R Core Team. In R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing , Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org/. (Vol. 55, pp. 275–286). https://www.r-project.org/

Rao, H., Korczykowski, M., Pluta, J., Hoang, A., & Detre, J. A. (2008). Neural correlates of voluntary and involuntary risk taking in the human brain: An fMRI Study of the Balloon Analog Risk Task (BART). NeuroImage, 42(2), 902–910. https://doi.org/10.1016/j.neuroimage.2008.05.046

Rogers, R. D. R., Everitt, B. J., Baldacchino, A., Blackshaw, A. J., Swainson, R., Wynne, K., Baker, N. B., Hunter, J., Carthy, T., Booker, E., London, M., Deakin, J. F. W., Sahakian, B. J., & Robbins, T. W. (1999). Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan-depleted normal volunteersEvidence for monoaminergic mechanisms. …, 20(4), 322–339. https://doi.org/10.1016/S0893-133X(98)00091-8

Roman, P., Estévez, A. F., Miras, A., Sánchez-Labraca, N., Cañadas, F., Vivas, A. B., & Cardona, D. (2018). A Pilot Randomized Controlled Trial to Explore Cognitive and Emotional Effects of Probiotics in Fibromyalgia. Scientific Reports, 8(1), 10965. https://doi.org/10.1038/s41598-018-29388-5

Rudorf, S., & Hare, T. A. (2014). Interactions between dorsolateral and ventromedial prefrontal cortex underlie context-dependent stimulus valuation in goal-directed choice. Journal of Neuroscience, 34(48), 15988–15996. https://doi.org/10.1523/JNEUROSCI.3192-14.2014

Sarkar, A., Lehto, S. M., Harty, S., Dinan, T. G., Cryan, J. F., & Burnet, P. W. J. (2016). Psychobiotics and the Manipulation of Bacteria–Gut–Brain Signals. Trends in Neurosciences, 39(11), 763–781. https://doi.org/10.1016/j.tins.2016.09.002

Scheperjans, F., Aho, V., Pereira, P. A. B., Koskinen, K., Paulin, L., Pekkonen, E., Haapaniemi, E., Kaakkola, S., Eerola-Rautio, J., Pohja, M., Kinnunen, E., Murros, K., & Auvinen, P. (2015). Gut microbiota are related to Parkinson's

disease and clinical phenotype. Movement Disorders, 30(3), 350–358. https://doi.org/10.1002/mds.26069

Sprenger, C. (2015). An Endowment Effect for Risk: Experimental Tests of Stochastic Reference Points. Journal of Political Economy, 123(6), 1456–1499. https://doi.org/10.1086/683836

Tangney, J. P., Baumeister, R. F., & Boone, A. L. (2004). High Self-Control Predicts Good Adjustment, Less Pathology, Better Grades, and Interpersonal Success. Journal of Personality, 72(2), 271–324. https://doi.org/10.1111/j.0022-3506.2004.00263.x

Thaler, R. H., & Johnson, E. J. (1990). Gambling with the House Money and Trying to Break Even: The Effects of Prior Outcomes on Risky Choice. Management Science, 36(6), 643–660. https://doi.org/10.1287/mnsc.36.6.643

Tillisch, K., Labus, J., Kilpatrick, L., Jiang, Z., Stains, J., Ebrat, B., Guyonnet, D., Legrain-Raspaud, S., Trotin, B., Naliboff, B., & Mayer, E. A. (2013). Consumption of fermented milk product with probiotic modulates brain activity. Gastroenterology, 144(7), 1394-1401.e4. https://doi.org/10.1053/j.gastro.2013.02.043

Tillmann, S., & Wegener, G. (2019). Probiotics reduce risk-taking behavior in the Elevated Plus Maze in the Flinders Sensitive Line rat model of depression. Behavioural Brain Research, 359, 755–762. https://doi.org/10.1016/j.bbr.2018.08.025

Wastyk, H. C., Fragiadakis, G. K., Perelman, D., Dahan, D., Merrill, B. D., Yu, F. B., Topf, M., Gonzalez, C. G., Van Treuren, W., Han, S., Robinson, J. L., Elias, J. E., Sonnenburg, E. D., Gardner, C. D., & Sonnenburg, J. L. (2021). Gut-microbiota-targeted diets modulate human immune status. Cell. https://doi.org/10.1016/J.CELL.2021.06.019

Weber, B. J., & Huettel, S. A. (2008). The neural substrates of probabilistic and intertemporal decision making. Brain Research, 1234, 104–115. https://doi.org/10.1016/j.brainres.2008.07.105

Xu, L., Liang, Z. Y., Wang, K., Li, S., & Jiang, T. (2009). Neural mechanism of intertemporal choice: From discounting future gains to future losses. Brain Research, 1261, 65–74. https://doi.org/10.1016/j.brainres.2008.12.061

Yazdi, K., Rumetshofer, T., Gnauer, M., Csillag, D., Rosenleitner, J., & Kleiser, R. (2019). Neurobiological processes during the Cambridge gambling task. Behavioural Brain Research, 356, 295–304. https://doi.org/10.1016/j.bbr.2018.08.017

6

GENERAL DISCUSSION

The topic of risk-taking behavior has garnered substantial attention in a variety of fields, including psychology, economics, and neuroscience, due to its pervasive role in people's daily decision-making. Gaining insight into how humans make choices in the face of risk is crucial for the development of theoretical and economic models, informing public policy design, and ultimately improving individual decision-making. Risk-taking behavior is a multifaceted phenomenon influenced by numerous internal and external factors (Galvan et al., 2006; Kohno et al., 2015; Schonberg et al., 2011). Although many studies have investigated this topic, there is still much to learn, and further research is needed to continue advancing our understanding of this complex form of behavior.

This doctoral dissertation aimed to investigate some of the factors influencing decision-making under risk by exploring important components in the neural processing of risk-taking behavior. That investigation included a series of studies combining different neuroscientific techniques and tasks founded on economic theory. The majority of studies in this dissertation employed noninvasive brain stimulation (NIBS), either in combination with behavioral tasks or with the addition of electrophysiological measurements. The use of these techniques is essential to properly understand the role of a specific brain area (or a specific pattern of activity in this area) in a cognitive process (Polanía et al., 2018). Key elements in the processing of risk-taking behavior were explored, both within and beyond the central nervous system (CNS), by also investigating the potential effects of the gut–brain axis (GBA) on this type of decision process.

Within the CNS, a crucial factor to investigate is the role of specific oscillatory patterns of brain activity in the processing and modulation of this type of behavior because understanding the electrophysiological mechanism employed in the modulation of risk-taking behavior is fundamental (Thut et al., 2012). There is considerable evidence of a correlation between individual levels of frontal theta-band activity and differences in risk proneness (Gianotti et al., 2009; Schiller et al., 2014; Studer et al., 2013a). To explore this topic, Part I of this thesis includes studies in which the functional relationship between frontal theta-band activity and risk-taking behavior is investigated with transcranial alternating current stimulation (tACS). Theta-band activity is believed to occur in frontal brain areas as part of an electrophysiological mechanism used to recruit cognitive control—namely, recruitment of the activity of the dorsolateral prefrontal cortex (DLPFC)—to modulate risk-taking behavior (Cavanagh & Frank, 2014; Vinogradova, 1995; Womelsdorf et al., 2010).

The DLPFC plays a fundamental role in cognitive control, as has been shown with different NIBS methods (e.g., Boggio et al., 2010; Cho et al., 2010; Hutcherson et al., 2012; Lowe et al., 2014; McNeill et al., 2018; Rudorf & Hare, 2014). A seminal study by Knoch and colleagues (2006) demonstrated with the use of transcranial magnetic stimulation

(TMS) that the inhibition of right DLPFC activity leads to a significant increase in risky decision-making, demonstrating the role of this brain area in the modulation of risk-taking behavior (Knoch et al., 2006). Following the rationale of this study and employing the latest technical advances in TMS, I targeted in Part II the right DLPFC, aiming at a replication of these findings by investigating how right DLPFC inhibition affects individual risk-taking behavior.

Still in Part II, the role of the ventromedial prefrontal cortex (VMPFC), another important area in the processing of risk-taking behavior long neglected in studies using NIBS, is explored (Clark et al., 2017; Figner et al., 2010; Hutcherson et al., 2012; Knoch et al., 2006; Pujara et al., 2015). To this end, I targeted the VMPFC using an inhibitory TMS protocol to evaluate how it affects individual risk-taking. In the literature, the VMPFC has been associated with many cognitive processes, including the valuation of options and the modulation of risk-taking behavior (Clark et al., 2017; D'Argembeau, 2013; Hiser & Koenigs, 2018a; Hutcherson et al., 2012; Koenigs et al., 2010). In Damasio's somatic marker hypothesis, the VMPFC is considered a fundamental hub of somatic information to be integrated during decision-making (Bechara & Damasio, 2005; Clark et al., 2017). According to this hypothesis, the VMPFC would collect somatic cues as markers of emotional states associated with the options being evaluated and would thus be essential to optimal human decision-making (Clark et al., 2017; Hänsel & von Känel, 2008). From the sources of somatic information in our bodies, the most complex in terms of innervation and neurochemistry is the gut, which is the focus of Part III of this dissertation (Carabotti et al., 2015; Ganz, 2021; Mayer, 2011).

Neuroimaging studies show significant changes in brain activity after prolonged use of probiotics, which affect the gut microbiota and influence brain activity via the GBA (Bagga et al., 2019; Papalini et al., 2019). Among other brain areas, the default mode network (DMN) has been shown to be affected by a prolonged intake of probiotics (Bagga et al., 2019). The DMN is an important network that includes the posterior cingulate cortex, precuneus, lateral parietal cortex, and the DLPFC and VMPFC, which are fundamental areas in human decision-making (Raichle, 2015). Hence, it is reasonable to hypothesize that the GBA also affects human decision-making and specifically decision-making under risk, which is tested in Part III.

The investigation of the effects of the GBA on human decision-making is a new and crucial step in neuroeconomics. For a long time, neuroscience ignored the potential effects of the peripheral nervous system, including here the information coming from the enteric nervous system, on cognition. Nevertheless, recent advances in neuroscience have shown the important role played by the GBA in mood, stress reactivity, cognition, and behavior (Dinan et al., 2013; Sarkar et al., 2016). Considering that this effect might

extend to human decision-making is an intuitive and major step that I begin to explore in this dissertation.

Overall, this dissertation applies a range of techniques to study the various aspects involved in the neural processing of risk-taking behavior. Each part of this dissertation is discussed in detail in the following sections.

6.1 PART I – THE CODE: THETA-BAND OSCILLATIONS AND COGNITIVE CONTROL

The first part of this dissertation delves into the study of neural oscillatory patterns that may play a role in modulating risk-taking behavior. EEG studies have shown a correlation between theta power in the prefrontal cortex and risk-taking behavior, both during task performance and in the resting-state (Gianotti et al., 2009; Massar et al., 2012, 2014; B. Schmidt et al., 2018, 2019). During task performance, frontal theta-band activity seems to play a fundamental role in the regulation of risk-taking behavior (Schiller et al., 2014; Studer et al., 2013b; Vinogradova, 1995; Womelsdorf et al., 2010). However, a more substantial contribution to the study of risk may come from studies focusing on resting-state frontal theta power. These studies show a correlation between resting-state frontal theta-band activity, measured independent of any task, and risk-taking behavior (Gianotti et al., 2009; Studer et al., 2013b). This means that a particular individual pattern of neural activity (frontal theta power) that might be measured independent of context (during the resting-state) can be an indicator of individual risk proneness (Gianotti et al., 2009; Studer et al., 2013b). The significance of these findings derives from the importance (and challenges) of properly measuring individual levels of risk aversion (Kahneman & Tversky, 2018).

Risk aversion can lead to a reduction in the subjective value of an option that would objectively be more advantageous. Thus, risk proneness (or aversion) is a key factor in individual decision-making (Abdellaoui et al., 2007; Kahneman & Tversky, 2018). However, despite the use of several methods to estimate risk proneness, there is limited consistency in the results obtained (Donkers et al., 2013; Fox & Tannenbaum, 2011; Wölbert & Riedl, 2013). One possible solution to the challenge of properly estimating individual risk proneness might be its estimation based on resting-state EEG activity.

Nevertheless, the aforementioned EEG studies indicate a correlation, which suggests that by estimating this specific electrophysiological pattern, it is possible to predict an individual's risk-taking behavior independent of a specific task (Gianotti et al., 2009; Studer et al., 2013b). However, frontal theta power might not play a causal role in the regulation of risk-taking behavior since the causal relationship between frontal theta-band activity and risk-taking behavior has not yet been established. To confirm this

functional relationship, NIBS are needed (Sela et al., 2012; Wischnewski & Compen, 2022). Once a causal relationship is established between this pattern of brain activity and risk proneness, not only can the underlying neural processing of risk-taking behavior be better understood, but also a new method to estimate individual risk-taking could be established. In Chapter 2, I addressed this topic by using a combination of tACS and electroencephalography EEG to examine the functional role of frontal theta-band activity in decision-making under risk.

In that chapter, the relationship between frontal theta-band activity and risk-taking behavior is investigated by comparing the behavioral responses during left DLPFC stimulation with theta-band, gamma-band, and sham tACS. The results showed a significant effect of theta-band stimulation on risk-taking behavior, thus confirming a functional relationship between frontal theta-band activity and risk-taking behavior. Moreover, by showing frequency-exclusive effects, it was demonstrated that risk-taking behavior is specifically influenced by theta-band activity. Overall, these results show that the occurrence of frontal theta-band activity is not simply occasionally correlated with risk-taking behavior but is an important part of the electrophysiological mechanism used by the brain to modulate risk-taking behavior. Hence, frontal theta power is likely a reliable indicator of individual risk proneness (Dantas et al., 2021; Gianotti et al., 2009; Schiller et al., 2014; Studer et al., 2013a).

Despite clear behavioral results, there were no significant electrophysiological changes observed in Chapter 2. These null results may be due to the lack of long-lasting effects of the stimulation paradigm used, which included low-intensity tACS (6.5 Hz; 1.5 mA peak-to-peak) (Dantas et al., 2021). To address this, Chapter 3 used a new design incorporating high-intensity (3 mA peak-to-peak) tACS to test the effects of different intensities on EEG and behavioral responses. Another limitation of Chapter 2 is the stimulation of only the left hemisphere. According to Sela et al. (2012), the stimulation of the right hemisphere would not be effective due to a ceiling effect (Sela et al ., 2012). However, this hypothesis was not tested in Chapter 2. Therefore, the study reported in Chapter 3 includes the stimulation of both the right and left DLPFC independently and its effects on both risk-taking behavior and frontal theta power, as measured with EEG.

By including a more complex design and exploring different aspects of how frontal theta-band activity modulates risk-taking behavior, Chapter 3 builds on the findings of Chapter 2 and deepens the understanding of this electrophysiological mechanism. The results in Chapter 3 confirm the importance of frontal theta-band activity in this mechanism by again demonstrating the neuromodulation of risk-taking behavior with theta-band tACS. Furthermore, these findings demonstrate the role of laterality in this mechanism once the behavioral changes observed after tACS are shown to be dependent on the stimulated

hemisphere. The findings in Chapter 3 are fundamental to a better understanding of how this electrophysiological mechanism involving theta-band oscillations occurs in the brain.

According to the results in Chapter 3, stimulation of the two hemispheres leads to opposite effects in risk-taking behavior, with an increase observed during left hemisphere stimulation and a reduction in risky choices during right DLPFC tACS. Hence, the two hemispheres play different roles in the modulation of risk-taking behavior. This insight is crucial for the use of theta-band tACS in the modulation of risk-taking behavior, which can be either experimental (in further studies) or possibly clinical, with applications developed to help patients affected by abnormal risk-taking behavior.

Interestingly, the direction of the behavioral effects was also dependent on the participant's baseline frontal theta power, which is an important factor in the potential use of theta-band tACS as an intervention for patients suffering from impaired risk-taking behavior modulation (Levasseur-Moreau & Fecteau, 2012). The correlation of this baseline activity with participant risk-taking behavior was also confirmed, which reinforces the potential use of resting-state frontal theta power as a measure of individual risk-taking behavior. In general terms, the findings in Chapter 3 indicate that baseline theta power is not only correlated with the levels of risk an individual is likely to take, but also a fundamental factor in defining how that individual is likely to respond to increases in frontal theta power using tACS.

Perhaps a more significant technical advance and more important finding in Chapter 3 involve the differential results observed during high-intensity tACS (3 mA), which yielded more consistent behavioral results, with significant effects observed after both right and left DLPFC stimulation. On the other hand, low-intensity stimulation yielded significant results only when applied to the left hemisphere, with nearly significant results during right DLPFC stimulation. These findings, in line with the latest studies exploring the efficacy of transcranial electric stimulation (tES), are an important step in decision neuroscience. While neuroimaging techniques are the dominant methodologies in this field, there are a growing number of studies experimenting with NIBS and tES in particular, including transcranial direct current stimulation (tDCS) and tACS. However, there is still inconsistency in the findings obtained across studies using similar research designs (Levasseur-Moreau & Fecteau, 2012). One possible cause of these divergent outcomes is the use of low-intensity tACS, which can lead to unreliable results (Alekseichuk et al., 2022; Widge, 2018). Hence, by pioneering the use of high-intensity tACS in decision neuroscience, the present study makes an important contribution to the field.

6.2 PART II – THE CONTROLLER: PREFRONTAL CORTEX AND RISK-TAKING BEHAVIOR

The second part of this dissertation evaluated the functional role of the right DLPFC and the VMPFC in risk-taking behavior. These two brain areas have been widely reported to be important parts of the network responsible for the processing of decision-making in general and risk-taking behavior in particular. Since the DLPFC is easily accessible due to its anatomical position, a number of studies using NIBS have explored its functional role in executive control and its role in the modulation of risk-taking behavior (e.g., Boggio et al., 2010; Fecteau et al., 2007; Figner et al., 2010; Gilmore et al., 2018; Guo et al., 2018; Khaleghi et al., 2020; Knoch et al., 2006; Wu et al., 2021). However, the VMPFC is in a less superficial area, making its stimulation using NIBS more challenging.

Therefore, most studies indicating a role of the VMPFC in risk-taking behavior are based on neuroimaging findings, and the functional relationship of this area with that type of behavioral response has not been established. It is only recently that technical developments with new coil designs have enabled access to this area using TMS (Cho et al., 2010). Hence, the study reported in Chapter 4 is one of the first in decision neuroscience to use that technique and to explore the VMPFC's functional role in risk-taking behavior. In Chapter 4, I used continuous theta burst stimulation (cTBS) over the right DLPFC and VMPFC to inhibit these areas' activity and evaluate the consequent changes in risk-taking behavior and associated valuation processes.

Chapter 4 replicates the findings of the seminal work of Knoch et al. (2006) by using an inhibitory protocol to increase risk-taking behavior after cTBS-induced right DLPFC suppression. The replication of these findings is important in itself for the field of decision neuroscience, which is lacking in published replication studies. Knoch et al.'s (2006) work is cited by a number of studies in this field, and the replication of its findings adds consistency to their findings. Furthermore, I employed a much faster TMS protocol than the one used by Knoch and colleagues (2006).

In their original design, a low-frequency (1 Hz) repetitive TMS (rTMS) protocol of 15 minutes duration was applied before task execution (Knoch et al., 2006); cTBS is an equally effective inhibitory TMS protocol, the application of which lasts only 40 seconds (Cho et al., 2010; McNeill et al., 2018). Considering the potential for discomfort during TMS, a faster application is desirable (Brückner et al., 2013; di Lazzaro et al., 2011). Moreover, faster stimulation protocols are easier to replicate in future studies and to administer in clinical settings (Lowe et al., 2014). In addition, cTBS has longer aftereffects than low-frequency rTMS (di Lazzaro et al., 2011; Huang et al., 2005). Hence, the findings in Chapter 4 confirming that this faster protocol yields comparable results in terms of risk-taking modulation is an important technical advance.

Those results also show a significant increase in risk-taking behavior after VMPFC stimulation, although a greater effect size was observed after right DLPFC cTBS. Equivalent results were observed when analyzing participants' average choices of values, with significant increases after both stimulation protocols. These findings suggest that there is network processing involving both areas to evaluate options and modulate risk-taking behavior (Dantas et al., 2023; Hare et al., 2009; Rudorf & Hare, 2014). This explanation is supported by these areas' close anatomical connections and previous studies that have demonstrated an interplay between the two areas during valuation and decision-making under risk (Hiser & Koenigs, 2018b; Hutcherson et al., 2012; Knoch et al., 2006).

However, these findings are contrary to previous assumptions in neuroeconomics regarding the role of the VMPC during decision-making. Neuroeconomics studies using functional magnetic resonance imaging (fMRI) frequently take the activity of the VMPFC during decision-making as a proxy for subjective valuation (Bartra et al., 2013; Lim et al., 2011). This assumption is based on the observed positive correlation between the activation of this area and declared value of the presented options, typically in binary choice tasks (Chib et al., 2009; Lim et al., 2011; Ruff & Fehr, 2014; L. Schmidt et al., 2017). Since these assumptions derive solely from neuroimaging studies, the results obtained with the use of NIBS and presented in Chapter 4 represent a significant step toward better understanding the role of the VMPFC in decision-making, especially risk-taking behavior.

It is important to highlight that the results in Chapter 4 show a regionally exclusive significant increase in response time after right DLPFC suppression. These region-exclusive effects exclude the possibility of overlapping stimulation fields when targeting the right DLPFC and the VMPFC. Since there is no stimulation overlap, the similar behavioral results indicate the strong interconnectivity of these two areas during risky decision-making, which is in line with previous research (Hutcherson et al., 2012). The increase in response time after right DLPFC suppression could be attributable to deliberation or the recruitment of other brain areas. However, more research is needed to explore this mechanism; for example, a combination of NIBS and neuroimaging techniques could be used (Dantas et al., 2023). With these findings, Chapter 4 provides new insights into the functional relationship between prefrontal brain regions and risk-taking behavior and contributes to the growing literature on the neural mechanisms of risk-taking behavior.

6.3 PART III – THE SECRET RULERS: BACTERIA AND A CERTAIN GUT FEELING

Finally, following a growing and influential line of research that explores the involvement of the bidirectional network GBA in human cognition, I extrapolate in Chapter 5 the limits of the CNS and investigate the involvement of the GBA in human decision-making,

particularly regarding intertemporal choices and risk-taking behavior. To that end, the study reported in Chapter 5 employs a placebo-controlled, double-blind design with two sessions separated by 28 days. During that period, participants received daily doses of either probiotics or placebo (Dantas et al., 2022).

The findings in Chapter 5 support the connection between changes in the GBA and decision-making. A noteworthy decrease in risky behavior after prolonged intake of probiotics was observed that could not be explained by dietary or mood changes, since these factors were controlled. The results derived from a significant increase in risk-taking behavior from session 1 to session 2 in the placebo group, while the probiotics group presented stable levels of risk across sessions.

Further analyses indicate that this increase observed in the placebo was related to the amount of money won by the participants between sessions, which is likely due to a house money effect and/or payoff belief distortion, which causes increases in risk-taking behavior in the presence of prior gains or optimism after a gain (Jiao, 2020; Thaler & Johnson, 1990). However, this distortion was not observed in the probiotics group, indicating a relative reduction in risk-taking behavior.

Furthermore, after the prolonged intake of probiotics, participants maintained a stable average choice of values and were less likely to choose options with lower probabilities (Dantas et al., 2022). These results indicate that participants in the probiotics group were less prone to take risks and potentially less susceptible to valuation distortions. Since the study reported in Chapter 5 is the first to explore the effects of probiotics in human decision-making, the specific cognitive aspects affected by the GBA during risk-taking behavior are still unclear (Foster et al., 2017; Mayer, 2011; Sarkar et al., 2016). Some possibilities include valuation, attention, mood, and stress reactivity (Anderson et al., 2019; Burokas et al., 2017; Forsythe et al., 2016; Foster et al., 2017; Tengeler et al., 2020). However, further research in this area is needed.

The results in Chapter 5 connecting probiotics to risk-taking behavior are in line with the existing literature. Animal studies indicate that germ-free rodents display riskier behaviors, which return to average levels when their gut microbiota is adjusted with either fecal transplantation or probiotic administration. In a study involving rats, administering the same probiotic combination for six weeks caused a significant decrease in risk-taking (Tillmann & Wegener, 2019). In humans, Bagga and colleagues (2018) demonstrated a significant decrease in risk aversion after four weeks of probiotics, though their study used a distinct probiotic blend and a self-reported, non-incentivized measure of risk (Bagga et al., 2018).

Regarding intertemporal choices, the results in Chapter 5 show that members of the probiotics group exhibited a greater future bias and a drop in time discounting compared to the placebo group in Session 2. This implies that after prolonged intake of probiotics, individuals were more likely to make decisions with the future in mind and to choose delayed rewards more often than those who received the placebo. Analyses of the data obtained from the intertemporal choice task also indicate that participants in the probiotics group were significantly more risk-averse than participants in the placebo group (Dantas et al., 2022). To my knowledge, Chapter 5 is the first study exploring the effects of GBA interaction on intertemporal choices.

Although the behavioral results presented in Chapter 5 show an effect of probiotics intake on human decision-making, the connection between the gut and brain when making decisions is still not clear. Three pathways that could be involved are the vagus nerve, immunological responses, and neurotransmitter production (Bonaz et al., 2018; Carabotti et al., 2015; Ganz, 2021; O'Mahony et al., 2015). At this time, their relative importance is still unknown, which shows the need for further investigation.

The study reported in Chapter 5 is a pioneer in the examination of the potential effects of the GBA on risk-taking behavior and intertemporal choices with the use of probiotics as manipulation. Given the results of that study, further research should be conducted on the link between nutrition and decision-making. Although factors such as genetics, health status, mode of birth, antibiotic use, and stress levels all influence gut microbiota, diet is a key factor in maintaining balanced gut microbiota (Luna & Foster, 2015; Wastyk et al., 2021; Wirt & Collins, 2009). This means that effects similar to those obtained with the prolonged use of probiotics might be achieved by improving dietary habits and limiting antibiotic use. Furthermore, considering that individuals with lower levels of economic resources typically have limited access to nutritious diets (Kachwaha et al., 2020; Wirt & Collins, 2009), the results in Chapter 5 indicate that they could be living in conditions that might lead to greater risk-taking and a preference for immediate gratification over long-term benefits, which could have dramatic negative financial, social, and economic consequences. Further studies in this regard are warranted.

In conclusion, Chapter 5 reports on an important advance in connecting the GBA to high-complexity cognitive processes such as decision-making. Those findings indicate that the connection between the gut and the brain could be a critical factor in the neurobiological processes that control decision-making. This implies that the neuroeconomic models we currently employ to analyze risk-taking conduct and decisions over time should take into consideration more than just the CNS.

6.4 CONCLUDING REMARKS

This dissertation investigates the explored the neural mechanisms underlying risk-taking behavior, which involves various neural networks within and beyond the CNS. Frontal theta-band activity plays a fundamental role in the electrophysiological mechanism that modulates risk-taking behavior (Chapter 2), with the two hemispheres playing distinct roles, as demonstrated through the use of tACS on both the right and left DLPFC (Chapter 3). Baseline theta power not only correlates with an individual's risk-taking levels but also determines how a person will react to an increase in frontal theta power due to tACS (Chapter 3).

The right DLPFC is specifically responsible for the modulation of risk-taking behavior, with increased risk-taking behavior after activity in this area is inhibited using cTBS (Chapter 4). Similar effects were observed after VMPFC inhibition, indicating that this area integrates the network by which both modulation and the valuation processing of decisions under risk occur. These specific frontal areas have been shown to be affected by changes in the GBA, motivating the investigation of its potential effects on human risk-taking behavior and intertemporal choices. The prolonged use of probiotics leads to significant relative reductions in risk-taking behavior, lower future bias and lower time discount (Chapter 5).

Taken together, these findings demonstrate the complexity of the neural processes involved in the modulation of human risk-taking behavior. The findings of this dissertation help elucidate how the recruitment of prefrontal areas during the modulation of risk-taking behavior occurs and the roles of two important frontal brain areas, the right DLPFC and VMPFC, during this type of decision-making. The thesis also represents a first step in the exploration of the importance of the GBA in human decision-making, thus extending the limits of existing theoretical and economic models. Overall, these results add important insights into how human risk-taking behavior is processed and thus contribute to the study of human decision-making.

6.5 REFERENCES

Aarts, E., Ederveen, T. H. A., Naaijen, J., Zwiers, M. P., Boekhorst, J., Timmerman, H. M., Smeekens, S. P., Netea, M. G., Buitelaar, J. K., Franke, B., van Hijum, S. A. F. T., & Vasquez, A. A. (2017). Gut microbiome in ADHD and its relation to neural reward anticipation. PLoS ONE, 12(9), e0183509. https://doi.org/10.1371/journal.pone.0183509

Abdellaoui, M., Bleichrodt, H., & Paraschiv, C. (2007). Loss Aversion Under Prospect Theory: A Parameter-Free Measurement. Management Science, 53(10), 1659–1674. https://doi.org/10.1287/mnsc.1070.0711

Alekseichuk, I., Wischnewski, M., & Opitz, A. (2022). A minimum effective dose for (transcranial) alternating current stimulation. Brain Stimulation, 15(5), 1221–1222. https://doi.org/10.1016/J.BRS.2022.08.018

Anderson, C., Cryan, J., & Dinan, T. (2019). The Psychobiotic Revolution: Mood, Food, and the New Science of the Gut-Brain Connection. National Geographic.

Bagga, D., Aigner, C. S., Reichert, J. L., Cecchetto, C., Fischmeister, F. P. S., Holzer, P., Moissl-Eichinger, C., & Schöpf, V. (2019). Influence of 4-week multi-strain probiotic administration on resting-state functional connectivity in healthy volunteers. European Journal of Nutrition, 58(5), 1821–1827. https://doi.org/10.1007/s00394-018-1732-z

Bagga, D., Reichert, J. L., Koschutnig, K., Aigner, C. S., Holzer, P., Koskinen, K., Moissl-Eichinger, C., & Schöpf, V. (2018). Probiotics drive gut microbiome triggering emotional brain signatures. Gut Microbes, 9(6), 486–496. https://doi.org/10.1080/19490976.2018.1460015

Bartra, O., McGuire, J. T., & Kable, J. W. (2013). The valuation system: A coordinate-based meta-analysis of BOLD fMRI experiments examining neural correlates of subjective value. NeuroImage, 76, 412–427. https://doi.org/10.1016/j.neuroimage.2013.02.063

Bechara, A., & Damasio, A. R. (2005). The somatic marker hypothesis: A neural theory of economic decision. Games and Economic Behavior, 52(2), 336–372. https://doi.org/10.1016/j.geb.2004.06.010

Boggio, P. S., Zaghi, S., Villani, A. B., Fecteau, S., Pascual-Leone, A., & Fregni, F. (2010). Modulation of risk-taking in marijuana users by transcranial direct current stimulation (tDCS) of the dorsolateral prefrontal cortex (DLPFC). Drug and Alcohol Dependence, 112(3), 220–225. https://doi.org/10.1016/j.drugalcdep.2010.06.019

Bonaz, B., Sinniger, V., & Pellissier, S. (2018). Vagus Nerve Stimulation at the Interface of Brain-Gut Interactions. Cold Spring Harbor Perspectives in Medicine, a034199. https://doi.org/10.1101/cshperspect.a034199

Burke, C. J., & Tobler, P. N. (2011). Coding of reward probability and risk by single neurons in animals. Frontiers in Neuroscience, 0(OCT), 121. https://doi.org/10.3389/fnins.2011.00121

Burokas, A., Arboleya, S., Moloney, R. D., Peterson, V. L., Murphy, K., Clarke, G., Stanton, C., Dinan, T. G., & Cryan, J. F. (2017). Targeting the Microbiota-Gut-Brain Axis: Prebiotics Have Anxiolytic and Antidepressant-like Effects and Reverse the Impact of Chronic Stress in Mice. Biological Psychiatry, 82(7), 472–487. https://doi.org/10.1016/j.biopsych.2016.12.031

Carabotti, M., Scirocco, A., Maselli, M. A., & Severi, C. (2015). The gut-brain axis: Interactions between

enteric microbiota, central and enteric nervous systems. Annals of Gastroenterology, 28(2).

Cavanagh, J. F., & Frank, M. J. (2014). Frontal theta as a mechanism for cognitive control. Trends in Cognitive Sciences, 18(8), 414–421. https://doi.org/10.1016/j.tics.2014.04.012

Chandrakumar, D., Feuerriegel, D., Bode, S., Grech, M., & Keage, H. A. D. (2018). Event-related potentials in relation to risk-taking: A systematic review. Frontiers in Behavioral Neuroscience, 12, 111. https://doi.org/10.3389/FNBEH.2018.00111/BIBTEX

Chib, V. S., Rangel, A., Shimojo, S., & O'Doherty, J. P. (2009). Evidence for a common representation of decision values for dissimilar goods in human ventromedial prefrontal cortex. Journal of Neuroscience, 29(39), 12315–12320. https://doi.org/10.1523/JNEUROSCI.2575-09.2009

Cho, S. S., Ko, J. H., Pellecchia, G., Van Eimeren, T., Cilia, R., & Strafella, A. P. (2010). Continuous theta burst stimulation of right dorsolateral prefrontal cortex induces changes in impulsivity level. Brain Stimulation, 3(3), 170–176. https://doi.org/10.1016/j.brs.2009.10.002

Clark, L., Bechara, A., Damasio, H., Aitken, M. R. F., & Sahakian, B. J. (2017). Differential effects of insular and ventromedial prefrontal cortex lesions on risky decision-making. November. https://doi.org/10.1093/brain/awn066

Cui, Y., Fang, H., Bao, C., Geng, W., Yu, F., & Li, X. (2022). Efficacy of Transcranial Magnetic Stimulation for Reducing Suicidal Ideation in Depression: A Meta-Analysis. Frontiers in Psychiatry, 12, 764183. https://doi.org/10.3389/FPSYT.2021.764183/FULL

Dantas, A. M., Sack, A. T., Bruggen, E., Jiao, P., & Schuhmann, T. (2021). Reduced risk-taking behavior during frontal oscillatory theta-band neurostimulation. Brain Research, 1759, 147365. https://doi.org/10.1016/j.brainres.2021.147365

Dantas, A. M., Sack, A. T., Bruggen, E., Jiao, P., & Schuhmann, T. (2022). The effects of probiotics on risk and time preferences. Scientific Reports, 12(1), 1–10. https://doi.org/10.1038/s41598-022-16251-x

Dantas, A. M., Sack, A. T., Bruggen, E., Jiao, P., & Schuhmann, T. (2023). The functional relevance of right DLPFC and VMPFC in risk-taking behavior. Cortex, 159, 64–74. https://doi.org/10.1016/j.cortex.2022.11.009

D'Argembeau, A. (2013). On the role of the ventromedial prefrontal cortex in self-processing: The valuation hypothesis. Frontiers in Human Neuroscience, JUN. https://doi.org/10.3389/fnhum.2013.00372

Dekkers, T. J., Popma, A., Sonuga-Barke, E. J. S., Oldenhof, H., Bexkens, A., Jansen, B. R. J., & Huizenga, H. M. (2020). Risk Taking by Adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD): a Behavioral and Psychophysiological Investigation of Peer Influence. Journal of Abnormal Child Psychology, 48(9), 1129–1141. https://doi.org/10.1007/S10802-020-00666-Z/FIGURES/2

Dinan, T. G., Stanton, C., & Cryan, J. F. (2013). Psychobiotics: A novel class of psychotropic. Biological Psychiatry, 74(10), 720–726. https://doi.org/10.1016/j.biopsych.2013.05.001

Donkers, B., Lourenço, C. J. S., Dellaert, B. G. C., & Goldstein, D. G. (2013). Using Preferred Outcome Distributions to Estimate Value and Probability Weighting Functions in Decisions under Risk. SSRN Electronic Journal. https://doi.org/10.2139/ssrn.2262354

Fecteau, S., Knoch, D., Fregni, F., Sultani, N., Boggio, P., & Pascual-leone, A. (2007). Diminishing Risk-

Taking Behavior by Modulating Activity in the Prefrontal Cortex : A Direct Current Stimulation Study. 27(46), 12500–12505. https://doi.org/10.1523/JNEUROSCI.3283-07.2007

Figner, B., Knoch, D., Johnson, E. J., Krosch, A. R., Lisanby, S. H., Fehr, E., & Weber, E. U. (2010). Lateral prefrontal cortex and self-control in intertemporal choice. Nature Neuroscience, 13(5), 538–539. https://doi.org/10.1038/nn.2516

Floden, D., Alexander, M. P., Kubu, C. S., Katz, D., & Stuss, D. T. (2008). Impulsivity and risk-taking behavior in focal frontal lobe lesions. Neuropsychologia, 46(1), 213–223. https://doi.org/10.1016/j.neuropsychologia.2007.07.020

Forsythe, P., Kunze, W., & Bienenstock, J. (2016). Moody microbes or fecal phrenology: what do we know about the microbiota-gut-brain axis? BMC Medicine 2016 14:1, 14(1), 1–14. https://doi.org/10.1186/S12916-016-0604-8

Foster, J. A., Rinaman, L., & Cryan, J. F. (2017). Stress & the gut-brain axis: Regulation by the microbiome. Neurobiology of Stress, 7, 124–136. https://doi.org/10.1016/j.ynstr.2017.03.001

Fox, C. R., & Tannenbaum, D. (2011). The elusive search for stable risk preferences. In Frontiers in Psychology (Vol. 2, Issue NOV, p. 298). Frontiers. https://doi.org/10.3389/fpsyg.2011.00298

Galvan, A., Hare, T. A., Parra, C. E., Penn, J., Voss, H., Glover, G., & Casey, B. J. (2006). Earlier Development of the Accumbens Relative to Orbitofrontal Cortex Might Underlie Risk-Taking Behavior in Adolescents. 26(25), 6885–6892. https://doi.org/10.1523/JNEUROSCI.1062-06.2006

Ganz, J. (2021). Revealing the complexity of the gut's brain. In Nature Neuroscience (Vol. 24, Issue 1, pp. 1–2). Nature Research. https://doi.org/10.1038/s41593-020-00769-2

Gianotti, L. R. R., Knoch, D., Faber, P. L., Lehmann, D., Pascual-Marqui, R. D., Diezi, C., Schoch, C., Eisenegger, C., & Fehr, E. (2009). Tonic activity level in the right prefrontal cortex predicts individuals' risk taking. Psychological Science, 20(1), 33–38. https://doi.org/10.1111/j.1467-9280.2008.02260.x

Gilmore, C. S., Dickmann, P. J., Nelson, B. G., Lamberty, G. J., & Lim, K. O. (2018). Transcranial Direct Current Stimulation (tDCS) paired with a decision-making task reduces risk-taking in a clinically impulsive sample. Brain Stimulation, 11(2), 302–309. https://doi.org/10.1016/j.brs.2017.11.011

Giorgetta, C., Grecucci, A., Zuanon, S., Perini, L., Balestrieri, M., Bonini, N., Sanfey, A. G., & Brambilla, P. (2012). Reduced risk-taking behavior as a trait feature of anxiety. Emotion, 12(6), 1373–1383. https://doi.org/10.1037/a0029119

Guo, H., Zhang, Z., Da, S., Sheng, X., & Zhang, X. (2018). High-definition transcranial direct current stimulation (HD-tDCS) of left dorsolateral prefrontal cortex affects performance in Balloon Analogue Risk Task (BART). Brain and Behavior, 8(2), e00884. https://doi.org/10.1002/brb3.884

Hänsel, A., & von Känel, R. (2008). The ventro-medial prefrontal cortex: A major link between the autonomic nervous system, regulation of emotion, and stress reactivity? BioPsychoSocial Medicine, 2, 1–5. https://doi.org/10.1186/1751-0759-2-21

Hare, T. A., Camerer, C. F., & Rangel, A. (2009). Self-control in decision-Making involves modulation of the vmPFC valuation system. Science, 324(5927), 646–648. https://doi.org/10.1126/science.1168450

Hiser, J., & Koenigs, M. (2018a). The Multifaceted Role of the Ventromedial Prefrontal Cortex in

Emotion, Decision Making, Social Cognition, and Psychopathology. Biological Psychiatry, 83(8), 638–647. https://doi.org/10.1016/J.BIOPSYCH.2017.10.030

Hiser, J., & Koenigs, M. (2018b). The Multifaceted Role of the Ventromedial Prefrontal Cortex in Emotion, Decision Making, Social Cognition, and Psychopathology. In Biological Psychiatry (Vol. 83, Issue 8, pp. 638–647). Elsevier USA. https://doi.org/10.1016/j.biopsych.2017.10.030

Hutcherson, C. A., Plassmann, H., Gross, J. J., & Rangel, A. (2012). Cognitive regulation during decision making shifts behavioral control between ventromedial and dorsolateral prefrontal value systems. Journal of Neuroscience, 32(39), 13543–13554. https://doi.org/10.1523/JNEUROSCI.6387-11.2012

Jiao, P. (2020). Payoff-Based Belief Distortion. The Economic Journal, 130(629), 1416–1444. https://doi.org/10.1093/ej/ueaa019

Kachwaha, S., Nguyen, P. H., DeFreese, M., Avula, R., Cyriac, S., Girard, A., & Menon, P. (2020). Assessing the Economic Feasibility of Assuring Nutritionally Adequate Diets for Vulnerable Populations in Uttar Pradesh, India: Findings from a "Cost of the Diet" Analysis. Current Developments in Nutrition, 4(12), 1–9. https://doi.org/10.1093/cdn/nzaa169

Kahneman, D., & Tversky, A. (2018). Prospect theory: An analysis of decision under risk. Experiments in Environmental Economics, 1, 143–172. https://doi.org/10.2307/1914185

Khaleghi, A., Pirzad Jahromi, G., Zarafshan, H., Mostafavi, S. A., & Mohammadi, M. R. (2020). Effects of transcranial direct current stimulation of prefrontal cortex on risk-taking behavior. In Psychiatry and Clinical Neurosciences (Vol. 74, Issue 9, pp. 455–465). Blackwell Publishing. https://doi.org/10.1111/pcn.13025

Knoch, D., Gianotti, L. R. R., Pascual-leone, A., Treyer, V., Regard, M., Hohmann, M., & Brugger, P. (2006). Disruption of Right Prefrontal Cortex by Low-Frequency Repetitive Transcranial Magnetic Stimulation Induces. 26(24), 6469–6472. https://doi.org/10.1523/JNEUROSCI.0804-06.2006

Koenigs, M., Kruepke, M., & Newman, J. P. (2010). Economic decision-making in psychopathy: A comparison with ventromedial prefrontal lesion patients. Neuropsychologia, 48(7), 2198–2204. https://doi.org/10.1016/j.neuropsychologia.2010.04.012

Kohno, M., Ghahremani, D. G., Morales, A. M., Robertson, C. L., Ishibashi, K., Morgan, A. T., Mandelkern, M. A., & London, E. D. (2015). Risk-taking behavior: Dopamine D2/D3 receptors, feedback, and frontolimbic activity. Cerebral Cortex, 25(1), 236–245. https://doi.org/10.1093/cercor/bht218

Kuhnen, C. M., & Knutson, B. (2005). The neural basis of financial risk taking. Neuron, 47(5), 763–770. https://doi.org/10.1016/j.neuron.2005.08.008

Levasseur-Moreau, J., & Fecteau, S. (2012). Translational application of neuromodulation of decision-making. In Brain Stimulation (Vol. 5, Issue 2, pp. 77–83). Elsevier. https://doi.org/10.1016/j.brs.2012.03.009

Lim, S.-L., O'Doherty, J. P., & Rangel, A. (2011). The Decision Value Computations in the vmPFC and Striatum Use a Relative Value Code That is Guided by Visual Attention. Journal of Neuroscience, 31(37), 13214–13223. https://doi.org/10.1523/JNEUROSCI.1246-11.2011

Lowe, C. J., Hall, P. A., & Staines, W. R. (2014). The Effects of Continuous Theta Burst Stimulation

to the Left Dorsolateral Prefrontal Cortex on Executive Function, Food Cravings, and Snack Food Consumption. Psychosomatic Medicine, 76(7), 503–511. https://doi.org/10.1097/PSY.0000000000000090

Luna, R. A., & Foster, J. A. (2015). Gut brain axis: Diet microbiota interactions and implications for modulation of anxiety and depression. Current Opinion in Biotechnology, 32(Figure 1), 35–41. https://doi.org/10.1016/j.copbio.2014.10.007

Massar, S. A. A., Kenemans, J. L., & Schutter, D. J. L. G. (2014). Resting-state EEG theta activity and risk learning: Sensitivity to reward or punishment? International Journal of Psychophysiology, 91(3), 172–177. https://doi.org/10.1016/j.ijpsycho.2013.10.013

Massar, S. A. A., Rossi, V., Schutter, D. J. L. G., & Kenemans, J. L. (2012). Baseline EEG theta/beta ratio and punishment sensitivity as biomarkers for feedback-related negativity (FRN) and risk-taking. Clinical Neurophysiology, 123(10), 1958–1965. https://doi.org/10.1016/j.clinph.2012.03.005

Mayer, E. A. (2011). Gut feelings: the emerging biology of gut–brain communication. Nature Reviews Neuroscience 2011 12:8, 12(8), 453–466. https://doi.org/10.1038/nrn3071

McNeill, A., Monk, R. L., Qureshi, A. W., Makris, S., & Heim, D. (2018). Continuous Theta Burst Transcranial Magnetic Stimulation of the Right Dorsolateral Prefrontal Cortex Impairs Inhibitory Control and Increases Alcohol Consumption. Cognitive, Affective and Behavioral Neuroscience, 18(6), 1198–1206. https://doi.org/10.3758/s13415-018-0631-3

O'Mahony, S. M., Clarke, G., Borre, Y. E., Dinan, T. G., & Cryan, J. F. (2015). Serotonin, tryptophan metabolism and the brain-gut-microbiome axis. Behavioural Brain Research, 277, 32–48. https://doi.org/10.1016/j.bbr.2014.07.027

Papalini, S., Michels, F., Kohn, N., Wegman, J., van Hemert, S., Roelofs, K., Arias-Vasquez, A., & Aarts, E. (2019). Stress matters: Randomized controlled trial on the effect of probiotics on neurocognition. Neurobiology of Stress, 10, 100141. https://doi.org/10.1016/J.YNSTR.2018.100141

Polanía, R., Nitsche, M. A., & Ruff, C. C. (2018). Studying and modifying brain function with non-invasive brain stimulation. In Nature Neuroscience (Vol. 21, Issue 2, pp. 174–187). Nature Publishing Group. https://doi.org/10.1038/s41593-017-0054-4

Pujara, M. S., Wolf, R. C., Baskaya, M. K., & Koenigs, M. (2015). Ventromedial prefrontal cortex damage alters relative risk tolerance for prospective gains and losses. Neuropsychologia, 79, 70–75. https://doi.org/10.1016/J.NEUROPSYCHOLOGIA.2015.10.026

Raichle, M. E. (2015). The Brain's Default Mode Network. Https://Doi.Org/10.1146/Annurev-Neuro-071013-014030, 38, 433–447. https://doi.org/10.1146/ANNUREV-NEURO-071013-014030

Rudorf, S., & Hare, T. A. (2014). Interactions between dorsolateral and ventromedial prefrontal cortex underlie context-dependent stimulus valuation in goal-directed choice. Journal of Neuroscience, 34(48), 15988–15996. https://doi.org/10.1523/JNEUROSCI.3192-14.2014

Ruff, C. C., & Fehr, E. (2014). The neurobiology of rewards and values in social decision making. Nature Reviews Neuroscience 2014 15:8, 15(8), 549–562. https://doi.org/10.1038/nrn3776

Sarkar, A., Lehto, S. M., Harty, S., Dinan, T. G., Cryan, J. F., & Burnet, P. W. J. (2016). Psychobiotics and the Manipulation of Bacteria–Gut–Brain Signals. Trends in Neurosciences, 39(11), 763–781.

https://doi.org/10.1016/j.tins.2016.09.002

Schiller, B., Gianotti, L. R. R., Nash, K., & Knoch, D. (2014). Individual differences in inhibitory control - Relationship between baseline activation in lateral PFC and an electrophysiological index of response inhibition. Cerebral Cortex, 24(9), 2430–2435. https://doi.org/10.1093/cercor/bht095

Schmidt, B., Kanis, H., Holroyd, C. B., Miltner, W. H. R., & Hewig, J. (2018). Anxious gambling: Anxiety is associated with higher frontal midline theta predicting less risky decisions. Psychophysiology, 55(10), e13210. https://doi.org/10.1111/psyp.13210

Schmidt, B., Kessler, L., Holroyd, C. B., & Miltner, W. H. R. (2019). Wearing a bike helmet leads to less cognitive control, revealed by lower frontal midline theta power and risk indifference. Psychophysiology, 56(12). https://doi.org/10.1111/psyp.13458

Schmidt, L., Skvortsova, V., Kullen, C., Weber, B., & Plassmann, H. (2017). How context alters value: The brain's valuation and affective regulation system link price cues to experienced taste pleasantness. Scientific Reports, 7(1), 1–13. https://doi.org/10.1038/s41598-017-08080-0

Schonberg, T., Fox, C. R., & Poldrack, R. A. (2011). Mind the gap : bridging economic and naturalistic risk-taking with cognitive neuroscience. Trends in Cognitive Sciences, 15(1), 11–19. https://doi.org/10.1016/j.tics.2010.10.002

Sela, T., Kilim, A., & Lavidor, M. (2012). Transcranial alternating current stimulation increases risk-taking behavior in the Balloon Analog Risk Task. Frontiers in Neuroscience, 6(FEB), 1–11. https://doi.org/10.3389/fnins.2012.00022

Studer, B., Pedroni, A., & Rieskamp, J. (2013a). Predicting Risk-Taking Behavior from Prefrontal Resting- State Activity and Personality. PLoS ONE, 8(10), 1–8. https://doi.org/10.1371/journal.pone.0076861

Studer, B., Pedroni, A., & Rieskamp, J. (2013b). Predicting Risk-Taking Behavior from Prefrontal Resting-State Activity and Personality. PLoS ONE, 8(10), e76861. https://doi.org/10.1371/journal.pone.0076861

Tengeler, A. C., Dam, S. A., Wiesmann, M., Naaijen, J., Bodegom, M. van, Belzer, C., Dederen, P. J., Verweij, V., Franke, B., Kozicz, T., Vasquez, A. A., & Kiliaan, A. J. (2020). Gut microbiota from persons with attention-deficit/hyperactivity disorder affects the brain in mice. Microbiome 2020 8:1, 8(1), 1–14. https://doi.org/10.1186/S40168-020-00816-X

Thaler, R. H., & Johnson, E. J. (1990). Gambling with the House Money and Trying to Break Even: The Effects of Prior Outcomes on Risky Choice. Management Science, 36(6), 643–660. https://doi.org/10.1287/mnsc.36.6.643

Thut, G., Miniussi, C., & Gross, J. (2012). The Functional Importance of Rhythmic Activity in the Brain. Current Biology, 22(16), R658–R663. https://doi.org/10.1016/J.CUB.2012.06.061

Tillmann, S., & Wegener, G. (2019). Probiotics reduce risk-taking behavior in the Elevated Plus Maze in the Flinders Sensitive Line rat model of depression. Behavioural Brain Research, 359, 755–762. https://doi.org/10.1016/j.bbr.2018.08.025

Vinogradova, O. S. (1995). Expression, control, and probable functional significance of the neuronal theta-rhythm. In Progress in Neurobiology (Vol. 45, Issue 6, pp. 523–583). Pergamon. https://doi.org/10.1016/0301-0082(94)00051-I

Wastyk, H. C., Fragiadakis, G. K., Perelman, D., Dahan, D., Merrill, B. D., Yu, F. B., Topf, M., Gonzalez, C. G., van Treuren, W., Han, S., Robinson, J. L., Elias, J. E., Sonnenburg, E. D., Gardner, C. D., & Sonnenburg, J. L. (2021). Gut-microbiota-targeted diets modulate human immune status. Cell. https://doi.org/10.1016/J.CELL.2021.06.019

Weissman, C. R., Blumberger, D. M., Brown, P. E., Isserles, M., Rajji, T. K., Downar, J., Mulsant, B. H., Fitzgerald, P. B., & Daskalakis, Z. J. (2018). Bilateral Repetitive Transcranial Magnetic Stimulation Decreases Suicidal Ideation in Depression. The Journal of Clinical Psychiatry, 79(3), 5831. https://doi.org/10.4088/JCP.17M11692

Widge, A. S. (2018). Cross-Species Neuromodulation from High-Intensity Transcranial Electrical Stimulation. Trends in Cognitive Sciences, 22(5), 372–374. https://doi.org/10.1016/J.TICS.2018.03.006

Wirt, A., & Collins, C. E. (2009). Diet quality - What is it and does it matter? Public Health Nutrition, 12(12), 2473–2492. https://doi.org/10.1017/S136898000900531X

Wischnewski, M., & Compen, B. (2022). Effects of theta transcranial alternating current stimulation (tACS) on exploration and exploitation during uncertain decision-making. Behavioural Brain Research, 426, 113840. https://doi.org/10.1016/j.bbr.2022.113840

Wölbert, E., & Riedl, A. (2013). Measuring Time and Risk Preferences: Reliability, Stability, Domain Specificity. www.RePEc.org

Womelsdorf, T., Johnston, K., Vinck, M., & Everling, S. (2010). Theta-activity in anterior cingulate cortex predicts task rules and their adjustments following errors. Proceedings of the National Academy of Sciences of the United States of America, 107(11), 5248–5253. https://doi.org/10.1073/pnas.0906194107

Wu, Y., Wang, L., Yu, F., Ji, G. J., Xiao, G., Feifei, X., Chunyan, Z., Xingui, C., & Wang, K. (2021). Intermittent Theta Burst Stimulation (iTBS) as an Optimal Treatment for Schizophrenia Risk Decision: an ERSP Study. Frontiers in Psychiatry, 12, 620. https://doi.org/10.3389/FPSYT.2021.594102/BIBTEX

7

IMPACT

Most of our daily decisions include some degree of risk. There are numerous examples of decisions involving risk, including financial investments, gambling, insurance purchases, or simply choosing a route to work based on potential traffic. Hence, risk-taking behavior is an important topic in the study of human decision-making. Different methodologies are used to explore decision-making and decision-making under risk. Decision neuroscience is a rapidly evolving discipline that studies decision-making through the lens of neuroscience, exploring the brain and the different cognitive processes involved in human decision-making. By understanding the underlying neural processes of decision-making, we advance our understanding of the human brain and how it shapes the decisions we make (Shiv et al., 2005). This thesis contributes to the field of decision neuroscience by providing a comprehensive examination of the neural mechanisms underlying human risk-taking behavior. By leveraging innovative combinations of neuroscientific research techniques with economic models, this thesis sheds light on the intricacies of risk-taking behavior from a neurobiological viewpoint.

The studies described here explored risk-taking using different neuroscientific methodologies, with a special focus on noninvasive brain stimulation (NIBS) techniques. Most studies on decision neuroscience that explore risk-taking behavior rely on neuroimaging methodologies, especially functional magnetic resonance imaging (fMRI). Therefore, the use of NIBS to study risk-taking behavior represents an important contribution to the field of decision neuroscience and to the study of risk-taking behavior in particular. NIBS allows noninvasive manipulation of neural activity in targeted areas. Thus, with the use of these techniques, one can directly evaluate the effects of changes in brain activity in specific areas on risk-taking behavior (Helfrich et al., 2014; Pettorruso et al., 2021; Polanía et al., 2018). This means that it is possible to clarify the functional relationship between specific patterns of neural activity and different aspects of risk-taking behavior. Hence, in general, this thesis contributes to the field of decision neuroscience by providing important insights into the processing of risk-taking behavior derived from experiments using different NIBS techniques.

My thesis begins by exploring the role of the prefrontal cortex and, more specifically, the dorsolateral prefrontal cortex (DLPFC) and the ventromedial prefrontal cortex (VMPFC) in risk-taking behavior. The involvement of these two areas in the processing of risk-taking behavior has been a common finding in several studies in decision neuroscience. Yet, how the prefrontal cortex recruits cognitive control during risky decision-making and the specific role of each of these areas remain unclear. Studies using electroencephalography have shown that theta-band oscillations, which compose a specific pattern of neural activity, correlate to individual differences in risk proneness. This same pattern of neural activity is thought to be used by the prefrontal cortex to recruit cognitive control. Hence, theta-band activity is potentially the electrophysiological mechanism used by

the brain to modulate risk-taking behavior (Cavanagh & Frank, 2014; Vinogradova, 1995; Womelsdorf et al., 2010). Yet, the functional relationship between frontal theta-band activity and the modulation of risk-taking behavior was yet to be established. To investigate this relationship, Chapters 2 and 3 report studies using combinations of transcranial alternating current stimulation (tACS), electroencephalography (EEG), and a computerized task to elicit and measure individual risk-taking behavior (Dantas et al., 2021; Gianotti et al., 2009; Studer et al., 2013). Therefore, these studies represent important steps in establishing the causal relationship between frontal theta-band activity and risk-taking behavior, which was hitherto not clearly established.

The results from Chapter 2 demonstrate the behavioral modulation of risk-taking behavior using left DLPFC (lDLPFC) tACS. This effect of theta-band tACS on risk-taking is frequency specific, meaning that only stimulation in a theta frequency (and not gamma-band tACS or sham stimulation) modulates behavior. These findings are an important step toward a better understanding of how the prefrontal cortex modulates risk-taking behavior, since they confirm for the first time that the modulation of risk-taking behavior can be achieved by stimulating the left prefrontal cortex specifically with theta-band tACS. These results confirm the functional relationship between frontal theta-band activity and risk-taking behavior. By confirming this relationship, Chapter 2 provides important evidence for the use of analysis of resting-state EEG activity in the frontal regions as a potential tool for inferring an individual's risk profile (Dantas et al., 2021; Gianotti et al., 2009; Studer et al., 2013).

As documented in Chapter 3, I tested the effects of theta-band tACS over the right and lDLPFC and the effects of stimulating at high (3 mA) and low (1.5 mA) intensity on risk-taking behavior. I was able to demonstrate that stimulation of each hemisphere leads to opposite behavioral effects; namely, while the lDLPFC theta-band tACS led to a significant increase in risky choices, right DLPFC (rDLPFC) stimulation led to a reduction in risk-taking behavior, which indicates hemispheric specificity. These findings represent an important contribution to the understanding of the electrophysiological mechanism via which the brain modulates risk-taking behavior by (1) confirming the importance of frontal theta-band activity in this mechanism and (2) showing that this same pattern of stimulation has different behavioral effects when applied to the right and left hemispheres, and therefore (3) the two hemispheres have specific roles in the modulation of risk-taking behavior. Although this difference in theta-band laterality has been shown in previous EEG studies, it had not yet been demonstrated with NIBS (Gianotti et al., 2009; Sela et al., 2012; Studer et al., 2013).

Chapter 3 also shows that the intensity at which tACS is applied plays a key role in the observed behavioral and EEG effects. Several recent studies on neurostimulation question the validity of studies using low-intensity transcranial electric stimulation, affirming that

only high-intensity stimulation would efficiently reach the cortex and generate actual results (Alekseichuk et al., 2022; Widge, 2018). Therefore, by implementing a novel approach compared to other studies in decision neuroscience, I used high-intensity (3 mA) theta-band tACS as part of this experimental design. Comparing the behavioral responses obtained with low-intensity (1.5 mA) and high-intensity (3 mA) tACS, more consistent responses were obtained after high-intensity stimulation. While significant behavioral effects were observed during the stimulation of the right and lDLPFC at high-intensity, 1.5 mA only yielded significant behavioral results over when applied to the left hemisphere.

Chapter 3 also demonstrates the importance of frontal baseline theta-power in determining the direction of behavioral effects obtained during theta-band tACS. Frontal resting-state theta-power indicates the level of theta-band activity in the prefrontal cortex before task or stimulation. According to the findings presented in Chapter 3, this intrinsic level of theta-power influences the effects of stimulation and can significantly affect participants' risk-taking behavior. The results in Chapter 3 indicate that the complex electrophysiological mechanism underlying the modulation of risk-taking behavior is state-dependent, meaning that the increase of theta-power in frontal areas with the use of tACS will have different effects depending on the participant's levels of resting-state frontal theta-power. These findings represent an important contribution to the development of potential clinical interventions targeting the neural underpinnings of risky behaviors using tACS. For instance, theta-band stimulation could be used to counteract increases in risk-taking behavior caused by the use of L-dopa or to help patients with attention deficit and hyperactivity disorder (ADHD). The results in Chapter 3 indicate that the use of this type of intervention should be based on individual levels of resting-state frontal theta-band activity. Nevertheless, the clinical application of this methodology should be explored in further studies.

I continue the study of the role of prefrontal areas in risk-taking behavior in Chapter 4, which details the use of transcranial magnetic stimulation (TMS) with a generally inhibitory continuous theta-band stimulation (cTBS) protocol to stimulate the rDLPFC and VMPFC (Dantas et al., 2023). By stimulating the VMPFC with an inhibitory protocol, I was able to test the functional relationship between the VMPFC and risk-taking behavior, which has long been assumed to be exclusively related to valuation processing, based uniquely on neuroimaging studies (Lim et al., 2011). The first important contribution of Chapter 4 is that its findings reinforce the idea of a strong functional interplay between the rDLPFC and the VMPFC during valuation in risk-taking behavior (Hare et al., 2011; Schiller et al., 2014). Thus, these results contradict the assumption that the rDLPFC is responsible only for executive control during risk-taking behavior and that the VMPFC is responsible exclusively for valuation. Instead, the evidence presented in Chapter 4 indicates that the rDLPFC and the VMPFC operate as an integrated network, processing

both the valuation during risk-taking behavior and the modulation of this same behavior (Dantas et al., 2023; Hare et al., 2009). These findings can certainly help to clarify neuroimaging findings related to valuation and risk-taking behavior. Furthermore, the results of Chapter 4 can potentially contribute to the development of more accurate economic models for predicting individual risk-taking behavior.

The second important contribution comes from the novel use of a double cone coil aiming to target the VMPFC with TMS (Cho et al., 2010; Roth et al., 2002). To our knowledge, no previous studies have used a double-cone TMS coil to explore its effects on risk-taking behavior. Although we have not recorded any brain data to validate the successful stimulation of the VMPFC, the here-demonstrated feasibility and tolerability of placing the double-cone TMS coil on a scalp area assumed to correspond to the VMPFC represents an important advance in the field of decision neuroscience, considering the importance of this area in human decision-making. In a next step, it would be paramount to evaluate whether the use of this coil targeting the here-described scalp position indeed successfully stimulates the VMPFC directly. If so, future studies could be designed to directly test the functional role of the VMPFC in, for example, memory consolidation, emotional regulation, fear extinction, and even morality. Moreover, successfully targeting the VMPFC directly would also have significant clinical implications, as this region is also involved in a number of psychiatric disorders, such as obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD), depression, and psychopathy (Battaglia et al., 2021; Blair, 2007; Hiser & Koenigs, 2018; Milad et al., 2005; Motzkin et al., 2015; Nieuwenhuis & Takashima, 2011; Zald et al., 2002).

Finally, in Chapter 4, I successfully replicated the work of Knoch and colleagues (2006) when showing that risk-taking behavior increased after rDLPFC stimulation (Knoch et al., 2006). The field of decision neuroscience and decision sciences in general suffer from a replication crisis. There are not enough replication studies published due to a general bias in academia favoring new results. As such, there is a lack of consistency across studies, and important assumptions are derived from studies that were never replicated, which might be misleading (Koch & Jones, 2016; Shrout & Rodgers, 2018). Thus, by successfully replicating Knoch and colleagues' (2006) study, Chapter 4 brings an important and needed confirmation of the role of the rDLPFC in risk-taking behavior to the field of decision neuroscience.

The next part of this dissertation expands the study of risk-taking behavior by exploring the potential influence of the gut-brain axis (GBA). To that end, Chapter 5 covers pioneering research on the connection between gut microbiota, risk, and intertemporal decisions in healthy humans. This study advances the scientific boundaries of neuroscience research on gut microbiota and decision-making, which to date largely focuses on animal models

or patients (Anderson et al., 2019; Dinan et al., 2013). The results in Chapter 5 show that participants in the placebo group increased their risk-taking behavior over time due to biases associated with payoff-based belief distortion and/or the house money effect, confirming biases widely reported in the economic literature (Dantas et al., 2022; Jiao, 2020; Thaler & Johnson, 1990). On the other hand, participants who received probiotics had stable risk-taking behavior, stable choices of values, and a higher preference for options with higher probabilities. These results confirm the involvement of the GBA in the processing of risk-taking behavior. Furthermore, these findings point to a positive influence of probiotics manipulation toward neutralizing choice distortions, indicating the potential of using probiotics or other manipulations focusing on the GBA to improve decision-making under risk. Nevertheless, further studies in this direction are needed.

The next important contribution of Chapter 5 comes from the analysis of participants' intertemporal choices. Numerous daily choices include time as a factor, such as financial investments, caloric intake, or exercising regularly. These choices are commonly affected by present bias, where immediate reward is chosen (present bias) and future outcomes are minimized (time discounting). In Chapter 5, I used the model proposed by Andreoni and Sprenger (2012) to estimate participants' present bias, time discounting, and risk preferences after either prolonged intake of probiotics or placebo. Participants that received probiotics showed significant increases in future bias and reductions in time discounting compared to those who received placebo. Overall, these results indicate that participants receiving probiotics were more patient and willing to invest in future options, which would objectively bring them a higher payoff. These novel findings confirm the influence of the GBA on human intertemporal choices.

Furthermore, high present bias can lead to negative future outcomes, including low pension investments leading to significant reductions in future financial well-being or high caloric intake and reduced exercising leading to a future decline in health (Brüggen et al., 2017; Hardisty et al., 2013; Liu et al., 2021; Rabin, n.d.). Hence, our findings indicate that (1) the composition of our gut microbiota might be a factor influencing our intertemporal choices, leading to the choice of more immediate gratification, and (2) interventions targeting the GBA might have positive effects on our choices by reducing our present bias. Again, further studies in this direction are necessary.

Besides its innovative character, Chapter 5 generates novel insights for research fields that study risk and intertemporal decisions, such as finance or economics. Chapter 5 has an important scientific impact, since it represents a first step to empirically validate the role of the GBA in risk-taking behavior and intertemporal choices (Dantas et al., 2022). These findings also bring potential societal impacts arising from, for example, recommendations for dietary choices that improve gut microbiota and consequently

improve economic decision-making. More importantly, by establishing this connection, it is possible to inform and educate the general public about how their dietary and lifestyle choices also impact their economic choices. These insights may allow the public to make simple changes in their diet that might have valuable long-term effects, such as improvements in financial wellbeing. Certainly, Chapter 5 is only a first step in this direction, but it is a fundamental one.

Finally, overall, the findings of this dissertation have potential applications in various domains. For example, our findings indicating that differences in risk-taking behavior are due to innate differences in frontal resting-state theta power (Chapters 2 and 3) open the door to the investigation of population-wise risk profiles using neuroforecasting. These different risk profiles can inform the development of investment strategies and economic models that take into account individual differences in risk-taking behavior. In the domain of psychology, our findings may inform the development of new interventions for individuals with problematic risk-taking behavior, such as individuals with addiction or impulsive behavior disorders. These interventions could take the form of, for example, individualized tACS interventions based on individual frontal theta-band activity (Chapters 2 and 3) or TMS interventions using cTBS (Chapter 4).

Additionally, our findings may inform the development of more precise and realistic models in neuroeconomics and behavioral economics. For example, based on our findings in Chapter 4 regarding the functional relationship between VMPFC activity and risk-taking behavior, neuroimaging studies can interpret VMPFC activation more accurately. Furthermore, the evidence of strong intercommunication between the VMPFC and rDLPFC during valuation processing and the modulation of risk-taking presented in Chapter 4 help in the development of more accurate models to understand and hence predict individual risk-taking behavior.

In general, this dissertation contributes to a deeper understanding of the underlying neural processing of human risk-taking behavior. To properly comprehend individual risk-taking behavior, one should account for the individual variability in risk proneness due to different levels of frontal theta-band activity, as presented in Chapters 2 and 3, the complex interplay between the rDLPFC and VMPFC, demonstrated in Chapter 4, and the influence of the gut microbiota (and all factors that might affect its balance), as shown in Chapter 5. In conclusion, the findings of this dissertation provide novel insights into the neural mechanisms underlying risk-taking behavior both within and beyond the central nervous system's limits, including the GBA as a potential key actor. These insights have a significant scientific impact and have the potential to inform various domains, including finance, clinical psychology, and behavioral economics, and to lead to new developments in these areas.

7.1 REFERENCES

Alekseichuk, I., Wischnewski, M., & Opitz, A. (2022). A minimum effective dose for (transcranial) alternating current stimulation. Brain Stimulation, 15(5), 1221–1222. https://doi.org/10.1016/J.BRS.2022.08.018

Anderson, C., Cryan, J., & Dinan, T. (2019). The Psychobiotic Revolution: Mood, Food, and the New Science of the Gut-Brain Connection. National Geographic.

Battaglia, S., Harrison, B. J., & Fullana, M. A. (2021). Does the human ventromedial prefrontal cortex support fear learning, fear extinction or both? A commentary on subregional contributions. Molecular Psychiatry 2021 27:2, 27(2), 784–786. https://doi.org/10.1038/s41380-021-01326-4

Blair, R. J. R. (2007). The amygdala and ventromedial prefrontal cortex in morality and psychopathy. Trends in Cognitive Sciences, 11(9), 387–392. https://doi.org/10.1016/J.TICS.2007.07.003

Brüggen, E. C., Hogreve, J., Holmlund, M., Kabadayi, S., & Löfgren, M. (2017). Financial well-being: A conceptualization and research agenda. Journal of Business Research, 79, 228–237. https://doi.org/10.1016/J.JBUSRES.2017.03.013

Cavanagh, J. F., & Frank, M. J. (2014). Frontal theta as a mechanism for cognitive control. Trends in Cognitive Sciences, 18(8), 414–421. https://doi.org/10.1016/j.tics.2014.04.012

Cho, S. S., Ko, J. H., Pellecchia, G., Van Eimeren, T., Cilia, R., & Strafella, A. P. (2010). Continuous theta burst stimulation of right dorsolateral prefrontal cortex induces changes in impulsivity level. Brain Stimulation, 3(3), 170–176. https://doi.org/10.1016/j.brs.2009.10.002

Dantas, A. M., Sack, A. T., Bruggen, E., Jiao, P., & Schuhmann, T. (2021). Reduced risk-taking behavior during frontal oscillatory theta-band neurostimulation. Brain Research, 1759, 147365. https://doi.org/10.1016/j.brainres.2021.147365

Dantas, A. M., Sack, A. T., Bruggen, E., Jiao, P., & Schuhmann, T. (2022). The effects of probiotics on risk and time preferences. Scientific Reports, 12(1), 1–10. https://doi.org/10.1038/s41598-022-16251-x

Dantas, A. M., Sack, A. T., Bruggen, E., Jiao, P., & Schuhmann, T. (2023). The functional relevance of right DLPFC and VMPFC in risk-taking behavior. Cortex, 159, 64–74. https://doi.org/10.1016/j.cortex.2022.11.009

Dinan, T. G., Stanton, C., & Cryan, J. F. (2013). Psychobiotics: A novel class of psychotropic. Biological Psychiatry, 74(10), 720–726. https://doi.org/10.1016/j.biopsych.2013.05.001

Gianotti, L. R. R., Knoch, D., Faber, P. L., Lehmann, D., Pascual-Marqui, R. D., Diezi, C., Schoch, C., Eisenegger, C., & Fehr, E. (2009). Tonic activity level in the right prefrontal cortex predicts individuals' risk taking. Psychological Science, 20(1), 33–38. https://doi.org/10.1111/j.1467-9280.2008.02260.x

Hardisty, D. J., Appelt, K. C., & Weber, E. U. (2013). Good or Bad, We Want it Now: Fixed-cost Present Bias for Gains and Losses Explains Magnitude Asymmetries in Intertemporal Choice. Journal of Behavioral Decision Making, 26(4), 348–361. https://doi.org/10.1002/bdm.1771

Hare, T. A., Camerer, C. F., & Rangel, A. (2009). Self-control in decision-Making involves modulation of the vmPFC valuation system. Science, 324(5927), 646–648. https://doi.org/10.1126/science.1168450

Hare, T. A., Malmaud, J., & Rangel, A. (2011). Focusing attention on the health aspects of foods changes value signals in vmPFC and improves dietary choice. The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 31(30), 11077–11087. https://doi.org/10.1523/JNEUROSCI.6383-10.2011

Helfrich, R. F., Schneider, T. R., Rach, S., Trautmann-Lengsfeld, S. A., Engel, A. K., & Herrmann, C. S. (2014). Entrainment of Brain Oscillations by Transcranial Alternating Current Stimulation. Current Biology, 24(3),

333–339.

Hiser, J., & Koenigs, M. (2018). The Multifaceted Role of the Ventromedial Prefrontal Cortex in Emotion, Decision Making, Social Cognition, and Psychopathology. Biological Psychiatry, 83(8), 638–647. https://doi.org/10.1016/J.BIOPSYCH.2017.10.030

Jiao, P. (2020). Payoff-Based Belief Distortion. The Economic Journal, 130(629), 1416–1444. https://doi.org/10.1093/ej/ueaa019

Knoch, D., Gianotti, L. R. R., Pascual-leone, A., Treyer, V., Regard, M., Hohmann, M., & Brugger, P. (2006). Disruption of Right Prefrontal Cortex by Low-Frequency Repetitive Transcranial Magnetic Stimulation Induces. 26(24), 6469–6472. https://doi.org/10.1523/JNEUROSCI.0804-06.2006

Koch, C., & Jones, A. (2016). Big Science, Team Science, and Open Science for Neuroscience. Neuron, 92(3), 612–616. https://doi.org/10.1016/J.NEURON.2016.10.019

Lim, S.-L., O'Doherty, J. P., & Rangel, A. (2011). The Decision Value Computations in the vmPFC and Striatum Use a Relative Value Code That is Guided by Visual Attention. Journal of Neuroscience, 31(37), 13214–13223. https://doi.org/10.1523/JNEUROSCI.1246-11.2011

Liu, H.-Z., Lyu, X.-K., Wei, Z.-H., Mo, W.-L., Luo, J.-R., Su, X.-Y., & Hong-Zhi Liu, C. (2021). Exploiting the dynamics of eye gaze to bias intertemporal choice. Journal of Behavioral Decision Making, 34(3), 419–431. https://doi.org/10.1002/BDM.2219

Milad, M. R., Quinn, B. T., Pitman, R. K., Orr, S. P., Fischl, B., & Rauch, S. L. (2005). Thickness of ventromedial prefrontal cortex in humans is correlated with extinction memory. Proceedings of the National Academy of Sciences, 102(30), 10706–10711. https://doi.org/10.1073/PNAS.0502441102

Motzkin, J. C., Philippi, C. L., Wolf, R. C., Baskaya, M. K., & Koenigs, M. (2015). Ventromedial Prefrontal Cortex Is Critical for the Regulation of Amygdala Activity in Humans. Biological Psychiatry, 77(3), 276–284. https://doi.org/10.1016/J.BIOPSYCH.2014.02.014

Nieuwenhuis, I. L. C., & Takashima, A. (2011). The role of the ventromedial prefrontal cortex in memory consolidation. Behavioural Brain Research, 218(2), 325–334. https://doi.org/10.1016/J.BBR.2010.12.009

Pettorruso, M., Miuli, A., di Natale, C., Montemitro, C., Zoratto, F., de Risio, L., d'Andrea, G., Dannon, P. N., Martinotti, G., & di Giannantonio, M. (2021). Non-invasive brain stimulation targets and approaches to modulate gambling-related decisions: A systematic review. Addictive Behaviors, 112. https://doi.org/10.1016/J.ADDBEH.2020.106657

Polanía, R., Nitsche, M. A., & Ruff, C. C. (2018). Studying and modifying brain function with non-invasive brain stimulation. In Nature Neuroscience (Vol. 21, Issue 2, pp. 174–187). Nature Publishing Group. https://doi.org/10.1038/s41593-017-0054-4

Rabin, M. (n.d.). Present Bias: Lessons Learned and To Be Learned. https://doi.org/10.1257/aer.p20151085

Roth, Y., Zangen, A., & Hallett, M. (2002). A coil design for transcranial magnetic stimulation of deep brain regions. Journal of Clinical Neurophysiology, 19(4), 361–370. https://doi.org/10.1097/00004691-200208000-00008

Schiller, B., Gianotti, L. R. R., Nash, K., & Knoch, D. (2014). Individual differences in inhibitory control - Relationship between baseline activation in lateral PFC and an electrophysiological index of response inhibition. Cerebral Cortex, 24(9), 2430–2435. https://doi.org/10.1093/cercor/bht095

Sela, T., Kilim, A., & Lavidor, M. (2012). Transcranial alternating current stimulation increases risk-taking behavior in the Balloon Analog Risk Task. Frontiers in Neuroscience, 6(FEB), 1–11. https://doi.org/10.3389/

fnins.2012.00022

Shiv, B., Bechara, A., Levin, I., Alba, J. W., Bettman, J. R., Dube, L., Isen, A., Mellers, B., Smidts, A., Grant, S. J., & Mcgraw, A. P. (2005). Decision neuroscience. Marketing Letters, 16(3–4), 375–386. https://doi.org/10.1007/s11002-005-5899-8

Shrout, P. E., & Rodgers, J. L. (2018). Psychology, Science, and Knowledge Construction: Broadening Perspectives from the Replication Crisis. Https://Doi.Org/10.1146/Annurev-Psych-122216-011845, 69, 487–510. https://doi.org/10.1146/ANNUREV-PSYCH-122216-011845

Studer, B., Pedroni, A., & Rieskamp, J. (2013). Predicting Risk-Taking Behavior from Prefrontal Resting- State Activity and Personality. PLoS ONE, 8(10), 1–8. https://doi.org/10.1371/journal.pone.0076861

Thaler, R. H., & Johnson, E. J. (1990). Gambling with the House Money and Trying to Break Even: The Effects of Prior Outcomes on Risky Choice. Management Science, 36(6), 643–660. https://doi.org/10.1287/mnsc.36.6.643

Vinogradova, O. S. (1995). Expression, control, and probable functional significance of the neuronal theta-rhythm. In Progress in Neurobiology (Vol. 45, Issue 6, pp. 523–583). Pergamon. https://doi.org/10.1016/0301-0082(94)00051-I

Widge, A. S. (2018). Cross-Species Neuromodulation from High-Intensity Transcranial Electrical Stimulation. Trends in Cognitive Sciences, 22(5), 372–374. https://doi.org/10.1016/J.TICS.2018.03.006

Womelsdorf, T., Johnston, K., Vinck, M., & Everling, S. (2010). Theta-activity in anterior cingulate cortex predicts task rules and their adjustments following errors. Proceedings of the National Academy of Sciences of the United States of America, 107(11), 5248–5253. https://doi.org/10.1073/pnas.0906194107

Zald, D. H., Mattson, D. L., & Pardo, J. V. (2002). Brain activity in ventromedial prefrontal cortex correlates with individual differences in negative affect. Proceedings of the National Academy of Sciences, 99(4), 2450–2454. https://doi.org/10.1073/PNAS.042457199

8

GENERAL SUMMARY

The majority of our daily choices include some degree of risk, including complex choices such as financial investments, and everyday choices such as deciding a route to work based on the information from a traffic app. Due to its prevalence and importance, various theories and models from different fields have explored risk-taking behavior. Nevertheless, our scientific understanding of the complex underlying neural processing of risk-taking behavior remains limited. This dissertation comprises a series of studies that investigate risk-taking behavior through the lens of decision neuroscience, investigating its neural processing from the brain to the gut.

In the first part of the thesis (Chapters 2 and 3), I used transcranial alternating current stimulation (tACS) and electroencephalography (EEG) to investigate the role of frontal theta-band activity in the modulation of risk-taking behavior. The results obtained demonstrate that it is possible to modulate risk-taking behavior with theta-band tACS, confirming a functional relationship between frontal theta-band activity and risk-taking behavior.

In Chapter 2, I used tACS in different frequencies to test the functional relationship between frontal theta-band activity and risk-taking behavior. To that end, I used theta-band (6.5 Hz), gamma-band (40 Hz), and sham tACS over left dorsolateral prefrontal cortex (DLPFC) during an experimental task, named Maastricht Gambling Task (MGT), to elicit and evaluate participants' risk-taking behavior. This study's results show that theta-band tACS, but not gamma band or sham stimulation, significantly modulates risk-taking behavior. Theta-band tACS over the left DLPFC, in the conditions of this study, led to a reduction in participants' risk-taking. The findings of Chapter 2 support the notion of a functional role of frontal theta-band activity in the modulation of risk-taking behavior and show that this effect is frequency exclusive.

Chapter 3 deepens the exploration of this electrophysiological mechanism by assessing the effects of theta-band stimulation on both the left and right DLPFC. The results showed that the stimulation of the different sides led to behavioral responses in opposite directions, with a significant reduction in risk-taking behavior during right DLPFC tACS and an increase after left theta-band tACS. Additionally, the results in Chapter 3 show that high-intensity (3 mA) theta-band tACS leads to significant behavioral results more consistently, while low-intensity (1.5 mA) tACS elicited significant behavioral changes only when applied to the left hemisphere. Furthermore, the levels of baseline frontal theta-power significantly affect participants' behavior and interact with the different tACS protocols. This means that this complex electrophysiological mechanism underlying the modulation of risk-taking behavior seems to be state-dependent. Therefore, considering the resting-state frontal theta power is important in determining the direction of the behavioral effects obtained during theta-band tACS.

Following up on the study of the underlying neural processing of risk-taking behavior, Chapter 4 explores the specific roles of the right DLPFC (rDLPFC) and the ventromedial prefrontal cortex (VMPFC) in this type of behavior. These two areas are important in the processing of decision-making under risk. Yet, although the role of the rDLPFC in cognitive control during risk-taking behavior has been demonstrated with the use transcranial magnetic stimulation (TMS) (Knoch et al., 2006), the role of the VMPFC has been correlated to valuation processing based mainly on neuroimaging evidence. The VMPFC is an area rarely targeted in TMS studies due to its anatomical position, being a deeper area and therefore harder to reach with noninvasive methods of brain stimulation. In Chapter 4 I employ a double cone coil aiming at stimulating deeper cortical areas and potentially reach the VMPFC to probe its role in risk-taking behavior. By using TMS with a continuous theta-band stimulation (cTBS) to suppress activity in each of these regions, I was able to experimentally increase risk-taking behavior and participants' average choices of values.

Its results show that stimulation of both the rDLPFC and the VMPFC with an inhibitory protocol increased risk-taking behavior. Both protocols also led to a significant increase in participants' average choices of value. These findings demonstrate that both areas are involved in valuation processing and the modulation of risk-taking behavior, reinforcing evidence of a strong functional interplay between the rDLPFC and VMPFC (Hare et al., 2009; Schiller et al., 2014). Furthermore, these results exclude the hypothesis that the VMPFC's activity alone could be taken as a measure of subjective valuation.

Finally, the neural basis of risk-taking behavior was explored by looking beyond the central nervous system in the last study (Chapter 5). The gut microbiota can influence the interaction between the central and enteric nervous systems via the gut-brain axis (GBA) and can affect brain regions linked to basic emotional and cognitive processes. However, the role of the gut microbiota in decision-making in healthy humans thus far remains largely unknown. Hence, in Chapter 5, I explored the influence of the GBA in human decision-making. This study used a double-blinded placebo-controlled design in combination with two economic decision-making tasks to evaluate both participants' risk-taking behavior and intertemporal choices, the MGT and the Maastricht Choice Task (MCT), respectively. Participants' behavioral responses were estimated both before and after a 30 days probiotics/placebo protocol. The study controlled for potential dietary, mood, and self-control changes.

Participants who received probiotics showed a relative reduction in risk-taking behavior compared with the placebo group. In particular, the placebo group had a significant increase in risk-taking behavior in session 2 compared with session 1, potentially due to the house money effect or payoff-based belief distortion (Jiao, 2020; Thaler & Johnson,

1990) whereas the probiotics group had no such significant increase. Participants who received probiotics presented stable risk-taking behavior over time, with a stable choice of values, and were likelier to choose options with higher probabilities. The probiotics group was also likelier to opt for delayed gratification in the intertemporal choices task, with reduced discount rates and lower risk proneness.

In conclusion, the findings of this dissertation provide novel insights into the neural mechanisms underlying risk-taking behavior, both within the central nervous system, but also looking beyond its limits and including the gut-brain axis as a potential key actor. With this series of studies, I was able to deepen the knowledge of the electrophysiological mechanisms occurring in the prefrontal cortex during risk-taking. Moreover, the findings demonstrated the relevance of the GBA in human decision-making under risk, expanding the scope of the underlying neural pathways involved in human risk-taking behavior.

8.1 REFERENCES

Hare, T. A., Camerer, C. F., & Rangel, A. (2009). Self-control in decision-Making involves modulation of the vmPFC valuation system. Science, 324(5927), 646–648. https://doi.org/10.1126/science.1168450

Jiao, P. (2020). Payoff-Based Belief Distortion. The Economic Journal, 130(629), 1416–1444. https://doi.org/10.1093/ej/ueaa019

Knoch, D., Gianotti, L. R. R., Pascual-leone, A., Treyer, V., Regard, M., Hohmann, M., & Brugger, P. (2006). Disruption of Right Prefrontal Cortex by Low-Frequency Repetitive Transcranial Magnetic Stimulation Induces. 26(24), 6469–6472. https://doi.org/10.1523/JNEUROSCI.0804-06.2006

Schiller, B., Gianotti, L. R. R., Nash, K., & Knoch, D. (2014). Individual differences in inhibitory control - Relationship between baseline activation in lateral PFC and an electrophysiological index of response inhibition. Cerebral Cortex, 24(9), 2430–2435. https://doi.org/10.1093/cercor/bht095

Thaler, R. H., & Johnson, E. J. (1990). Gambling with the House Money and Trying to Break Even: The Effects of Prior Outcomes on Risky Choice. Management Science, 36(6), 643–660. https://doi.org/10.1287/mnsc.36.6.643

9

ALGEMENE SAMENVATTING

De meeste van onze dagelijkse keuzes omvatten een zekere mate van risico, inclusief complexe keuzes zoals financiële investeringen, en dagelijkse keuzes zoals het bepalen van een route naar het werk op basis van de informatie van een verkeersapp. Vanwege de prevalentie en het belang van risicogedrag, hebben verschillende theorieën en modellen uit verschillende vakgebieden het nemen van risico's onderzocht. Niettemin blijft ons wetenschappelijk begrip van de complexe onderliggende neurale verwerking van risicogedrag beperkt. Dit proefschrift bestaat uit een reeks studies die risicogedrag onderzoeken door de lens van beslissingsneurowetenschappen, waarbij de neurale verwerking van de hersenen naar de darm wordt onderzocht.

In het eerste deel van het proefschrift (hoofdstukken 2 en 3) gebruikte ik transcraniële wisselstroomstimulatie (tACS) en elektro-encefalografie (EEG) om de rol van frontale theta-bandactiviteit in de modulatie van risicogedrag te onderzoeken. De verkregen resultaten tonen aan dat het mogelijk is om risicogedrag te moduleren met theta-band tACS, wat een functionele relatie bevestigt tussen frontale theta-bandactiviteit en risicogedrag.

In hoofdstuk 2 gebruikten ik tACS in verschillende frequenties om de functionele relatie tussen frontale theta-bandactiviteit en risicogedrag te testen. Daartoe gebruikten ik theta-band (6,5 Hz), gammaband (40 Hz) en 'sham' (controle) tACS over de linker dorsolaterale prefrontale cortex (DLPFC) tijdens een experimentele taak, genaamd de Maastricht Gambling Task (MGT), om het risicogedrag van deelnemers uit te lokken en te meten. De resultaten van deze studie tonen aan dat theta-band tACS, maar niet gammaband- of schijnstimulatie, het risicogedrag aanzienlijk moduleert. Theta-band tACS over de linker DLPFC, in de omstandigheden van deze studie, leidde tot een vermindering van het nemen van risico's door deelnemers. De bevindingen van hoofdstuk 2 ondersteunen het idee van een functionele rol van frontale theta-band activiteit in de modulatie van risicogedrag en tonen aan dat dit effect afhangt van de frequentie.

Hoofdstuk 3 gaat dieper in op dit elektrofysiologische mechanisme door de effecten van theta-band stimulatie op zowel de linker als de rechter DLPFC te beoordelen. De resultaten toonden aan dat de stimulatie van de verschillende kanten leidde tot gedragsreacties in tegengestelde richtingen, met een significante vermindering van risicogedrag tijdens rechter DLPFC tACS en een toename na linker theta-band tACS. Bovendien laten de resultaten in hoofdstuk 3 zien dat hoge intensiteit (3 mA) theta-band tACS consistenter tot significante gedragsresultaten leidt, terwijl tACS met lage intensiteit (1,5 mA) alleen significante gedragsveranderingen teweegbracht wanneer het op de linkerhersenhelft werd toegepast. Bovendien hebben de niveaus van baseline frontale theta-kracht een aanzienlijke invloed op het gedrag van de deelnemers en interageren ze met de verschillende tACS-protocollen. Dit betekent dat dit complexe elektrofysiologische

mechanisme dat ten grondslag ligt aan de modulatie van risicogedrag afhankelijk lijkt te zijn van de hersenstaat. Daarom is het overwegen van de rusttoestand frontale theta-kracht belangrijk bij het bepalen van de richting van de gedragseffecten die worden verkregen tijdens theta-band tACS.

In navolging van de studie van de onderliggende neurale verwerking van het nemen van risico's, onderzoekt hoofdstuk 4 de specifieke rollen van de recht DLPFC (rDLPFC) en de ventromediale prefrontale cortex (VMPFC) in dit type gedrag. Deze twee gebieden zijn belangrijk bij de verwerking van besluitvorming onder risico. Maar terwijl de rol van de rDLPFC in cognitieve controle tijdens het nemen van risico's is aangetoond met het gebruik van transcraniële magnetische stimulatie (TMS) (Knoch et al., 2006), is de rol van de VMPFC gecorreleerd aan het waarderingsproces, voornamelijk gebaseerd op neuroimaging-bewijs. De VMPFC is een gebied dat zelden beïnvloed wordt in TMS-studies vanwege de anatomische positie, omdat het een dieper gebied is en daarom moeilijker te bereiken is met niet-invasieve methoden van hersenstimulatie. In Hoofdstuk 4 gebruik ik een dubbele kegelspoel die gericht is op het stimuleren van diepere corticale gebieden en mogelijk de VMPFC kan bereiken, om de rol van VMPFC in het nemen van risico's te onderzoeken. Door TMS te gebruiken met een continue theta-band stimulatie (cTBS) om activiteit in elk van deze regio's te onderdrukken, was ik in staat om experimenteel het risicogedrag en de gemiddelde waardenkeuzes van deelnemers te verhogen.

De resultaten tonen aan dat stimulatie van zowel de rDLPFC als de VMPFC met een remmend protocol het risicogedrag verhoogde. Beide protocollen leidden ook tot een aanzienlijke toename van de gemiddelde waardekeuzes van deelnemers. Deze bevindingen tonen aan dat beide gebieden betrokken zijn bij waarderingsverwerking en de modulatie van risicogedrag, wat het bewijs van een sterk functioneel samenspel tussen de rDLPFC en VMPFC versterkt (Hare et al., 2009; Schiller et al., 2014). Bovendien sluiten deze resultaten de hypothese uit dat alleen de activiteit van de VMPFC als een maat voor subjectieve waardering zou kunnen worden genomen.

Ten slotte werd de neurale basis van risicogedrag onderzocht door verder te kijken dan het centrale zenuwstelsel in de laatste studie (hoofdstuk 5). De darmmicrobiota kan de interactie tussen het centrale en enterische zenuwstelsel beïnvloeden via de darm-hersenas (GBA) en kan hersengebieden beïnvloeden die verband houden met elementaire emotionele en cognitieve processen. De rol van de darmmicrobiota in de besluitvorming bij gezonde mensen blijft tot nu toe echter grotendeels onbekend. Daarom heb ik in hoofdstuk 5 de invloed van de GBA op de menselijke besluitvorming onderzocht. Deze studie gebruikte een dubbelblind placebo-gecontroleerd ontwerp in combinatie met twee economische besluitvormingstaken, namelijk de MGT en de Maastricht Choice Task (MCT), om het risicogedrag en de intertemporele keuzes van

beide deelnemers te evalueren. De gedragsreacties van de deelnemers werden zowel voor als na een 30 dagen probiotica / placebo-protocol geschat. De studie controleerde op potentiële veranderingen in voeding, stemming en zelfbeheersing.

Deelnemers die probiotica kregen, vertoonden een relatieve vermindering van het risicogedrag in vergelijking met de placebogroep. In het bijzonder had de placebogroep een significante toename van risicogedrag in sessie 2 in vergelijking met sessie 1, mogelijk als gevolg van het huisgeldeffect of op "payoff-based belief distortion" (Jiao, 2020; Thaler & Johnson, 1990), terwijl de probioticagroep niet zo'n significante toename had. Deelnemers die probiotica kregen, vertoonden in de loop van de tijd stabiel risicogedrag, met een stabiele keuze van waarden, en kozen vaker opties met hogere waarschijnlijkheden. De probioticagroep koos ook vaker voor vertraagde bevrediging in de intertemporele keuzetaak, met lagere discontovoeten en lagere risicogevoeligheid.

De bevindingen van dit proefschrift bieden nieuwe inzichten in de neurale mechanismen die ten grondslag liggen aan het nemen van risicogedrag, zowel binnen het centrale zenuwstelsel als buiten deze grenzen, en nemen de darm-hersenas als een potentiële hoofdrolspeler op. Met deze reeks studies kon ik de kennis van de elektrofysiologische mechanismen die optreden in de prefrontale cortex tijdens het nemen van risico's verder verdiepen. Bovendien toonden de bevindingen de relevantie van de GBA aan voor de menselijke besluitvorming onder risico, waardoor de reikwijdte van de onderliggende neurale paden die betrokken zijn bij menselijk risicogedrag werd uitgebreid.

9.1 VERWIJZINGEN

Hare, T. A., Camerer, C. F., & Rangel, A. (2009). Self-control in decision-Making involves modulation of the vmPFC valuation system. Science, 324(5927), 646–648. https://doi.org/10.1126/science.1168450

Jiao, P. (2020). Payoff-Based Belief Distortion. The Economic Journal, 130(629), 1416–1444. https://doi.org/10.1093/ej/ueaa019

Knoch, D., Gianotti, L. R. R., Pascual-leone, A., Treyer, V., Regard, M., Hohmann, M., & Brugger, P. (2006). Disruption of Right Prefrontal Cortex by Low-Frequency Repetitive Transcranial Magnetic Stimulation Induces. 26(24), 6469–6472. https://doi.org/10.1523/JNEUROSCI.0804-06.2006

Schiller, B., Gianotti, L. R. R., Nash, K., & Knoch, D. (2014). Individual differences in inhibitory control - Relationship between baseline activation in lateral PFC and an electrophysiological index of response inhibition. Cerebral Cortex, 24(9), 2430–2435. https://doi.org/10.1093/cercor/bht095

Thaler, R. H., & Johnson, E. J. (1990). Gambling with the House Money and Trying to Break Even: The Effects of Prior Outcomes on Risky Choice. Management Science, 36(6), 643–660. https://doi.org/10.1287/mnsc.36.6.643

Schiller, B., Gianotti, L. R. R., Nash, K., & Knoch, D. (2014). Individual differences in inhibitory control - Relationship between baseline activation in lateral PFC and an electrophysiological index of response inhibition. Cerebral Cortex, 24(9), 2430–2435. https://doi.org/10.1093/cercor/bht095

Thaler, R. H., & Johnson, E. J. (1990). Gambling with the House Money and Trying to Break Even: The Effects of Prior Outcomes on Risky Choice. Management Science, 36(6), 643–660. https://doi.org/10.1287/mnsc.36.6.643

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SUMÁRIO GERAL

A maioria de nossas escolhas diárias envolve algum grau de risco, incluindo escolhas complexas, como investimentos financeiros, e escolhas cotidianas, como determinar uma rota para o trabalho com base nas informações de um aplicativo de trânsito. Devido à prevalência e importância dos comportamentos de risco, diferentes teorias e modelos de diferentes campos da ciência têm investigado a tomada de decisão de risco. No entanto, nossa compreensão científica do complexo processamento neural involvido em comportamentos de risco, permanece limitada. Esta dissertação consiste em uma série de estudos que examinam o comportamento de risco através das lentes da neurociência da tomada de decisão, examinando o processamento neural do cérebro ao intestino.

Na primeira parte da tese (capítulos 2 e 3), utilizei estimulação transcraniana por corrente alternada (ETCA) e a eletroencefalografia (EEG) para investigar o papel da atividade frontal cerebral em frequência theta na modulação do comportamento de risco. Os resultados obtidos mostram que é possível modular o comportamento de risco com ETCA em frequência theta, confirmando uma relação funcional entre a atividade frontal em frequência theta e o comportamento de risco.

No Capítulo 2, usei ETCA em diferentes frequências para testar a relação funcional entre a atividade theta e o comportamento de risco. Para tanto, utilizei ETCA em frequência theta (6,5 Hz), gama (40 Hz) e ETCA 'placebo' (controle) sobre o córtex pré-frontal dorsolateral esquerdo (CPFDL) durante uma tarefa experimental, denominada Maastricht Gambling Task (MGT), para provocar e medir o comportamento de risco dos participantes. Os resultados deste estudo mostram que a ETCA em frequência theta, mas não gama ou placebo, modula significativamente o comportamento de risco. ETCA em frequência theta sobre o CPFDL esquerdo, nas condições deste estudo, levaram a uma redução na tomada de risco pelos participantes. Os achados do Capítulo 2 apoiam a ideia de um papel funcional da atividade frontal theta na modulação do comportamento de risco e mostram que esse efeito é específico desta frequência.

O capítulo 3 aprofunda esse mecanismo eletrofisiológico avaliando os efeitos de ETCA em frequência theta no CPFDL direito e esquerdo. Os resultados mostraram que a estimulação dos diferentes lados levou a respostas comportamentais em direções opostas, com uma redução significativa no comportamento de risco durante a ETCA do CPFDL direito e um aumento após a ETCA do hemisfério esquerdo. Além disso, os resultados do Capítulo 3 mostram que a ETCA de alta intensidade (3 mA) leva a resultados comportamentais significativos de forma mais consistente, enquanto ETCA de baixa intensidade (1,5 mA) só produziu mudanças comportamentais significativas quando aplicada ao hemisfério esquerdo. Além disso, os níveis de atividade theta frontal durante repouso afetam significativamente o comportamento dos participantes e interagem com os vários protocolos de ETCA. Isso significa que esse complexo mecanismo

eletrofisiológico subjacente à modulação do comportamento de risco parece depender do estado cerebral. Portanto, considerando o estado de repouso, a atividade theta é importante na determinação da direção dos efeitos comportamentais obtidos durante ETCA em frequência theta.

Após o estudo do processamento neural subjacente da tomada de risco, o Capítulo 4 examina os papéis específicos do CPFDL direito (CPFDLd) e do córtex pré-frontal ventromedial (CPFVM) nesse tipo de comportamento. Essas duas áreas são importantes no processamento de decisões sob risco. Mas, embora o papel do CPFDLd no controle cognitivo durante a assunção de risco tenha sido demonstrado com o uso da estimulação magnética transcraniana (EMT) (Knoch et al., 2006), o papel do CPFVM está correlacionado ao processo de valorização, baseado principalmente em evidências de neuroimagem. O CPFVM é uma área raramente foco nos estudos da EMT devido à sua posição anatômica, por ser uma área mais profunda e, portanto, mais difícil de alcançar com métodos não invasivos de estimulação cerebral. No Capítulo 4, utilizo um coil de cone duplo destinada a estimular áreas corticais mais profundas e potencialmente atingir o CPFVM, para investigar seu papel no comportamento de tomada de decisão de risco. Usando EMT com estimulação contínua em banda theta (ECBT) para suprimir a atividade em cada uma dessas regiões, pude aumentar experimentalmente os comportamentos de risco dos participantes e as escolhas de valor médio.

Os resultados mostram que a estimulação tanto do CPFDLd quanto do CPFVM com um protocolo inibitório aumentou o comportamento de risco. Ambos os protocolos também levaram a um aumento significativo nas escolhas de valor médio dos participantes. Esses achados mostram que ambas as áreas estão envolvidas no processamento da valoração e na modulação do comportamento de risco, o que reforça evidências de uma forte interação funcional entre o CPFDLd e o CPFVM (Hare et al., 2009; Schiller et al., 2014). Além disso, esses resultados descartam a hipótese de que apenas a atividade do CPFVM poderia ser tomada como medida de valoração subjetiva.

Finalmente, a base neural do comportamento de risco foi investigada olhando além do sistema nervoso central, no último estudo (Capítulo 5). A microbiota intestinal pode influenciar a interação entre os sistemas nervoso central e entérico através do eixo intestino-cérebro (EIC) e pode afetar áreas cerebrais relacionadas a processos emocionais e cognitivos básicos. No entanto, o papel da microbiota intestinal na tomada de decisões em pessoas saudáveis permanece em grande parte desconhecido até agora. É por isso que no capítulo 5 investiguei a influência do EIC na tomada de decisão humana. Este estudo utilizou um desenho duplo-cego controlado por placebo em combinação com duas tarefas de tomada de decisão econômica, a saber, o MGT e o Maastricht Choice Task (MCT), para avaliar o comportamento de risco e as escolhas intertemporais de ambos os

participantes. As respostas comportamentais dos participantes foram estimadas antes e depois de um protocolo de 30 dias de probióticos/placebo. O estudo verificou possíveis mudanças na dieta, humor e autocontrole.

Os participantes que receberam probióticos mostraram uma redução relativa no comportamento de risco em comparação com o grupo placebo. Em particular, o grupo placebo teve um aumento significativo no comportamento de risco na sessão 2 em comparação com a sessão 1, possivelmente devido ao efeito "dinheiro da casa" ou à "distorção de crença baseada em pagamento" (Jiao, 2020; Thaler (Johnson, 1990), enquanto o grupo dos probióticos não teve um aumento significativo. Os participantes que receberam probióticos mostraram comportamentos de risco estáveis ao longo do tempo, com uma escolha estável de valores, e foram mais propensos a escolher opções com probabilidades mais altas. O grupo probióticos também foi mais propenso a optar por satisfação tardia na tarefa de escolha intertemporal, com menores taxas de desconto e menor sensibilidade ao risco.

Os resultados desta tese fornecem novos insights sobre os mecanismos neurais subjacentes aos comportamentos de risco, tanto dentro do sistema nervoso central quanto além dessas fronteiras, e incluem o eixo intestino-cérebro como um protagonista potencial. Esta série de estudos permitiu-me aprofundar ainda mais o meu conhecimento dos mecanismos eletrofisiológicos que ocorrem no córtex pré-frontal durante a assunção de riscos. Além disso, os resultados demonstraram a relevância da EIC para a tomada de decisão humana sob risco, expandindo o escopo das vias neurais subjacentes envolvidas no comportamento de risco humano.

10.1 REFERÊNCIAS

Hare, T. A., Camerer, C. F., & Rangel, A. (2009). Self-control in decision-Making involves modulation of the vmPFC valuation system. Science, 324(5927), 646–648. https://doi.org/10.1126/science.1168450

Jiao, P. (2020). Payoff-Based Belief Distortion. The Economic Journal, 130(629), 1416–1444. https://doi.org/10.1093/ej/ueaa019

Knoch, D., Gianotti, L. R. R., Pascual-leone, A., Treyer, V., Regard, M., Hohmann, M., & Brugger, P. (2006). Disruption of Right Prefrontal Cortex by Low-Frequency Repetitive Transcranial Magnetic Stimulation Induces. 26(24), 6469–6472. https://doi.org/10.1523/JNEUROSCI.0804-06.2006

Schiller, B., Gianotti, L. R. R., Nash, K., & Knoch, D. (2014). Individual differences in inhibitory control - Relationship between baseline activation in lateral PFC and an electrophysiological index of response inhibition. Cerebral Cortex, 24(9), 2430–2435. https://doi.org/10.1093/cercor/bht095

Thaler, R. H., & Johnson, E. J. (1990). Gambling with the House Money and Trying to Break Even: The Effects of Prior Outcomes on Risky Choice. Management Science, 36(6), 643–660. https://doi.org/10.1287/mnsc.36.6.643

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ABOUT THE AUTHOR

Aline M. Dantas was born in Anápolis, Brazil, on August 29th, 1985. She graduated high school in 2002, at COC, in Uberlândia, Brazil. She studied Psychology (Uberlândia Federal University, 2006), has a bachelor degree in Marketing (Anhembi Morumbi University, 2010), a MBA in Marketing (Getulio Vargas Foundation, 2014), and a masters in Applied Psychology and Neuroscience (Mackenzie Presbyterian University, 2019. During this master, she worked at the Cognitive and Social Neurosciences Laboratory, led by Prof. Boggio, where she learned about different neuroscientific techniques, including electroencephalography (EEG), transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS), among others. From 2006 to 2015, Aline worked as a product manager at companies such as Adidas and Nike.

Her interest in understanding human decision-making and her passion for teaching and research brought her back to academia. From 2016-2018 she completed the Research Master in Cognitive Neuroscience, with specialization in Neuroeconomics, at Maastricht University. During this period, she volunteered as a research assistant in Prof. Dr. Alexander Sack's research group.

In 2018, she started her PhD trajectory, under the interdisciplinary supervision of Prof. Dr. Elisabeth Brüggen, Dr. Peiran Jiao, Prof. Dr. Alexander Sack and Dr. Teresa Schuhmann. Aline's work explores the underlying neural basis of human risk-taking behavior with the use of multiple neuroscientific techniques such as TMS, tCDS, or EEG. In 2022, she spent a 6 months research visit at the Donders Institute (Radboud University, Nijmegen, The Netherlands), visiting, developing a project on the use of noninvasive vagus nerve stimulation in the study of risk-taking behavior and collaborating with current projects on reciprocity using fMRI. She also has a keen interest in teaching and therefore coordinated and tutored the master course Consumer Psychology. She supervised bachelor and master students from different backgrounds, always fostering the spirit of collaboration, collegiality and interdisciplinarity.

As a researcher, Aline is creative, innovative, thorough, and passionate. She is able to work independently while fostering important collaborations. Aline is a strong Latina, female and first-generation researcher, proud of her origins with a clear and enthusiastic vision for her academic future.

11.1 PEER-REVIEWED PUBLICATIONS

Dantas, A. M., Sack, A. T., Bruggen, E., Jiao, P., & Schuhmann, T. (2022). The functional relevance of right DLPFC and VMPFC in risk-taking behavior. Cortex. https://doi.org/10.1016/J.CORTEX.2022.11.009

Dantas, A. M., Sack, A. T., Bruggen, E., Jiao, P., & Schuhmann, T. (2022). The effects of probiotics on risk and time preferences. Scientific Reports 2022 12:1, 12(1), 1–10. https://doi.org/10.1038/s41598-022-16251-x. Impact Factor 4.996.

Dantas, A. M., Sack, A. T., Bruggen, E., Jiao, P. & Schuhmann, T. Reduced risk-taking behavior during frontal oscillatory theta-band neurostimulation. Brain Res. 147365 (2021). https://doi:10.1016/j.brainres.2021.147365. Impact factor 3.610.

11.2 TALKS

Risk-taking behavior modulation using tACS. Oral presentation by invitation of the Cognitive Neurosciences Department of Bern University, 2021 (Online due to COVID-19).

Dantas, A. M., Bruggen, E., Jiao, P., Sack, A. ,Schuhmann, T. – The functional roles of right DLPFC and VMPFC in risk-taking behavior. Society for NeuroEconomics Symposium, 2021 (Online due to COVID-19).

Dantas, A. M., Bruggen, E., Jiao, P., Sack, A. ,Schuhmann, T. – A gut feeling – how your brain (and your guts) affect your decisions. Reading Emotions, 2021. University of Reading – London – United Kingdom (Online due to COVID-19).

Dantas, A. M., Bruggen, E., Jiao, P., Sack, A. ,Schuhmann, T. - Risk-taking behavior modulation using tACS. Non-invasive Brain Stimulation Workshop 2020 – Minesotta – USA (Online due to COVID-19).

Invited by the department of Cognitive Neurosciences in Bern University to give a presentation on our study “Reduced risk-taking behavior during frontal oscillatory theta-band neurostimulation”. (Online due to COVID-19).

Dantas, A. M., Schuhmann, T., Sack, A., Disruption of frontal asymmetry using tACS to modulate risk-taking behavior. Poster presentation – HDPD seminar 2018 – Maastricht – The Netherlands.

11.3 POSTERS

Dantas, A. M., Bruggen, E., Jiao, P., Sack, A. ,Schuhmann, T. – The functional roles of right DLPFC and VMPFC in risk-taking behavior. Society for Judgment and Decision Making Annual meeting 2022 – San Diego – USA.

Dantas, A. M., Bruggen, E., Jiao, P., Sack, A. ,Schuhmann, T. – A gut feeling – how your brain (and your guts) affect your decisions. Subjective Probability Utility and Decision Making Conference 2021 (Online due to COVID-19).

Dantas, A. M., Bruggen, E., Jiao, P., Sack, A. ,Schuhmann, T. – The functional roles of right DLPFC and VMPFC in risk-taking behavior. Society for NeuroEconomics Symposium

2021 (Online due to COVID-19).

Dantas, A. M., Bruggen, E., Jiao, P., Sack, A. ,Schuhmann, T. – A gut feeling – how your brain (and your guts) affect your decisions. Reading Emotions 2021. University of Reading – London – United Kingdom (Online due to COVID-19).

Dantas, A. M., Bruggen, E., Jiao, P., Sack, A. ,Schuhmann, T. – A gut feeling – how your brain (and your guts) affect your decisions – preliminary results. Society for Neuroeconomics Symposium 2020 (Online due to COVID-19)

Dantas, A. M., Bruggen, E., Jiao, P., Sack, A., Schuhmann, T. – A gut feeling – how your brain (and your guts) affect your decisions – preliminary results. NeuroPsychoEconomics conference 2020 (Online due to COVID-19).

Dantas, A. M., Bruggen, E., Jiao, P., Sack, A. ,Schuhmann, T. - Risk-taking behavior modulation using tACS. NeuroPsychoEconomics conference 2020 (Online due to COVID-19).

Dantas, A. M., Bruggen, E., Jiao, P., Sack, A., Schuhmann, T. - Disruption of frontal asymmetry using tACS to modulate risk-taking behavior. Society for Neuroeconomics Symposium 2019– Dublin- Ireland.

Dantas, A. M., Bruggen, E., Jiao, P., Sack, A., Schuhmann, T. - Disruption of frontal asymmetry using tACS to modulate risk-taking behavior. Consumer Neuroscience symposium 2019– Dublin- Ireland.

Dantas, A. M., Murrins, L. M., Boggio, P. S. (2016). Neuromodulation of the herding effect in the purchase decision-making process: A study of transcranial direct current stimulation as modulator of herding behavior. ESCAN 2018 – Leiden – The Netherlands.

Dantas, A. M., Murrins, L. M., Boggio, P. S. (2016). Neuromodulation of the herding effect in the purchase decision-making process: A study of transcranial direct current stimulation as modulator of herding behavior. Neuroeconomics Talks – Maastricht – The Netherlands.

Dantas, A. M., Murrins, L. M., Boggio, P. S. (2016). Neuromodulation of the herding effect in the purchase decision-making process: A study of transcranial direct current stimulation as modulator of herding behavior. VII International Symposium of Neuromodulation – São Paulo – Brazil.

Dantas, A. M., Melo, D. C., Mendes, F. A., Beneton, F. M., Antunes, M. P. (2003). Autism x Learning. North Northeast Congress of Psychology – João Pessoa – Brazil

Oliveira, D. T. L., Dantas, A. M., Melo, D. C., Mendes, F. A., Beneton, F. M., Antunes, M. P. (2003). Pre-menstrual dysphoric disorder in university students. Brazilian society of Psychology.

11.4 RESEARCH GRANTS

Maastricht University - Behavioral Insight Center (UM-BIC) Interdisciplinary seeding grant (Maastricht, Limburg, NL). €5.000,00.

SWOL University Fund Limburg (Maastricht, Limburg, NL). €7.000,00.

GSBE Primary data collection grant. Maastricht University (Maastricht, Limburg, NL). €5.200,00.

11.5 RESEARCH HONORS/AWARDS

Dantas, A. M., Bruggen, E., Jiao, P., Sack, A., Schuhmann, T. - Risk-taking behavior modulation using tACS. Best abstract – Non-invasive Brain Stimulation Workshop 2020 – Minnesota – USA (Online due to COVID-19

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ACKNOWLEDGEMENTS

Once upon a time there was a woman in Brazil called **Maria**. Her tale of resilience and determination shows her incredible strength. Through her tireless efforts and the aid of a sewing machine, she single-handedly raised her two daughters **Regina** (my mom) and **Gina** (my aunt). Despite the daunting challenges they faced, they pressed on. **Maria** instilled in her daughters the value of chasing dreams, emphasizing the significance of education and hard work. To my cherished late grandmother, **Vó Maria**, I extend my heartfelt thanks. As my initial role model, you demonstrated that women can accomplish anything.

The story continues with **Regina** and **Gina**, who navigated hunger and scarcity, and yet, united by mutual support and their mother's example, forged ahead. Although I never experienced **Gina**'s presence firsthand, she left an indelible mark on our family's history. Her legacy lives on through her son **Rafael**, my beloved cousin/brother, and her husband **Walter**, a pivotal father figure in my life.

A few years later, my mom **Regina** met **José Luiz (aka. Dantas)** and from this unlikely relationship I was born. Though his time in our home was brief, my father gifted me with precious siblings (Viviane, Joacy, Ivana, Junior, Danilo, and Daniel), the sole and priceless inheritance I got from him. My mom, following this lineage of strong women, navigated motherhood alone, armed with determination and tireless effort. Her life's mission centered on ensuring that Rafael and I received the best education possible. Thank you so much, **Mamãe**, for this and so much more. You shaped the person I am today, and I'm honored to be your daughter.

As you probably noticed, I grew up in an unconventional family. I was raised by a solo mom (that was a boss lady already in the early 90's), an amazing grandma (that could make even the toughest grown man shake in his boots and be loving and carrying at the same time) and a great extended family. This inclusive circle included **Rafael**, his father, my cherished uncle **Walter** (affectionately referred to as **Papi**), his remarkable stepmother, my aunt **Beila**, and his siblings **Vinicius** and **Brunna**. Their presence added happiness to my childhood so I extend to them my deepest gratitude. They remain an integral part of my heart, regardless of time or distance.

Within this diverse family tapestry, there are numerous siblings who were well into adulthood, married, and parenting by the time of my birth. Consequently, I am blessed with numerous nieces and nephews, some of whom are now parents themselves. To each of them, my deepest gratitude for their respect, affection, and inspiration. My special thanks goes to my dear sisters **Joacy** and **Viviane**, and my big brother **Junior**. I also extend my thanks to my nieces **Ana Pérola, Monyque, Marcella, Mayra**, and **Polyanna**. I also must dedicate a little space to the memory of my sister **Ivana**, my niece **Danielli** and

my nephew **Marvin**. You taught me what a family really is. I love you infinitely!

During my early childhood I discovered my first great love: dancing! With this passion came some of the people that helped shape my personality and even my work ethics. This journey was guided by **Sandra Cavalcante**'s sweetness and **Elza Cavalcante**'s unwavering love and support. Alongside these influences were friends like **Jackelinne, Isaura, Nowhah, Juliane, Renata,** and my dearest **Gizelle**. These connections, love, and support formed a foundation of friendship that holds immeasurable significance to me until now.

My journey led me to Uberlândia, where I first discovered my passion for Neuroscience (and not so much for Psychology). There I met **Gabriela Mattos**, to whom this dissertation is dedicated. She was my best friend, confidant, and one of the most important people in my life. But I will get back to this later. My list of amazing friends expanded greatly during this period, but I will mention especially **Julia, Carol Mattos, Pedro, Fabio, Tiago Faria, Tiago Toledo, Giordano, Fernanda, Ana Clara,** and **Geleia**, who are still dear and important friends in my life.

The next chapter unfolded in São Paulo, a city of growth and independence. There I made new friendships, had a few relationships, and partied a little too much (Oh my 20's!). **São Paulo** deserves its own acknowledgment. This city was my greatest school and is still my favorite city in the whole world. Amidst a very busy life of work, the people I met were certainly exceptional. I could list dozens of people here, but I will focus on **Isabella, Paulinha, Jessica, Mia, Dani,** and **Tata**. Thank you so much for being my constant source of love, support, and empowerment.

Of course, during all this time I worked a lot, traveled a lot and in parallel I studied (a lot!). The pursuit of knowledge that was deeply ingrained in me, influenced by my family legacy and inspiring educators I met along the way, led to a master's degree in Neuroscience. Although I was working with product marketing for quite some time, I went back to Neuroscience this simply for the pleasure of studying brains. It was during this period that I met the amazing professors **Paulo Boggio, Camila Campanhã, Gabriel Rego,** and **Lucas Murrins Marques**, who played pivotal roles in shaping my academic aspirations.

In Brazil, I did not yet have the means to follow an academic career. So this dream was in definite hold until I received some wise advice during a coffee break with my dear friends, **Lívia, Luiz** and **Adolfo**. The advice was: "Forget the future you think you will have and focus on the one you want to have". These words changed my life. So here I thank my dear **Livia** for giving me this life-changing nudge and putting me on the right

track. After this, I started preparing for this big career shift. This led me to Maastricht University, where I started studying Neuroeconomics.

My journey at Maastricht University has been an overall transformative experience filled with invaluable interactions. My deepest gratitude is extended to a group of professors who played significant roles in the master's program, including **Martin Strobel, Matthias Wibral, Arkadi Predtetchinski, Jona Linde, Teresa Schuhmann, Vincent van Ven, Fren Smulders, Giancarlo Valente,** and **Arno Riedl**. Their patience and expertise enhanced my fascination with Neuroeconomics and Decision Neuroscience.

However, this story took a challenging turn during the master's second year. In a span of two months I lost my father to pancreatic cancer and was myself diagnosed with cervical cancer. Throughout this trying period, the support from **Maastricht University** and newfound friends became an essential lifeline. I must specially thank **Marcia, Suvi, Maja, , Andrea Fariña, Andrea Aguirre, Jasper, Roos** and all my colleagues in the Neuroeconomics track that literally took care of me during all the steps of my diagnosis, treatment, and recovery. Acknowledgments also to professor **Matthias Wibral** for fully supporting me, even adjusting course locations to accommodate my medical needs, allowing me to balance radiotherapy sessions and classes. And to all the professors that allowed me to follow classes online (which before COVID was not a possibility) when physical presence was not possible anymore. Being able to focus on my masters was what kept me strong and fighting. This saved my life.

Numerous individuals lent their unwavering support, playing essential roles in my treatment's success. This includes a vast network of friends, my entire family, a multitude of caring nurses, and dedicated doctors. Among them, I am deeply grateful for the contributions of **Sandra Kloss, Dr. Lambrecht, Dr. Lalisang,** and **Dr. den Haas**. Your collective efforts have brought me to where I am today, and my appreciation knows no bounds.

The most profound support I encountered during this challenging period came from two extraordinary groups of women. The first one were my amazing team of friends, my "magical unicorns": **Suvi, Marcia, Lina** and **Maja**. They were there for me through good and bad. Although our lives took each of us to different paths, they will always be in my heart.

The second group of fantastic women are the ones who were also going through this unfortunate battle, fondly referred to as my "teal sisters". They offered guidance, camaraderie, and assistance while battling their own cancer diagnoses. Among these remarkable women, my longtime friend **Gabriela Mattos,** my treatment partner **Wendy**

and the dear **Sandra Pitta**, who shared with me a mission to support and empower other women navigating the same battle with knowledge and compassion. Words cannot express the depth of my gratitude and love for each one of these amazing women. I am forever grateful.

Back to the story. Despite the storm, I managed to somehow finish my Master's (I told you I could, **Dr. Lalisang**!) and get a PhD position. The complexities of the PhD journey were accompanied by a lengthy and arduous recovery. But guess what? I did it!

None of this would have been possible without my exceptional supervision team: **Prof. Dr. Elisabeth (Lisa) Bruggen, Prof. Dr. Alexander (Alex) Sack, Dr. Teresa Schuhmann** and **Dr. Peiran Jiao**.

Lisa is certainly one of the most admirable women I had the luck of meeting. Her belief in me shaped my PhD journey. Over the years, she became the leader of this extraordinary supervision team, seamlessly managing the interdisciplinary and occasionally challenging nature of our work. **Lisa**, your presence as a strong female researcher provided me with motivation, inspiration, and resilience during tough times. And for all that, I cannot thank you enough!

Another role model for me is **Teresa**. Throughout my years in Maastricht, she has been a constant presence. First as a teacher and mentor, later as a supervisor and friend. She stood by me during lows and propelled me to reach my best. **Teresa**, thank you hardly seems sufficient. You teach me daily to be a better person and professional. Thank you for everything!

Besides these two strong women, there were two brilliant men – **Alex** and **Peiran**. Since I started working with **Alex**'s group, I have had the privilege of watching his mind working and coming up with the most insightful and brilliant solutions when everyone else seemed lost. I am certainly very lucky to have him as a promotor during this journey. **Alex**, thank you for taking time to embark with me on all these ambitious research ideas. Thank you for everything!

Peiran, every interaction with you has been a great learning opportunity for me. Thank you for your patience and openness to new ideas (even when they included publishing in neuroscience journals with their very weird paper structures). This dissertation would not have happened without you! Thank you so much!

My PhD trajectory was divided between two different departments: **Marketing and Supply Chain Management (MSCM)** and **Cognitive Neuroscience (CN)**. Without the

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In CN I was part of the **Brain, Stimulation and Cognition (BSC)** research group, commonly known as the NIBS group. This team played a fundamental role in the development of my PhD. Its members were a constant source of support, knowledge, and great discussions. I want to thank you all, with special thanks to **Alex** and **Teresa** (again), **Tom, Felix, Sanne, Inge, Sanne, Alix (Charlie), Lukas, Stefano, Geraldine, Mathilde, Samantha, Olof, Jeannette** and (my dear paranymph) **Shanice**.

In the MSCM department I had the opportunity of joining **the Consumer Behavior (CB)** group with **Caroline, Kelly, Anouk, Cara, Emir,** and many other remarkable researchers. I am deeply grateful for the invaluable lessons I gained from this group. Your research quality and professionalism inspire me, and I look forward to potential collaborations!

Of course, not everything is work in a PhD's life. Besides many hours of work there was also some fun and many friends. First, I want to especially thank the one that was always by my side during my PhD: **Niels Neven**. Boo, thank you for being my support, my partner, and the source of so much laughter and love during all these years! Thanks also to your (and a little bit mine) lovely family, **Marina, Ludo, Hanne, Stef, Ólafur** and baby **Lenù**.

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And of course, there are my amazing fellow PhDs. I would like to thank each one of you, with special mentions to MSCM's **Mathilde, Marcia, Gitta, Eric, Sammy, Jenna,** and **Jacqueline** (my two amazing SBE paranymphs) and to CN's Julian, Daniele, Hannah, Alex, Marta, Sebastian, Andreas, Vaish, Peppe, Selma, Johannes, Giada, Fabian, and Shanice (my other two amazing paranymphs, from FPN).

Talking about my paranymphs, I would like to make a special mention to this fantastic group that was with me through all (or most of) my PhD trajectory. They certainly made this journey easier, more motivating, and much more fun. To my official paranymphs **Shanice** and **Jenna**, and to my extra paranymphs (yes, because I am a little extra), **Fabian** and **Jacqueline**.

Besides being a strong, brilliant woman, with an admirable intelligence and professionalism, **Shanice** is also an amazingly kind and present friend, whom I really admire. Beste **Shanice**, hartelijk bedankt!

Jenna is my little sister, partner in crime and loyal fellow member of **Lisa**'s fan club. What a gift she has been during these years! I'm really glad to have her as a colleague and friend. Thank you, dear!

Fabian is one of these guys that arrives quietly and suddenly becomes one of your favorite people on Earth. He is a guaranteed source of funny facts, incredible insights, and the best hugs in town. Thank you dear! A huge hug to you!

And last but not least, **Jacqueline**! My fellow neuroeconomics warrior and dear friend! She is sweet, determined and always willing to learn and help. A brilliant woman growing stronger and wiser every day. Thank you **Jacquie**!

I would like to also thank my Assessment Committee: **Prof. Dr. Caroline Goukens, Prof. Dr. Alan G. Sanfey, Dr. Matthias Wibral** and **Dr. Vincent G. van de Ven** for taking time of your very busy schedules to read my thesis and come up with stimulating questions.

With the collective support of these remarkable individuals and a touch of serendipity, I got here. This dissertation closes a beautiful chapter of my life and hopefully opens the doors for many more to come. I am immensely thankful to all the brilliant, loving and supporting people that brought me here. I thank God (and myself too!) for the strength to overcome all the obstacles, the faith to keep going and the passion that turned my life into an amazing adventure. And I thank you for reading this lengthy (but hopefully enjoyable) acknowledgement/story! To the next adventures!

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Era uma vez uma mulher no Brasil chamada **Maria**. Sua história é de pura resiliência e determinação. Através de seus esforços incansáveis e da ajuda de uma máquina de costura, ela criou sozinha suas duas filhas, **Regina** (minha mãe) e **Gina** (minha tia). Apesar dos desafios assustadores que enfrentaram, eles seguiram em frente. **Maria** incutiu nas filhas o valor de correr atrás dos sonhos, enfatizando a importância da educação e do trabalho árduo. À minha querida e saudosa avó, **Vó Maria**, estendo os meus sinceros agradecimentos. Como meu modelo, você demonstrou que as mulheres podem alcançar realmente qualquer coisa.

A história continua com **Regina** e **Gina,** que apesar da fome e escassez, unidas pelo apoio mútuo e pelo exemplo da mãe, seguiram em frente. Embora eu nunca tenha conhecido minha tia **Gina**, ela deixou uma marca indelével na história da nossa família. Seu legado continua vivo através de seu filho **Rafael**, meu amado primo/irmão, e seu marido **Walter**, uma figura paterna fundamental na minha vida.

Alguns anos depois, minha mãe **Regina** conheceu José **Luiz (também conhecido como Dantas)** e desta relação improvável eu nasci. Embora seu tempo em nossa casa tenha sido breve, meu pai me presenteou com preciosos irmãos (Viviane, Joacy, Ivana, Junior, Danilo e Daniel), a única e inestimável herança que recebi dele. Minha mãe, seguindo essa linhagem de mulheres fortes, navegou sozinha pela maternidade, armada de determinação e esforço incansável. A missão de vida dela era garantir que Rafael e eu recebessemos a melhor educação possível. Muito obrigada, **Mamãe**, por isso e muito mais. Você moldou a pessoa que sou hoje, sou muito honrada de ser sua filha.

Como você deve ter notado, eu cresci em uma família não convencional. Fui criada por uma mãe solo (que era uma mulher poderosa já no início dos anos 90), uma avó incrível (que podia fazer até o homem adulto mais duro tremer nas botas e ser amorosa e querida ao mesmo tempo) e uma grande família. Esse círculo familiar inclui **Rafael**, seu pai, meu querido tio **Walter** (carinhosamente chamado de **Papi**), sua admirável madrasta, minha tia **Beila**, e seus irmãos **Vinicius** e **Brunna**. A presença deles acrescentou felicidade à minha infância, por isso estendo a eles minha mais profunda gratidão. Eles continuam sendo parte integrante do meu coração, independentemente do tempo ou da distância.

Dentro dessa constelação familiar diversificada, há inúmeros irmãos que já estavam na idade adulta, casados e pais na época do meu nascimento. Consequentemente, sou abençoada com numerosas sobrinhas e sobrinhos, alguns dos quais agora já tem seus próprios filhos. A cada um deles, minha mais profunda gratidão pelo respeito, carinho e inspiração que sempre me deram. Meu agradecimento especial às minhas queridas irmãs **Joacy** e **Viviane**, e ao meu irmão mais velho **Junior**. Agradeço também às sobrinhas **Ana Pérola, Monyque, Marcella, Mayra** e **Polyanna**. Também devo dedicar

um pequeno espaço à memória da minha irmã **Ivana**, da minha sobrinha **Danielli** e do meu sobrinho **Marvin**. Vocês me ensinaram o que realmente é uma família. Eu amo vocês infinitamente!

Ainda na infância descobri meu primeiro grande amor: a dança! Com essa paixão vieram algumas das pessoas que ajudaram a moldar minha personalidade e até mesmo minha ética de trabalho. Essa jornada foi guiada pela doçura de **Sandra Cavalcante** e pelo amor e apoio inabaláveis de **Elza Cavalcante**. Ao lado dessas influências estavam amigas como **Jackelinne, Isaura, Nowhah, Juliane, Renata** e minha querida **Gizelle**. Essas conexões, amor e apoio formaram uma base de amizade que tem um significado imensurável para mim até hoje.

Minha jornada me levou a Uberlândia, onde descobri minha paixão pela Neurociência (e não tanto pela Psicologia). Lá conheci **Gabriela Mattos**, a quem esta dissertação é dedicada. Ela era minha melhor amiga, confidente e uma das pessoas mais importantes da minha vida. Mas voltarei a isso mais tarde. Minha lista de amigos incríveis aumentou muito nesse período, mas vou citar especialmente **Julia, Carol Mattos, Pedro, Fábio, Tiago Faria, Tiago Toledo, Giordano, Fernanda, Ana Clara** e **Geleia**, que são amigos queridos e ainda muito importantes na minha vida.

O capítulo seguinte se desenrolou em São Paulo, cidade de crescimento e independência. Lá fiz novas amizades, tive alguns relacionamentos e festejei um pouco demais (Ai meus 20 anos!). **São Paulo** merece seu próprio reconhecimento. Esta cidade foi a minha maior escola e ainda é a minha cidade favorita em todo o mundo. Em meio a uma vida de trabalho muito agitada, as pessoas que conheci certamente foram excepcionais. Eu poderia listar dezenas de pessoas aqui, mas vou focar na **Isabella, Paulinha, Jéssica, Mia, Dani** e **Tata**. Muito obrigado por ser minha fonte constante de amor, apoio e empoderamento.

Claro que durante todo esse tempo trabalhei muito, viajei muito e paralelamente estudei (muito!). A busca pelo conhecimento que estava profundamente arraigada em mim, influenciada pelo meu legado familiar e educadores inspiradores que conheci ao longo do caminho, levou a um mestrado em Neurociências. Embora eu estivesse trabalhando com marketing de produto há algum tempo, voltei para a Neurociência simplesmente pelo prazer de estudar cérebros. Foi nesse período que conheci os incríveis professores **Paulo Boggio, Camila Campanhã, Gabriel Rego** e **Lucas Murrins Marques**, que desempenharam papéis fundamentais na formação de minhas aspirações acadêmicas.

No Brasil, eu ainda não tinha condições de seguir uma carreira acadêmica. Então, esse sonho ficou definitivamente em dia até que recebi alguns conselhos sábios durante um

coffee break com meus queridos amigos**, Lívia, Luiz** e **Adolfo**. O conselho era: "Esqueça o futuro que você acha que terá e foque no que você quer ter". Essas palavras mudaram a minha vida. Então, aqui eu agradeço a minha querida **Lívia** por me dar esse empurrão que mudou a vida e me colocar no caminho certo. Depois disso, comecei a me preparar para essa grande mudança de carreira. Isso me levou à Universidade de Maastricht, onde comecei a estudar Neuroeconomia.

Minha jornada na Universidade de Maastricht tem sido uma experiência transformadora cheia de interações inestimáveis. Minha mais profunda gratidão é estendida a um grupo de professores que desempenharam papéis significativos no meu mestrado, incluindo **Martin Strobel, Matthias Wibral, Arkadi Predtetchinski, Jona Linde, Teresa Schuhmann, Vincent van Ven, Fren Smulders, Giancarlo Valente** e **Arno Riedl**. Sua paciência e experiência aumentaram meu fascínio pela Neuroeconomia e pela Neurociência da Decisão.

No entanto, essa história tomou um rumo desafiador durante o segundo ano do mestrado. Em um período de dois meses, perdi meu pai para um câncer no pâncreas e fui diagnosticada com câncer de colo de útero. Durante todo este período difícil, o apoio da **Universidade de Maastricht** e dos novos amigos tornou-se um suporte essencial. Devo agradecer especialmente **a Marcia, Suvi, Maja, Andrea Fariña, Andrea Aguirre, Jasper, Roos e** todos os meus colegas da trilha de Neuroeconomia que literalmente cuidaram de mim durante todas as etapas do meu diagnóstico, tratamento e recuperação. Agradecimentos também ao professor **Matthias Wibral** por me apoiar totalmente, até mesmo ajustando os locais dos cursos para acomodar minhas necessidades médicas, permitindo-me equilibrar sessões de radioterapia e aulas. E a todos os professores que me permitiram acompanhar as aulas online (que antes da COVID não era uma possibilidade) quando a presença física já não era possível. Poder focar nos meus mestres foi o que me manteve forte e lutando. Isso salvou a minha vida!

Inúmeras pessoas prestaram seu apoio inabalável, desempenhando papéis essenciais no sucesso do meu tratamento. Isso inclui uma vasta rede de amigos, toda a minha família, uma infinidade de enfermeiros atenciosos e médicos dedicados. Entre eles, sou profundamente grata a **Sandra Kloss, Dr. Lambrecht, Dr. Lalisang** e **Dr. den Haas.** Seus esforços coletivos me trouxeram até onde estou hoje, eu não consigo agradecer o suficiente.

O apoio mais profundo que encontrei durante este período desafiador veio de dois grupos de mulheres extraordinárias. O primeiro foi meu incrível time de amigos, meus "unicórnios mágicos": **Suvi, Marcia, Lina** e **Maja**. Eles estavam lá para mim durante o bom e o ruim. Embora nossas vidas tenham nos levado a caminhos diferentes, elas

sempre estarão no meu coração.

O segundo grupo de mulheres fantásticas são as que também estavam passando por essa mesma batalha, carinhosamente chamadas de minhas "irmãs". Eles ofereceram orientação, camaradagem e assistência enquanto lutavam contra seus próprios diagnósticos de câncer. Entre essas mulheres notáveis, minha amiga de longa data **Gabriela Mattos,** minha parceira de tratamento **Wendy** e a querida **Sandra Pitta**, que compartilharam comigo a missão de apoiar e empoderar outras mulheres que navegam na mesma batalha com conhecimento e compaixão. Palavras não podem expressar a minha gratidão e amor por cada uma dessas mulheres incríveis. Sou eternamente grata.

De volta à história. Apesar da tempestade, consegui de alguma forma terminar meu mestrado (eu disse que podia, **Dr. Lalisang**!) e conseguir uma vaga de doutorado. As complexidades da jornada de doutorado foram acompanhadas por uma longa e árdua recuperação. Mas adivinha? Eu consegui!

Nada disso teria sido possível sem meu excepcional time de supervisores: **Prof. Dr. Elisabeth (Lisa) Bruggen, Prof. Dr. Alexander (Alex) Sack, Dra. Teresa Schuhmann** e **Dr. Peiran Jiao.**

Lisa é certamente uma das mulheres mais admiráveis que tive a sorte de conhecer. Sua confiança em mim moldou minha jornada de doutorado. Ao longo dos anos, ela se tornou a líder dessa equipe de supervisão extraordinária, gerenciando perfeitamente a natureza interdisciplinar e, ocasionalmente, desafiadora de nosso trabalho. **Lisa**, sua presença como uma pesquisadora forte me proporcionou motivação, inspiração e resiliência durante os momentos difíceis. E por tudo isso, não posso agradecer o suficiente!

Outro exemplo para mim é **Teresa**. Ao longo dos meus anos em Maastricht, ela tem sido uma presença constante. Primeiro como professora e mentora, depois como supervisora e amiga. Ela ficou ao meu lado durante os meiores desafios e me impulsionou a alcançar o meu melhor. **Teresa**, obrigada parece insuficiente. Você me ensina a ser uma pessoa e profissional melhor. Obrigada por tudo!

Além dessas duas mulheres fortes, há também dois homens brilhantes – **Alex** e **Peiran**. Desde que comecei a trabalhar com o grupo do **Alex**, tive o privilégio de ver sua mente trabalhando e chegar às soluções mais perspicazes e brilhantes quando todos os outros pareciam perdidos. Com certeza tenho muita sorte de tê-lo como promotor durante essa jornada. **Alex**, obrigada por reservar um tempo para embarcar comigo em todas essas ideias de pesquisa tão ambiciosas. Obrigada por tudo!

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Minha trajetória de doutorado foi dividida entre dois departamentos distintos: **Marketing e Supply Chain Management (MSCM) e Neurociência Cognitiva (CN).** Sem o apoio de cada departamento, essa dissertação não aconteceria. Quero agradecer especialmente a **Christl** e **Peter de Weerd** (CN), **Pascalle, Nicole, Kelly, Diogo** e **Dominik** (MSCM).

Na CN fiz parte do grupo de pesquisa **Cérebro, Estimulação e Cognição (BSC),** comumente conhecido como grupo NIBS. Essa equipe teve um papel fundamental no desenvolvimento do meu doutorado. Seus membros foram fonte constante de apoio, conhecimento e grandes discussões. Quero agradecer a todos, com agradecimentos especiais a **Alex** e **Teresa** (novamente), **Tom, Felix, Sanne, Inge, Sanne, Alix (Charlie), Lukas, Stefano, Geraldine, Mathilde, Samantha, Olof, Jeannette** e (minha querida paraninfa) **Shanice**.

No departamento de MSCM tive a oportunidade de me juntar ao grupo de **Comportamento do Consumidor (CB)** com **Caroline, Kelly, Anouk, Cara, Emir** e muitos outros pesquisadores notáveis. Sou profundamente grata pelas lições inestimáveis que ganhei deste grupo. Sua qualidade de pesquisa e profissionalismo me inspiram, e espero termos muitas colaborações futuras!

É claro que nem tudo é trabalho na vida de um doutorando. Além de muitas horas de trabalho, havia também alguma diversão e muitos amigos. Primeiro, quero agradecer especialmente àquele que sempre esteve ao meu lado durante meu doutorado: **Niels Neven**. Boo, obrigada por ser meu apoio, meu parceiro, e a fonte de tantas risadas e amor durante todos esses anos! Obrigada também à sua (e um pouco minha) linda família, **Marina, Ludo, Hanne, Stef, Ólafur** e **Lenù**.

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(meus outros dois paraninfos incríveis, da FPN).

E por falar em paraninfos, eu gostaria de fazer uma menção especial a esse grupo fantástico que esteve comigo durante toda (ou a maior parte) da minha trajetória de doutorado. Eles certamente tornaram essa jornada mais fácil, mais motivadora e muito mais divertida. Às minhas paraninfas oficiais **Shanice** e **Jenna**, e aos meus paraninfos extra (sim, porque sou um pouco extra), **Fabian** e **Jacqueline.**

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Jenna é minha irmã mais nova, parceira no crime e fiel colega do fã-clube de **Lisa**. Que presente ela foi para mim durante esses anos! Fico muito feliz em tê-la como colega e amiga. Obrigada, querida!

Fabian é um desses caras que chega quietinho e de repente se torna uma de suas pessoas favoritas na Terra. Ele é uma fonte garantida de fatos engraçados, insights incríveis e os melhores abraços da cidade. Obrigada querido! Um grande abraço para você!

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Com o apoio dessas pessoas notáveis e um toque de sorte, cheguei aqui. Esta dissertação encerra um belo capítulo da minha vida e espero que abra as portas para muitos mais. Sou imensamente grata a todas as pessoas brilhantes, amorosas e solidárias que me trouxeram até aqui. Agradeço a Deus (e a mim também!) pela força para superar todos os obstáculos, pela fé para seguir em frente e pela paixão que transformou minha vida em uma aventura incrível. E agradeço a você por ler este longo (mas espero que agradável) agradecimento/história! Até as próximas aventuras!