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BRAIN MECHANISMS UNDERLYING PREDICTION DURING CONFLICT AND VALUE-BASED DECISION MAKING

BY: MARÍA PAZ MARTÍNEZ MOLINA

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THESIS ADVISOR:

PhD Pablo Billeke Bobadilla

THESIS CO-ADVISOR:

PhD Patricia Soto Icaza

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SANTIAGO

DEDICATION

Dedico esta tesis a mi familia, quienes son mi orgullo,

mi ejemplo, y mi principal apoyo y contención.

María Paz

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LIST OF ABBREVIATIONS

ADHD: Attention Deficit Hyperactivity Disorder

BOLD: Blood oxygen level dependent imaging

CTD: Cluster Threshold Detection

DLPFC: dorsolateral prefrontal cortex

EEG: Electroencephalography

Exp: Expectative of conflict stimuli

fMRI: Functional Magnetic Resonance Imaging

GNG: Go-Nogo

HDI: High density interval

Hz: Hertz

IFJ: Inferior Frontal Junction

mm: Millimeters

MSIT: Multi Source Interference Task

pCE: Previous commission error

PFC: Prefrontal cortex

pOE: Previous omission error

RL: Reinforcement Learning

RT: Reaction time

SFG: Superior Frontal Gyrus

TMS: Transcranial Magnetic Stimulation

ABSTRACT

People are able to solve conflictive situations and even anticipate them thanks to adaptive behavior derived from their experience and learning of contextual changes, that allows them to predict what might happen. This prediction is also known as proactive cognitive control, since it allows anticipating what is going to happen and to a possible conflict. According to scientific evidence, theta band oscillatory activity in the prefrontal cortex is associated with cognitive control. Specifically, findings are shown that lateral prefrontal areas are related to the capacity to anticipate an approaching conflict (proactive cognitive control). However, although theta oscillations have been described as a candidate mechanism for cognitive control, it remains unclear whether proactive cognitive control involves theta activity in lateral prefrontal areas in conflictive situations.

In more complex scenarios, like value-based decision making, additional factors such as reward expectancy, reward sensitivity, prediction of what might happen, and choice of actions are also involved. It has been described that individuals choose what means the most value to them, according to the reward and the expectancy of the availability of that reward. In spite of reward sensitivity has shown to be fundamental in making decisions, it is still unclear how reward sensitivity modulates behavioral control in the context of prediction and choice during value-based decision making.

Considering this background, we carried out two investigations described in sections 3 and 4 of this document.

In the first research (section 3), we studied whether theta oscillatory activity plays a causal role in conflict expectancy. Functional Magnetic Resonance Imaging (fMRI), Electroencephalography (EEG), and Transcranial Magnetic Stimulation (TMS) were carried out during cognitive tasks (MSIT and Go Nogo tasks) to establish a causal relationship between theta brain oscillations and cognitive activity in the lateral prefrontal cortex. Results indicated that conflict expectancy increases reaction time, and that there is brain activity in the superior frontal gyrus (SFG) and the inferior frontal junction (IFJ) during the MSIT Task related to the expectancy of conflict and behavioral inhibition, respectively. We also observed that the SFG TMS at theta frequency enhances cognitive control (expectancy of conflict) and modulates theta oscillations in lateral prefrontal regions during the Go Nogo task.

In the second research (section 4), we studied how reward sensitivity modulates prediction and choice during value-based decision-making. Two experiments (behavior and fMRI) were performed during a Risk-Learning task to study the effect of reward sensitivity on prediction and choice during value-based decision-making. Preliminary results indicated that the rate of learning increases as reward increases, and that with this increased reward there is an increase in ventral

striatal activity. The increase in the learning rate indicates that participants are reward-sensitive, as they are guided by rewards when making their decisions and do not incorporate the experience.

Taken together, these findings show that theta-band oscillatory activity has a causal role in the expectation of conflict and that reward influences our learning and decision-making.

Keyword: Conflict, cognitive control, conflict expectancy, theta band activity, value-based decision making, reward sensitivity, predictive model, and selective model.

1. INTRODUCTION

In everyday life, people must perform different activities to meet their needs and respond to their responsibilities. In such situations, people constantly learn from and make predictions about the environment. Prediction refers to the anticipation (thinking) of what might happen when performing an action according to individual and contextual changes. This prediction is relevant when conflict situations must be resolved and when decisions must be made because it allows to internally construct an expectation and a probability of what is expected to happen and respond accordingly. The neurobiological mechanisms underlying these conductual processes were investigated in this thesis.

Humans can solve and even anticipate or predict a conflict because they have learned the context and have made predictions, which allows them to respond adaptively. Thus, as they face a situation and pay attention to changes in the environment, they can internally construct a conflict expectancy and a probability of conflict to be attentive to the response that they must exercise. This has been referred to as conflict, as this is a difficult situation that must be resolved, in which control of automatic response is required in order to give an adapted and flexible response, known as cognitive control (Braver, 2012; Koechlin et al., 2003; Shenhav et al., 2016). For instance, an unexpected situation might demand a quick reaction (reactive cognitive control), and a known experience (previously

experienced), could make it possible to anticipate possible contextual changes (proactive cognitive control) (Chang et al., 2017). This ability to inhibit or suppress unwanted or inappropriate actions is an essential component of an executive function in which reactive and proactive mechanisms both facilitate successful inhibitory control (Brockett & Roesch, 2021). Therefore, cognitive control is necessary to flexibly adjust behavior in accord with internal goals and moving away from behaviors that are more automatic that distract from those goals (Braver, 2012; Koechlin et al., 2003; Shenhav et al., 2016).

Conflicts typically arise in situations that call for sudden changes in behavior. For this, its resolution is challenging, and is prone to errors (Kaiser et al., 2022). Although these errors inevitably occur, the brain's inhibitory control systems help to keep this number low and to integrate behavioral strategies to minimize future errors (Brockett & Roesch, 2021). That is how we can improve chances to successfully resolve conflicts by preparing us for potential behavioral adjustments (Kaiser et al., 2022). In this respect and considering that human beings live in a complex and changing environment, they have to adapt their behavior to respond efficiently. This adjustment is possible thanks to higher cognitive abilities such as learning, planning, reasoning and creativity integrated in the prefrontal cortex (PFC) (Koechlin, 2016). As individuals face uncertain, variable, and open-ended environments, gain experience, form internal models (mental schemas that associate stimuli, actions, and outcomes) of how the world

works, and incorporate it as learning that can be used in future situations. For example, when a person has to decide which means of transport to use to get to work faster, he thinks about the possible courses of action and their potential results, i.e., they make a prediction of what may happen, which they analyze according to the context in which he finds himself and the objectives he intends to achieve, in order to select an option and carry out that action.

In both conflict situations and decision-making, research in behavioral modeling has shown internal models that could account for the process of learning from the environment and making predictions from the environment. Specifically, this processing has been described as three models (selective, predictive, and contextual) that interact to give rise to the behavioral manifestation (Koechlin, 2016; Soltani & Koechlin, 2022). The selective model refers to the selection and implementation of the most desirable action, according to learned stimulus–action associations through rewards (Koechlin, 2016; Soltani & Koechlin, 2022). The predictive model refers to the anticipated outcome according to stimulus- and/or action–outcome associations through statistical inferences, without physically acting (Koechlin, 2016; Soltani & Koechlin, 2022). That is, predicts the outcomes of actions of a selective model, according to the current motivational state of people (Koechlin, 2016). The contextual models refer to external cues associated with latent states of the environment (Soltani & Koechlin, 2022). The interaction and integration of these models allow for an adapted behavioral

response and learning from experience. In this regard, prediction allows people to make inferences about what could happen depending on the course of action they decide to take. In turn, when performing actions, they learn from the associations previously made in order to think proactively about their future decisions, for example, when a conflict or a change of context is approaching, that implies changing behavioral strategy.

1.1. Cognitive control during conflict

Humans often are confronted with situations in which they must inhibit a response, for example, stop walking because the traffic light changed color, or making a decision, such as what transportation to use on a rainy day, according to their objectives and the context in which they find themselves. As described above, inhibitory control enables to inhibit of automatic responses, and proactive cognitive control allows to anticipate or predict an approaching conflict (conflict expectancy and conflict probability). The brain areas and neural mechanisms underlying cognitive control have been studied by different research groups. Senhav and collaborators developed a model of cognitive control which reports on 3 key stages from receiving a stimulus to responding to it. The first two stages, monitoring and specification, are carried out mainly by the anterior cingulate cortex, and the third stage, regulation, which accounts for the manifestation of cognitive control, by the lateral prefrontal cortex (Shenhav et al., 2013). This last

precedent has been supported by Koechlin and collaborators, who have verified the participation of the lateral prefrontal cortex in the manifestation of control (Koechlin et al., 1999; Koechlin et al., 2003; Koechlin and Summerfield, 2007). Proactive cognitive control has been associated with a specific brain area, the dorsolateral prefrontal cortex (DLPFC) (Lesh et al., 2013).

These brain processes, that underlie behavior, require cellular activity and neuronal communication. Specifically, electrical activity is essential for neuronal communication (Lin & Gervasoni, 2008). Neurons tend to fire in a coordinated way within a given neural network, this neural coordination results in complex oscillatory activity patterns. Therefore, unveiling the physiological mechanisms generating such complex oscillatory neural activity patterns is key to achieve a better understanding of how the brain operates in human behavior (Lin & Gervasoni, 2008).

Brain oscillations have been postulated as the candidate mechanism by which neurons could communicate cognitive control (Cavanagh & Frank, 2014; van Driel, 2015). Specifically, it has been described five main frequencies of brain oscillations: delta (1-4 Hz), theta (4-7 Hz), alpha (8-14 Hz), beta (14-30 Hz) and gamma (30-120 Hz) (Palva & Palva, 2018) each one with different physiological functions. While theta-band oscillatory neuronal activity has been tied to adaptive control mechanisms during response conflict (van Driel et al., 2015), it remains

unclear whether proactive cognitive control causally involves theta activity in lateral prefrontal areas in conflictive situations.

1.2. Learning

Human behaviors range from sequences of action that are nearly automatic (that can be performed without thinking) to planned and intentional actions (Graybiel, 2016). The transition between these behavioral routines is possible thanks to experiential learning (Graybiel, 2016) that makes anticipating and adapting to contextual changes possible. Specifically, learning is a process of modifying behavior or acquiring new behavior due to experience and updating models of the world in the face of contingency changes.

Different types of learning have been described according to their level of complexity and the factors they incorporate. Reinforcement Learning (RL) refers to a basic adaptive process consisting of adjusting online stimulus–action associations to the rewarding/punishing values of action outcomes (Koechlin, 2016). RL requires learning an internal model that specifies the outcomes resulting from actions, regardless of rewarding values, according to outcome likelihoods given actions and current states (Koechlin, 2016). Model-based Reinforcement Learning (model-based RL) allows behavior to be adjusted according to prior knowledge or experience about the world. Thus, as people

predict, select, act, and make decisions, they gain experience and form internal models of how the world works, which can be integrated into their future decisions. In turn, it allows them to adapt more quickly to external changes in contingencies and/or outcome values (Koechlin, 2016), allowing in subsequent situations predictions of possible actions to be adjusted to the context. Finally, Counterfactual Learning refers to a more complex type of model-based RL in which human beings have the ability to infer how an event could have unfolded differently, without directly experiencing this alternative reality. This counterfactual reasoning allows people to make sense of the past, plan courses of action, make emotional and social judgments, and guide adaptive behavior (Van Hoeck et al., 2015).

Considering that in everyday life most interactions occur repeatedly, inferences (thinking and planning) during decision making generate learning as people face the same or similar situations, allowing for a more adjusted response (Lee and Seo, 2016). During these repeated interactions, people may update not only their internal models about others' behaviors but also the value functions for their own actions (Lee and Seo., 2016). Because as they move about and act in the environment, the brain constantly updates not only the physical position and the stimuli, but also updates the value of the actions that they perform (Graybiel, 2016). Thereby, adaptive behavior is based on specific interactions among predictive models, selective models, and the context (Soltani & Koechlin, 2022).

At the brain level, the PFC combines these internal models to drive behavior and predict contextual changes (Soltani & Koechlin, 2022) for people to respond and obtain the results they expect. However, this prior analysis will not always lead to the expected results or reward, which is known as reward prediction error and refers to when the actual result (obtained) is different from the predicted result (prediction) (Schultz & Dickinson, 2000).

The study of RL models in experimental animals has demonstrated the involvement of the dopaminergic system in reward prediction error (Fiorillo et al., 2003; Babayan et al., 2018), hinting that the integrity of this system is fundamental for learning. On the other hand, it has been described that the behavioral flexibility inherent to learning is also related to the cognitive control system. Hence, the integrity and interaction of the reward and cognitive control systems enable flexibility in learning and decision-making behavior, and explains different behavioral processes (Braver et al., 2014).

1.3. Value-based decision making

Decisions, regardless of their level of complexity, are results of brain processes, which are based both on accumulated experience and social knowledge, as well as on predictions about how life will be in the future (Pearson et al., 2014). This allows people to analyze the possible courses of action and make a prediction of

the possible results to be obtained through each option, which will guide the selection of action. However, when there are rewards that mediate decision making, action selection may be biased by the reward. Decision making requires the involvement of executive functions that are integrated and processed in the prefrontal cortex to control and incorporate the experiences and the assessment of future consequences (Gordillo et al., 2011).

Specifically, value-based decision making refers to how people weigh costs and benefits to select an action and execute it (Frömer & Shenhav, 2022), choosing what means the most value for them. Value is related to choosing objects in the world and has a linkage between sensation and reward (Fellows, 2011): what sensation it provokes and how much reward it generates. Thereon, value is subjective because it is an internal construction of each individual.

1.4. Reward sensitivity during value-based decision making

Reward is the pleasant or positive affective experience obtained by performing an action (Gottfried, 2011), for example, what it feels like to drink water when you are very thirsty, to eat your favorite food, or to make a decision that delivers the results you expected. Hence, the reward is often used to describe an event that increases the probability of performing a behavior. However, it is not the only process that can influence behavior (Gottfried, 2011), because people integrate

internal objectives, goals, expectations of conflict, expectations of reward, value, among others, in their behavioral manifestation.

A reward can have different effects on people. For some it may motivate them to perform an action and for others it may be irrelevant. These differential responses are known as reward sensitivity. Hence, reward sensitivity refers to the degree to which an individual's behavior is motivated by reward-relevant stimuli, whereas sensitivity to punishment refers to the degree to which an individual's behavior is inhibited by punishment-relevant stimuli (Kim et al., 2015). Thus, depending on the effect that the stimulus has on the individual, it will guide his/her actions and learning.

As described above, people select an action according to their prediction of the outcome. In turn, decision making is guided by value. However, it is not clear whether the same lateral prefrontal machinery is involved in these processes of decision making as that described during prediction in conflictive situations. In addition, it is not clear how reward sensitivity affects behavioral control in the context of predictive and selective models, considering that expectation of reward may bias de choice.

This thesis aimed to study the brain processes underlying prediction during conflict and value-based decision making, integrating, and analyzing processes

such as proactive cognitive control, theta oscillatory activity, reward sensitivity and bias. This thesis presents 2 researches:

First research (section 3) addresses conflict and how the internal construction of prediction and its consequent expectation of conflict influences how people respond to a behavioral task. Considering that theta oscillatory activity is involved in proactive cognitive control processes, which can be associated with expectancy construction, this research focused on answering whether theta oscillatory activity plays a causal role in conflict expectancy. Second chapter (section 4) studies value-based decision making and how reward sensitivity modulates the choice of people during a task involving different amounts of rewards, and may deviate from the prediction, from experience and from what has been learned in the task context. Considering that reward is relevant in action selection, this research focused on answering How does reward sensitivity modulate the prediction and choice during value-based decision making?

Finally, in the conclusion section, the results are interpreted in an integrated analysis, and different perspectives and future steps of the work developed are presented.

2. RESEARCH TECHNIQUES

Social neuroscience studies the brain mechanisms underpinning human behavior by integrating the study of behavior with brain measurement such as Functional Magnetic Resonance Imaging (fMRI) and Electroencephalography (EEG), and intervention techniques such as Transcranial Magnetic Stimulation (TMS).

2.1. Functional Magnetic Resonance Imaging (fMRI)

fMRI is a non-invasive clinical and research procedure for functional brain mapping, whose signal is dependent on the level of blood oxygenation (BOLD signal). This technique makes it possible to identify areas of the brain involved in different tasks, from moving a hand to making a decision (Sell, 2007). The purpose of fMRI is to perform an anatomical localization of a functional process. During a mental process there is an increase in neuronal activity, which is supported by a local increase in blood flow. Thus, fMRI does not measure neuronal activity per se, but rather the metabolic demands evidenced by blood flow (Sell, 2007). The recording of cerebral hemodynamic changes assesses the function of regions responsible for sensory, motor, cognitive and affective processes in normal and pathological brains (Rosales, 2003).

fMRI acquisition technology can detect signal changes, which reflect the functional changes of blood oxygen, cerebral blood flow, and cerebral blood volume. BOLD fMRI is based on spatial segmentation of brain function (Jian et al., 2022) and is a local cerebral vascular oxygenation index. In BOLD imaging, deoxyhemoglobin acts as an intrinsic MRI contrast agent. MRI signal can detect the changes of deoxyhemoglobin content and functional activation (Jian et al., 2022).

2.2. Electroencephalography (EEG)

Electroencephalogram (EEG) is a noninvasive clinical and research procedure for studying neurophysiological activity of the brain (Kadian et al., 2022). EEG recording electrodes are placed over the scalp to study the brain's electrical activity of neurons in brain (Kadian et al., 2022; Rayi & Murr, 2022), measuring the absolute electrical potentials generated by the neurons of the underlying cerebral cortex (Rayi & Murr, 2022). The most frequently used method to classify EEG waveforms is the frequency. The most commonly encountered waveform frequencies in EEGs are alpha, beta, theta, and delta (Rayi & Murr, 2022).

EEG is used to study the activity of brain areas and networks in processes such as attention and working memory (Huynh & Kerzel, 2022), cognitive control

(Cavanagh and Frank, 2014; van Driel, 2015), and is even used in conjunction with other research techniques, such as TMS (Albouy et al., 2017).

2.3. Transcranial Magnetic Stimulation (TMS)

Transcranial magnetic stimulation (TMS) is a neurostimulation and neuromodulation technique based on the principle of electromagnetic induction of an electric field in the brain: a magnetic field penetrates the skull and meninges and causes a secondary electric current in the brain tissue that produces neuronal depolarization. This technique can be applied in a single stimulus, in pairs of stimuli separated by intervals or in trains of repeated stimuli at various frequencies, depending on the objective and study design (Rossi et al., 2009; Rossini et al., 2015).

The stimulus is applied through a flat coil, with an outer diameter of 100 mm. The magnetic field flux lines pass perpendicular to the plane of the coil (Hallet., 2000; Ziemann., 2017). The magnetic stimulus coming out of the coil, located on the scalp, stimulates the axons of the neurons (Rossini et al., 2015). The biological effect will depend on the neuronal circuits involved and may be anatomically different from the site where the axons are activated by the TMS-induced electric field (Rossini et al., 2015). Stimulus intensity TMS is calculated as a percentage of motor threshold, depending on the objective and design of the study. Motor

threshold is defined as the minimum intensity of motor cortex stimulation necessary to obtain a reliable minimum amplitude motor evoked potential in the target muscle (muscle contraction distinguishable by visual inspection or electromyography).

TMS has been combined with electroencephalography (EEG), which allows real-time monitoring of brain waves, in addition to neuroimaging techniques such as structural magnetic resonance imaging (MRI) and functional magnetic resonance imaging (fMRI) (Rossi et al., 2009). Neuronavigation devices that integrate resonance imaging allow precise localization of the magnetic coil with respect to the anatomy of the brain, as they use brain images of each individual. The subject's head and fMRI are registered in a common reference space using a set of anatomical landmarks (fiduciary: nose and ears), this allows for co-registration of images and actual anatomy and three-dimensional orientation by visual navigation (Rossini et al., 2015).

3. RESEARCH 1

A causal role for the lateral prefrontal theta oscillation in the expectancy of conflicting stimuli in humans

María Paz Martínez-Molina[1], Gabriela Valdebenito-Oyarzo[1], Patricia Soto-Icaza[1], Francisco Zamorano[1,2], Alejandra Figueroa-Vargas[1], Ximena Stecher[2], César Salinas[2], Antonie Valero-Cabré[3,4,5], Rafael Polania[6] & Pablo Billeke[1].

[1] Laboratorio de Neurociencia Social y Neuromodulación, Centro de Investigación en Complejidad Social, (neuroCICS), Facultad de Gobierno, Universidad del Desarrollo, Santiago, Chile.

[2] Departamento de Imágenes, Clínica Alemana de Santiago, Chile.

[3] Causal Dynamics, Plasticity and Rehabilitation Group, FRONTLAB team, Institut du Cerveau et de la Moelle Epinière (ICM), CNRS UMR 7225, INSERM U 1127 and Sorbonne Université, Paris, France.

[4] Laboratory for Cerebral Dynamics Plasticity and Rehabilitation, Boston University, School of Medicine, Boston, MA, USA

[5] Cognitive Neuroscience and Information Technology Research Program, Open University of Catalonia (UOC), Barcelona, Spain

[6] Decision Neuroscience Lab, Department of Health Sciences and Technology, ETH Zurich, Zurich, Switzerland.

3.1. Summary

Subjects have the ability to anticipate or predict conflictive situations and give an adapted response through experience and learning from environmental changes. Proactive cognitive control is a brain mechanism necessary to integrate this experience and build a conflict expectancy. Studies with electroencephalography have described that oscillations in theta band over the frontal midline are associated with cognitive control. On the other hand, neuroimaging has shown that lateral and medial prefrontal cortex are associated with cognitive control. Specifically, proactive cognitive control has been associated with the dorsolateral prefrontal cortex (DLPFC). However, it is not clear if theta activity in lateral prefrontal areas causally participate in proactive cognitive control processing necessary for the construction of the prediction and the conflict expectancy.

We have hypothesized that theta oscillatory activity in the lateral prefrontal cortex (lPFC) plays a causal role in conflict expectancy in humans. To evaluate this hypothesis we performed 3 experiments, using tasks that produce conflict expectancy. First, we fit conflict expectancy with behavioral models, then we used fMRI to identify brain areas implicated in this activity and finally we study whether rhythmic non-invasive brain stimulation induces theta activity during the task. Results indicated that conflict expectancy increases reaction time, that there is brain activity in the superior frontal gyrus (SFG) and in the inferior frontal junction

(IFJ) and that brain stimulation in SFG enhances conflict expectancy, showing a causal role of lPFC in conflict expectancy.

3.2. Introduction

In conflictive situations, for example, to stop an automated action or to solve an unexpected event, subjects have the ability to give a response adapted to the context. This happens because their experience and learning of environmental changes allows them to predict what might happen (possible outcomes). Thus, as situations repeat themselves, they are able to anticipate or predict conflict situations and construct a conflict expectancy. Conflict expectancy is internally constructed, that is, an internal estimation of the probability that a conflictive stimulus or situation will occur. Hence, as these situations are repeated, people learn from the environment, which allows them to be attentive in order to respond appropriately to future situations.

In these behavioral processes it is necessary to involve executive functions at the prefrontal cortex level that allows to subjects to coordinate their thoughts and actions according to their objectives (Braver, 2012; Koechlin et al., 2003; Shenhav et al., 2016), and to make adjustments to the behavior to potential changes in the environment (Braver, 2012; Chang et al., 2017; van Driel, 2015) known as cognitive control. Cognitive control can be reactive or proactive in

nature (Irlbacher, 2014). Reactive control is associated with the resolution of interference or conflict, so it starts after such interference appears (Irlbacher, 2014) for example, inhibitory control, which allows stopping an automatic response. Proactive control involves the anticipation and prevention of interference or conflict prior to its occurrence (Irlbacher, 2014) thanks to experiential learning about how the world works.

Electroencephalographic evidence has shown that oscillatory activity in theta band over frontal midline are associated with detecting, communicating, and implementing cognitive control (Cavanagh y Frank, 2014; van Driel, 2015). On the other hand, neuroimaging studies show that the lateral prefrontal cortex plays a central role in the regulation of cognitive control, controlling behavior according to the current perceptual context and the temporal sequences in which stimuli occur (Koechlin et al., 1999; Koechlin et al., 2003). Specifically, proactive cognitive control has been associated with the prefrontal dorsolateral cortex (DLPFC) (Lesh et al., 2013), however, a causal account of prefrontal theta oscillatory activity in proactive cognitive control during conflict expectancy is still unclear.

Studies with Transcranial Magnetic Stimulation (TMS) at theta frequency over parietal cortex have shown that it is possible to induce such brain activity to favor associated cognitive processes (Albouy et al., 2017). Hence, with TMS it is

possible to train oscillatory activity and to establish a causal relationship between brain oscillations and cognitive activity. TMS is a neuromodulation technique, which can excite or inhibit brain areas according to the intensity of the stimulus (Rossi et al., 2009). TMS has a good safety profile (Malavera et al., 2014), so it is being used as a research technique to study human behavior and associated brain mechanisms (Albouy et al., 2017; Beynel et al., 2020; Baumgartner et al., 2011; Buckholtz et al., 2015).

Integrating this background, we tested the hypothesis that theta oscillatory activity in the lateral prefrontal cortex plays a causal role in conflict expectancy. We expect at a behavioral level, that reaction time increases when the expectancy of a conflicting event increases. At a brain level, we expected that lateral prefrontal brain network correlates with the expectancy of conflict events, and that non-invasive brain stimulation at theta frequency over lateral prefrontal cortex increases the effect of the expectancy of conflicting events. In order to test these hypotheses, we carried out three experiments using tasks that produce expectancy for conflict stimuli. In the first one, we modeled reaction time in order to identify the computation of expectancy of conflict stimuli, in the second one, by using a fMRI we identify brain areas that correlate with such computation, and finally, by the means of TMS, we tested the causal account of theta prefrontal activity in the expectation of conflict (Figure 3-1).

3.3. Methods

3.3.1. Participants

Fifty-nine healthy subjects, who meet inclusion criteria (Appendix nº 1), participated in this research approved by the Ethics Committee of the Universidad del Desarrollo, Chile. In the first experiment, 30 subjects (15 women, 18-20 years) participated in the behavioral session. In the subsequent experiments, another sample of subjects participated as follows. In the experiment 2, 26 subjects (15 women, 18-35 years) participated in the fMRI session, and in the experiment 3, 24 subjects (13 women, 18-35 years) participated in the EEG - TMS sessions. A total of 18 subjects participated in both experiments 2 and 3. All participants gave informed consent. Experiments were conducted in the Social Neuroscience and Neuromodulation Laboratory at the Centro de Investigación en Complejidad Social (neuroCICS) at the Universidad del Desarrollo and the Unidad de Imágenes Cuantitativas Avanzadas (UNICA) at the Clínica Alemana de Santiago.

3.3.2. Experimental design

For the first experiment, subjects participated in the GNG task. With these data, different behavioral models were tested to explain conflict expectancy and

variations in reaction time. The best-fitted model was used to analyze the data from experiment 3 (Figures 3-1, 3-4, and 3-5).

For the second experiment, subjects participated in a fMRI session and solved the MSIT task. Imaging data were analyzed using FSL 5.08 (Figure 3-3) integrating regressors from behavioral modeling of the MSIT task to identify target sites in experiment 3.

In the third experiment, subjects participated in two sessions of TMS-EEG (Figure 3-4 and 3-5) while they performed the GNG task. In one of the sessions the stimulation was delivered over the superior frontal gyrus (SFG) and in the other session was in the inferior frontal junction (IFJ). The stimulation site for each session was randomized and the sessions were balanced.

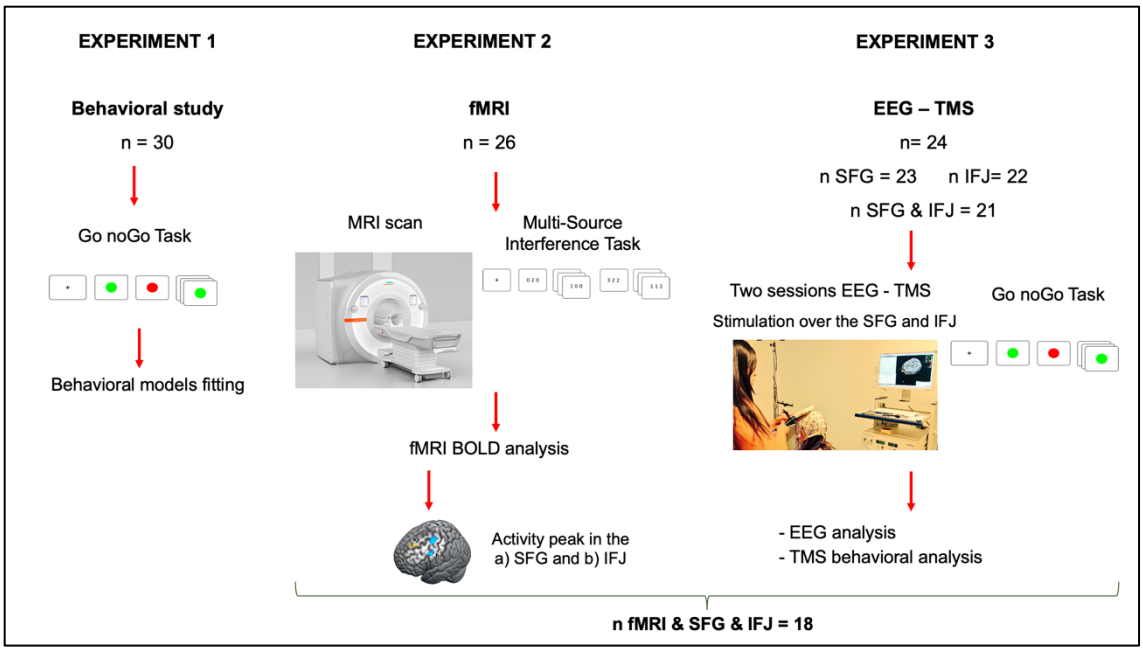

Figure 3-1: Experimental design. Three experiments were carried out. Experiment 1: Behavioral study (n=30) with GNG task. Experiment 2: fMRI session with MSIT task (n=26). Experiment 3: Two randomized EEG-TMS sessions, one in the SFG and other in the IFJ with GNG task (n=24). GNG: Go Nogo; fMRI: Functional Magnetic Resonance Imaging; SFG: Superior Frontal Gyrus; IFJ: Inferior Frontal Junction; EEG: Electroencephalography, TMS: Transcranial Magnetic Stimulation.

3.3.3. Tasks

Go Nogo Task: During the behavioral and TMS-EEG experiments (experiments 1 and 3), participants completed the GNG task, which involved viewing green or red stimuli on a screen. Participants were instructed to press a keypad button for

the green stimuli (Go stimulus) but not to press the button for the red stimuli (Nogo stimulus). In the behavioral experiments (experiment 1), participants completed two blocks, each consisting of 150 trials (Figure 3-1). In the TMS-EEG sessions (experiment 3), participants completed four blocks, with each block containing three sub-blocks of 100 stimuli. The stimuli were separated into five runs of 20 stimuli each. Before the start of each 20-stimuli run, 10 TMS pulse series were applied for 2 seconds in different patterns: rhythmic (5 Hz), arrhythmic, or sham (Figure 3-4). Behavioral results of the GNG task were analyzed by fitting different models to estimate the probability of conflict and the expectation of conflict occurrence.

MSIT Task: During the fMRI session of the experiment 2, participants were presented with a set of stimuli consisting of three numbers and were asked to identify the number that was different from the other two using a keypad. The task included congruent and incongruent trial sequences of variable duration (3 to 8 trials). During congruent trial sequences, the different number matched their position on the keypad. In incongruent trial sequences, which were associated with high difficulty, the number and position did not match (Figure 3-3).

3.3.4. Behavioral analysis

Behavioral analysis was conducted using a Hierarchical Bayesian approach, which leverages the aggregated information from the entire population sample to inform and constrain the parameter estimates for each individual. This approach incorporated two levels of random variation: the trial level (i) and the participant level (s). Models were compared using the Deviance Information criterion (DIC). All the models were fitted to the reaction times (RT) and were adjusted using R and JAGS software. Given its proposed influence on the speed-accuracy tradeoff that underlies cognitive control (Lerche, & Voss, 2019), we assumed that all regressors would affect the drift-diffusion model's boundary, and we set the bias parameter to 0.5. Additionally, we examined the effect of cognitive control (CC) on accuracy by constraining the model to include reaction time in the current trial (t) and accuracy (Acu) of the Nogo stimulus in the subsequent trial (where applicable) as follows.

$$CC = \beta_1 Exp + \beta_2 pCE + \beta_3 pOE \quad \text{Eq. 1}$$

$$RT \sim \beta_0 + CC_t \quad \text{Eq. 2}$$

$$Acu \sim \beta_{a_0} + \beta_{a_1} CC_{t-1} \quad \text{Eq. 3}$$

In the TMS-EEG experiment, we used the following model:

Eq. 1

$$CC = \beta_1 Exp + \beta_2 pCE + \beta_3 pOE + \beta_4 Exp * TMS + \beta_5 Exp * TMS_{theta} + \beta_6 Exp * TMS_a + \beta_7 Exp * TMS_{theta*a}$$

Eq. 2

$$RT \sim \beta_0 + CC_t + \beta_8 TMS + \beta_9 TMS_{theta} + \beta_{10} TMS_a + \beta_{11} TMS_{theta*a}$$

Eq. 3

$$Acu \sim \beta_{a0} + \beta_{a1} * CC_{t-1} + \beta_{a2} TMS + \beta_{a3} TMS_{theta} + \beta_{a4} TMS_a + \beta_{a5} TMS_{theta*a}$$

where TMS represents the main effect of TMS stimulation, TMS_{theta} represents the effect of theta rhythmic stimulation, TMS_a the stimulation in SFG and, $TMS_{theta*a}$ represent the specific effect of theta stimulation over SFG.

All beta parameters were parameterized using normal distributions, while the alpha parameter (learning rate) was parameterized using a beta distribution. At the participant level, the model parameters were constrained by group-level hyperparameters. We assumed flat distributions for each parameter at the highest level of the hierarchy (hyperparameters).

We used the Gibbs sampler and Markov Chain Monte Carlo technique to perform posterior inference on the parameters in our hierarchical Bayesian models. To ensure convergence, we drew a minimum of 2,000 samples from an initial burn-in sequence, followed by 5,000 new samples using three chains generated from different random number generators with different seeds. We thinned the resulting sample by a factor of 5 to reduce autocorrelation among the final samples for each parameter, resulting in a final set of 3,000 samples. Gelman-Rubin tests confirmed the convergence of all latent variables in our models, with a statistic near 1 indicating convergence to the target posterior distribution.

Due to computational constraints in the TMS-EEG experiment, we estimated the alpha parameter using 20% of the data (the fifth run of each sub-block) and used this individual alpha parameter to estimate the remaining parameters using the complete data series.

3.3.5. Anatomical Data

All participants of the experimental 2 and 3 underwent a 3D anatomical MPRAGE T1-weighted and T2-weighted Magnetic Resonance Imaging scan on a 3T Siemens Skyra scanner (Siemens AG, Erlangen, Germany). The anatomical volume consisted of 160 sagittal slices of an isotropic voxel (1x1x1 mm), covering the entire brain. The T1-weighted / T2-weighted corrected anatomical MRI was

used to extract the scalp and cortical surfaces using a pipeline available from the Human Connectome Project. This process yielded a surface triangulation for each envelope (Fischl, 2012), resulting in individual high-resolution cortical surfaces with approximately 300,000 vertices per surface. These surfaces were then down-sampled to approximately 5,000 vertices. In addition, a five-layer segmentation based on T1-weighted / T2-weighted corrected and T2-weighted images were performed using the algorithm implemented by the SimNIBS tool and SMP12.

3.3.6. Functional MRI Data

During the fMRI experiment, functional images were acquired using a weighted echo-planar T2* sequence while participants performed the MSIT task (3x3x3 mm voxels). The acquired volumes of each participant were then coregistered to the 2-mm standard imaging using the nonlinear algorithm implemented in FSL. To analyze the imaging data, a model was used that isolated the activity associated with the expectancy of conflict using three regressors of interest: conflict stimuli, non-conflict stimuli, and conflict expectancy (Figure 3-3). Second-level activation maps were calculated using a mixed-effects model in FSL, which evaluated two contrasts: conflict higher than no conflict and expectancy of conflict stimuli (Exp=Q, Figure 3-3). Cluster correction was applied with a cluster

threshold detection (CTD) of $z>3.01$ and a significance level of $p<0.05$ using FLAME1.

3.3.7. TMS-EEG

In both TMS-EEG sessions, the stimulation coordinates were individually set to each subject's brain space. One session was conducted according to the group peak of contrast 1 in the SFG, while the other session was based on the peak of contrast 2 in the IFJ (Figure 3-3). The induced electromagnetic field was aligned perpendicular to the gyrus, based on the individual anatomy, and the stimulation intensity was set to the maximum tolerance level for each subject in this area, ranging from 80% to 120% of their motor threshold, as previously measured. A 70-mm double coil (PMD70) was used for TMS pulses, which were delivered in three conditions: the theta condition (10 rhythmic pulses every 200 ms), the no-theta condition (10 arrhythmic pulses within 2 seconds), and the sham condition. Theta and non-theta stimulation were performed at specific sites for each participant. Sham stimulation was performed in the same area but with the coil tilted, so participants did not receive actual stimulation. EEG recordings were obtained throughout the task in both sessions.

3.3.8. TMS behavioral analysis

A model over reaction times (RT) for Go stimuli was adjusted in R program with different regressors to explain the effect of TMS: sequence of go stimuli, TMS, TMS cerebral area, the interaction of go stimulus sequence with TMS, and interaction of go stimuli sequence with the theta frequency TMS.

3.3.9. TMS electrophysiological analysis

For both sites of stimulation, EEG power was modeled in two-time windows: one between the last TMS pulse and the first Go stimulus and the other around Go stimuli. These analyses were performed using the LAN package (https://github.com/neurocics/LAN_current) in Matlab software (https://matlab.mathworks.com/).

In the analysis between the last TMS pulse and the first Go, data from each participant were preprocessed by interpolating signal segments between TMS pulses and decreasing the sampling rate to 1000. We removed the segment between -10 to 30 ms around each TMS stimulation and replaced it with an inverse-distance weighted interpolation [Y = sum(X/D^3)/sum(1/D^3)] plus a Gaussian noise with the standard deviation extracted to a reference period set to be 55 to -15 ms before the respective first TMS pulse and 0 of the mean. Then,

the raw signal was segmented -0.5 to 1.5 seconds around the last TMS pulse. Automatic artifact detection was used to remove noisy trials, including voltage threshold (150 uV, and 3 std dev.) and FFT-amplitude threshold (power spectrum greater than two std. dev. for more than 10% of the 0.5-to-40-Hz spectrum). Then the independent component analysis (ICA) was used to remove components such as blinks and eye movement. A final manual review of all trials was performed to check for remaining noise trials, and mastoid electrodes were removed. A Morlet-type frequency analysis was performed (5-cycle width), and a model with two dummy regressors was fitted for each participant: Theta TMS and No-Theta TMS.

In the analysis around Go stimuli, data from each participant were preprocessed by decreasing the sampling rate to 1000. Go and Nogo stimuli were segmented, noisy trials were removed by automatic artifact detection, and ICA was performed as in the preceding analysis. Mastoid electrodes were removed, and a manual review of all trials was carried out. The channels noisy were interpolated and Morlet-type frequency analysis was performed. A model with seven regressors was fitted for each participant: Go, Nogo error probability, Go error probability, Go sequence-TMS interaction, Go sequence-TMS Theta interaction, TMS, and TMS Theta interaction.

Second-level analysis was performed in both time windows by incorporating the models of each participant to model the power according to EEG and analyze brain electrical activity according to areas, conditions, times, and frequencies.

3.4. Results

3.4.1. Experiment 1, Behavioral: Modeling Expectancy of conflict

For the GNG task, we expect subjects to adjust the cognitive control concerning the estimated probability of occurrence of conflicting stimuli (Nogo stimuli) and the expectancy of this occurrence in context of past stimuli. For probing this and based on prior work (Zamorano et al., 2014; Zamorano et al., 2020), we tested several models in a sample of subjects who carried out the GNG task without TMS stimulation. Then, we selected the best-fitted model to evaluate TMS effects.

We used reaction time as a proxy of cognitive control and tested two linking functions for each model, namely a lognormal and a Wiener (Drift Diffusion Model, Vandekerckhove et al., 2011) distributions. We use in a null model (M0) all relevant regressors without including the expectancy of the occurrence of conflicting stimuli. These regressors included the expected slowing of the

response following an error separated by the type of error, namely previous commission error (pCE) and previous omission error (pOE).

M0: $$RT \sim \beta_0 + \beta_2 pCE + \beta_3 pOE$$ Eq. 1

Then, in the first cognitive model (M1), we assume that the expectative of conflict stimuli (Exp) linearly increases in relation to the number of consecutive Go stimuli in a sequence (nSeq) of stimuli. That is, Exp = nSeq.

M1: $$RT \sim \beta_0 + \beta_1 Exp + \beta_2 pCE + \beta_3 pOE$$ Eq. 2

In the second model (M2), the expectative of conflict stimuli (Exp) is given by the rational calculation of the complementary probability of the occurrence of the given sequence of Go stimuli as expressed in the following equation:

M2: $$Exp = 1 - ((1 - Q)^{(nSeq-1)})$$ Eq. 3

In the preceding equation, Q represents the rate of occurrence of conflicting stimuli, and for the M2 model was set to 0.25 (the programmed rate of Nogo stimuli). The -1 of the exponent indicates the impossibility, known by the subject, of the occurrence of two consecutive Nogo stimuli. In other words, the probability of the occurrence of Nogo stimuli in the first position in the sequence is zero.

In the third model (M3), the rate of occurrence of a conflict stimuli Q is learned by the subject following a learning algorithm as follows:

$$\text{M3:} \qquad Q_t = Q_{t-1} + \alpha(C_{t-1} - Q_{t-1}) \qquad \text{Eq. 4}$$

In the preceding equation, α represents the learning rate, and C_{t-1} indicates the presence (C_{t-1}=1) or absence (C_{t-1}=0) of a conflicting stimulus in the preceding trial.

3.4.2. Experiment 1, Behavioral: Conflict expectancy effect for GNG Task

We first tested a general behavioral index of expectancy modulation by contrasting the reaction time (RT) for the first two "go" stimuli in a sequence with the other "go" stimuli. This division generated a relatively balanced number of trials for the contrast (43% vs 57%). We found that the RTs for the first trials of a sequence were faster than those of the last trials (327 ms vs 341 ms, Wilcoxon test, p=0.0001, n=30). Additionally, we observed that the probability of faster trials (RTs less than the median of all RTs) occurring in the first trials of sequences was significantly higher than expected by chance (mixed logit model, beta estimate=0.44, SEM=0.1, z=4.3, p=1.6e-5, n=7575, df=7570).

We then applied the models described in the previous section to evaluate which formulation best explained the mechanism underlying the increase in reaction time (RT) associated with the expectancy of conflict stimuli (Table 3-1). Among the different models tested, the best-fitted model was M3 using the drift-diffusion model (DDM) with Wiener distribution. In this model, the regressor of conflict expectancy had a significant impact on reaction time (beta Expectancy mean = 44.7, 95% high-density interval (HDI) of [35 54], p_{MCMC} <0.001, p_{MCMC} is a p-value derived by comparing the posterior distributions of the estimated parameters sampled via Markov Chain Monte Carlo). Additionally, commission error, which refers to the previous error in a "Nogo" stimulus, was found to significantly increase the reaction time for the "Go" stimuli (beta pCE mean = 19.3, HDI = [8 29.3], p_{MCMC}<0.001). However, no significant effects were found for a previous omission error (beta pOE mean = -3.6, HDI = [-13 6], p_{MCMC}=0.49, Figure 3-2 D). The posterior distribution of the learning rate was a mean of 0.29 and an HDI of [0.22 0.37]. Then, we test if the expectancy of conflict stimuli would have a significant influence on inhibitory control accuracy, as measured by the proportion of successful Nogo responses. Results showed a significant positive effect of expectancy on inhibitory control accuracy ($beta_{a1}$ $\beta\alpha_1$ mean= 1.1, HDI=[0.17 1.98], p_{MCMC}=0.012).

In summary, individuals adjust their RT according to the expectancy of the conflict stimuli. Such processing, which could reflect cognitive control allocations, involved learning from past experiences in the environment.

Table 3-1: Summary of the models and their indicators of adjustment.

Model	**Linking function**	**Free parameter**	**DIC**	**LOO**
M0 null	lognormal	4 (3 betas, sigma)	427.1	480.1
	wiener	5 (3 betas, drift, tau)	233.0	257.5
M1 linear	lognormal	5 (4 betas, sigma)	286.7	326.4
	wiener	6 (4 betas, drift, tau)	102.1	109.6
M2 Exp	lognormal	5 (4 betas, sigma)	243.6	279.5
	wiener	6 (4 betas, drift, tau)	71.7	71.3
M3 exp+LR	lognormal	6 (4 betas, alpha, sigma)	161.5	24.1
	wiener	7 (4 betas, alpha, drift, tau)	0 (reference)	0 (reference)

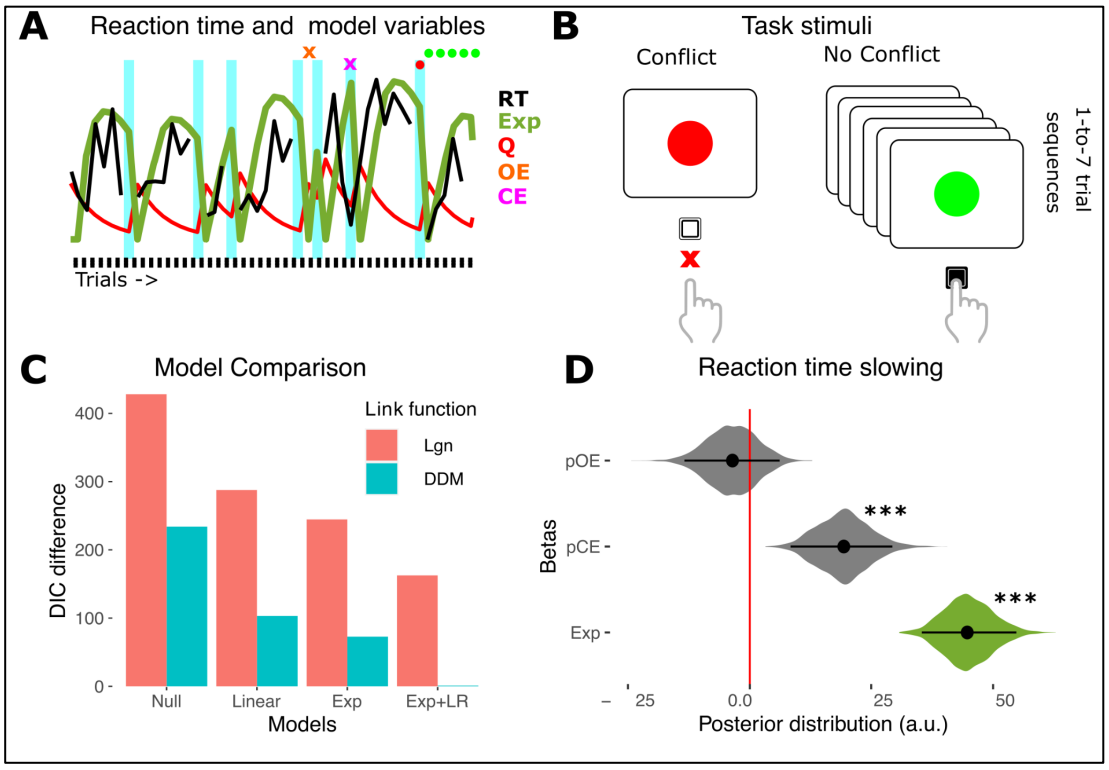

Figure 3-2: Behavioral analysis of GNG Task. A) Single trials example of reaction time and model variables. B) GNG Task. C) Model comparison. D) Posterior distribution of model parameters.

3.4.3. Experiment 2, MRI: Modeling MSIT

Our next objective was to identify the brain areas responsible for computing the expectancy of conflict stimuli. To achieve this, we utilized the fMRI technique due to its high spatial resolution. However, the slow dynamics of hemodynamic responses precluded using fast stimuli presentation tasks and, therefore, the generation of sequence effects, as seen in the GNG task (Zamorano et al., 2014).

To overcome this limitation, we designed a task and analysis based on the same rationale as the behavioral experiments adapted for fMRI. Specifically, we used the MSIT task, which involved variable sequences of congruent and incongruent stimuli, to obtain a balanced number of trials for the contrast. Furthermore, for the analysis, we used expectancy as equivalent to the probability of conflict (i.e., Exp = Q, instead of Eq. 3, Figure 3-3A) as has been done in other research studies with large stimuli intervals (Chang et al., 2017; Fu et al., 2022). Following this rationale, we tested if subjects adjusted their reaction time according to the expectancy of the occurrence of conflict stimuli. We applied the best-fitted model for the GNG task (M3 using DDM) for this. The results showed that the probability of conflict significantly increases the RT in the MSIT task (beta Expectancy mean = 1.07, HDI: [0.74 1.43], p_{MCMC}<0.001). As expected, conflict stimuli are slower than no conflict stimuli (beta Conf mean = 0.32, HDI: [0.22 0.41], p_{MCMC}<0.001). To summarize, in the MSIT task, it is possible to identify homologous expectancy processing to that specified in the GNG task.

3.4.4. Experiment 2, MRI: Brain activity correlating with expectancy of conflict

To evaluate the brain areas in which activity correlated with the expectancy of conflicting stimuli, we modeled the BOLD activity using the expectancy of conflict for each trial, along with the presentation of a conflicting or non-conflicting

stimulus in the current trial. The population analysis of BOLD signals showed that the regressor of expectancy (Exp) exhibited a significant correlation with the activity in the SFG (Contrast 1, Figure 3-3C) and the medial parietal cortex. Furthermore, the contrast between conflict and non-conflict stimuli presented a significant correlation with the activity in the frontal eye field (FEF) and inferior frontal junction (IFJ) in the lateral prefrontal cortex, as well as other brain areas (Contrast 2, Figure 3-3C).

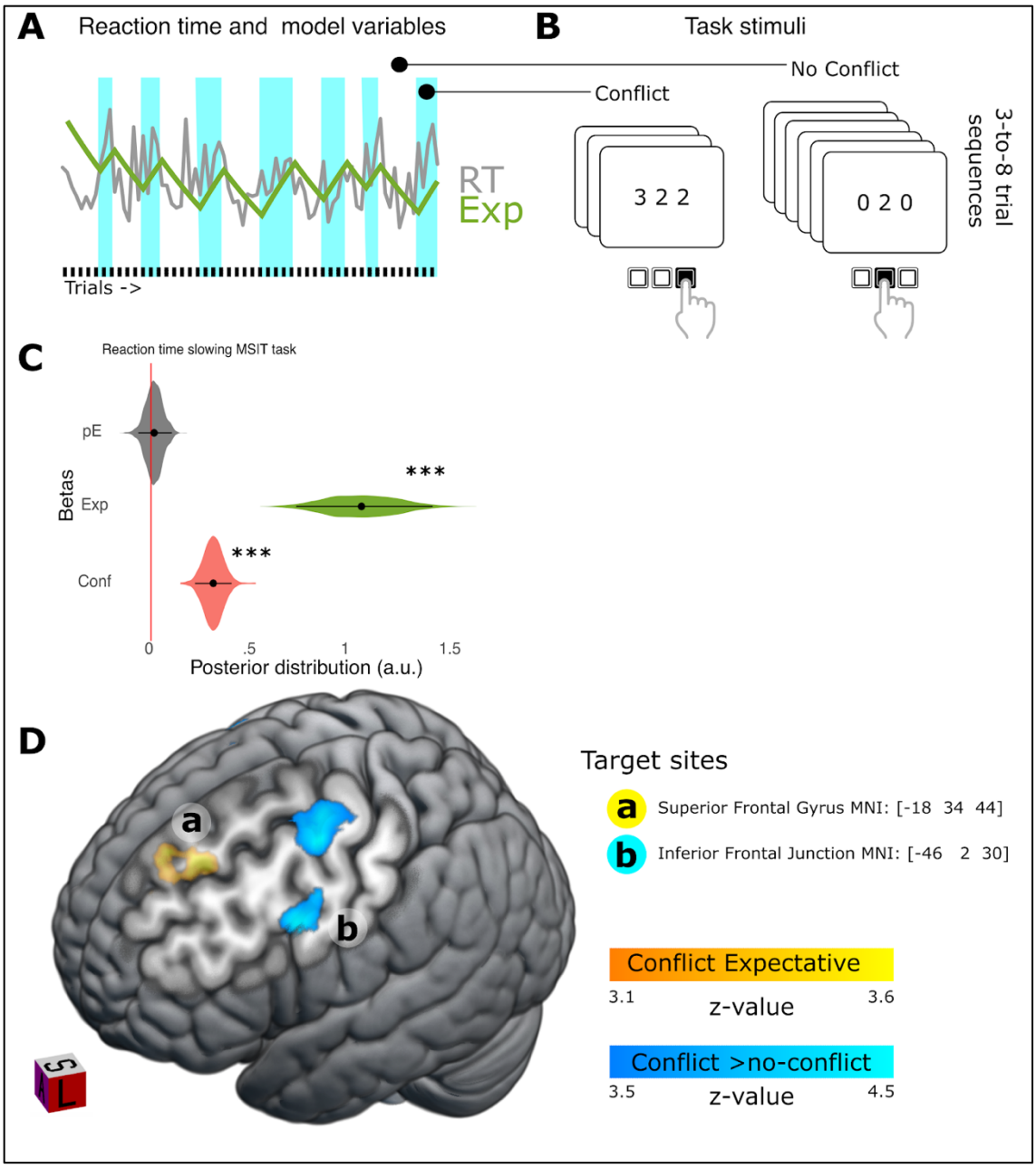

Figure 3-3: MRI experiment results. A) Single trials example of reaction time and model variables. B) MSIT Task. C) Posterior distribution of model parameters. D) Brain activity related to the expectation of conflict in the lateral prefrontal cortex

(yellow) and conflict stimulus processing (blue). Letters a and b indicate the target sites for TMS experiments.

3.4.5. Experiment 3, EEG-TMS: SFG TMS at theta frequency enhance conflict expectancy during GNG Task

We aimed to investigate the causal relationship between theta activity in the SFG and the expectancy of conflict. To this end, we conducted a TMS-EEG experiment using TMS stimulation before each 20-stimuli run of the GNG task. Since both lateral prefrontal cortex and theta activity have been associated with proactive cognitive control (Lesh et al., 2013; Zamorano et al., 2017; Zamorano et al., 2020) we selected 5Hz frequency for stimulation and used arrhythmic TMS and sham stimulation as control. We stimulated two different areas, SFG and IFJ, in separate sessions to test their involvement in the expectancy of conflict (SFG) controlling for possible effects in inhibitory control (IFJ; Barber et al., 2013; Sundermann, & Pfleiderer, 2012).

Using the peak activity in the SFG as our target site, we explored the causal relationship between theta activity and expectancy of conflict (Table 3-2 and Figure 3-4B). Our behavioral results revealed that participants exhibited slower RT as the expectancy of Nogo stimuli increased. Specifically, we found that participants during sham stimulation in both sessions showed similar behavior to

those in the behavioral experiment, increasing their reaction time in response to the expectancy of conflict stimuli ($beta_1$ Exp mean: 15.6, HDI: [11.5, 18.9], $p < 0.001$). Regarding TMS stimulation, we observed that the main effect of TMS, regardless of its frequency or target site, did not significantly impact participants' RT ($beta_8$ TMS mean: -0.07, HDI: [-1.7, 1.6], $p = 0.93$; $beta_4$ Exp*TMS mean: 0.25, HDI: [-4.6, 4.7], $p = 0.91$). However, we found that theta stimulation over the SFG specifically resulted in an expectancy-related increase in RT. This was evidenced by a significant interaction between expectancy, TMS, theta, and site "a" ($\beta_7 Exp * TMS_{theta*a}$, $beta_7$ Exp*$TMS_{theta*a}$ mean= 8.4, HDI= [1.9 13.7], $p_{MCMC} = 0.006$; Figure 3-4B). In relation to the accuracy, the TMS stimulation had no direct effect on the accuracy ($beta_{11a}$ TMS_a mean= 0.057, HDI = [-0.25 0.37], p_{MCMC}=0.7). However, we did observe that TMS stimulation modified the impact of expectancy on the accuracy of Nogo stimuli ($beta_{a7}$ Exp*$TMS_{theta*a}$ mean= 0.36, HDI = [0.06 0.66], p_{MCMC}=0.006; $beta_{1a}$ Exp: mean= 0.63, HDI = [0.29 0.97], p_{MCMC}<0.001;). The findings suggest that theta stimulation over SFG may modulate specifically cognitive processes related to conflict expectancy.

Table 3-2: Drift Diffusion Model over reaction time (RT) for Go stimuli related to conflict expectancy.

	Lower95	Median	Upper95	Mean	p	psrf
beta0	121.1	123	128.1	125	<0.001	1.040178
beta Exp	11.1	15	18.7	15.0	<0.001	1.002064

beta pCE	-2.07828	1.764545e+00	6.07973	1.780214e+00	0.4	1.000819
beta pOE	-10.21500	-6.452025e+00	-2.84427	-6.470562e+00	0.001	1.001397
beta Exp:TMS	-4.24812	1.384600e-01	5.20368	1.928212e-01	0.91	1.009051
beta Exp:TMS:th	-7.20015	-2.670380e+00	1.79882	-2.657305e+00	0.19	1.006101
beta Exp:TMS:A	-6.75441	-1.341885e+00	4.64548	-1.259575e+00	0.6	1.055828
beta Exp:TMS:th:A	1.88871	7.898940e+00	13.80720	7.956209e+00	0.006	1.008787
beta TMS	-1.85972	-6.374320e-02	1.63240	-7.688773e-02	0.93	1.003714
beta TMS:th	-2.89258	-7.686270e-01	1.25154	-7.825213e-01	0.5	1.000724
beta TMS:A	-5.81616	-7.779905e-01	4.26365	-7.571793e-01	0.82	1.046268

3.4.6. Experiment 3, EEG-TMS: TMS stimulation in Superior Frontal Gyrus increases endogenous theta oscillation

To determine whether TMS theta stimulation induces oscillatory brain activity in the theta range, we conducted a power analysis of the EEG signal. We examined the time windows after TMS stimulation and just before task stimuli presentation and found a specific effect of TMS stimulation. Rhythmic theta stimulation over the SFG produced a significant increase in theta activity compared to both sham and arhythmic stimulation (Figure 3-4C). In contrast, we observed that both rhythmic and arhythmic stimulation over the IFJ generated an increase in delta activity which was not different between them (Figure 3-4C). Overall, TMS theta stimulation can generate brain oscillatory activity in the theta range depending on the stimulated brain region.

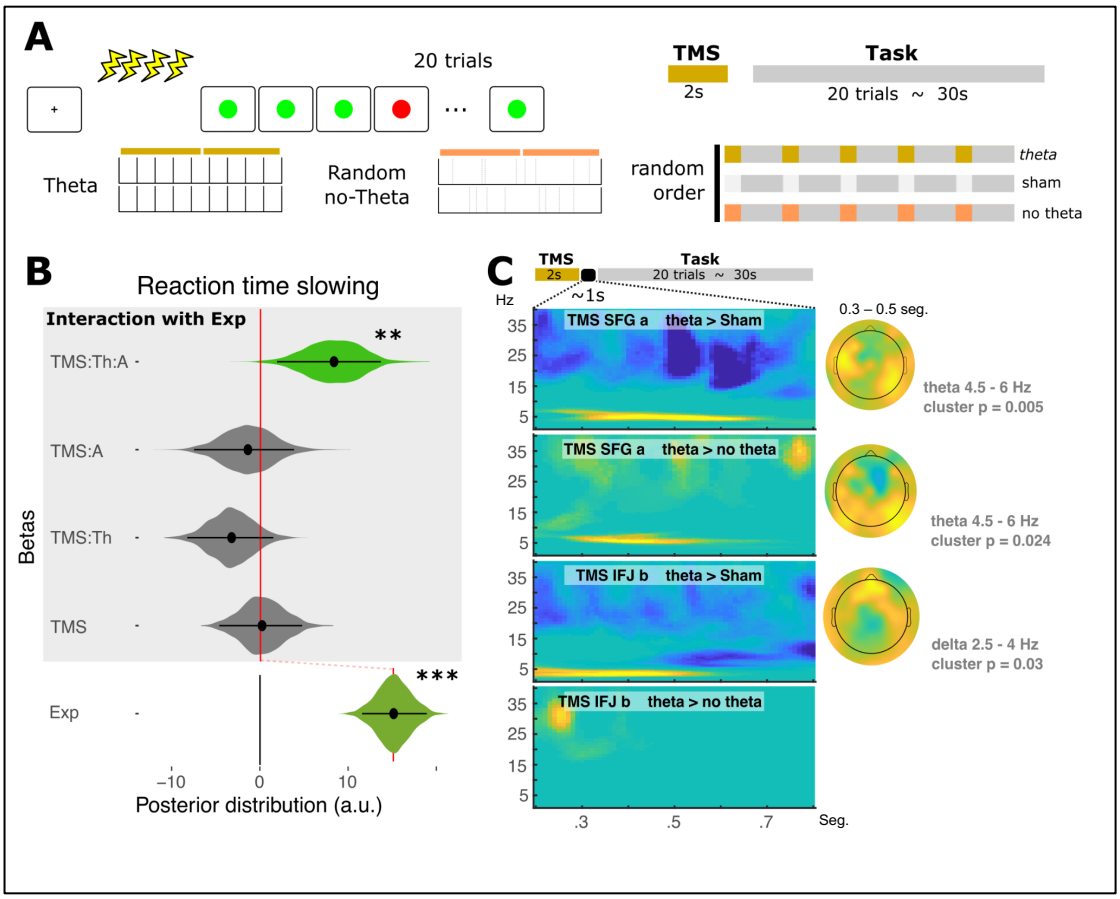

Figure 3-4: EEG-TMS experiment results. A) Experimental design. Go-Nogo Task during EEG-TMS sessions. B) Posterior distribution of model parameters. C) Electrophysiological analysis of EEG related to expectative of conflict (0.2 - 0.3 ms after TMS).

3.4.7. Experiment 3, EEG-TMS: TMS stimulation modulates theta oscillations in lateral prefrontal regions during Go Nogo Task

Power analysis of the electrophysiological recordings indicated that there is a statistically significant difference in theta activity associated with an expectation of conflict. Figure 3-5 shows the time-frequency chart in the left and right prefrontal areas. In SFG (TMS a), theta activity is negatively modulated by TMS in the left prefrontal, and this activity is not observed in the right prefrontal. In IFJ (TMS b), delta activity is negatively modulated by TMS in the left prefrontal, and this activity is not observed in the right prefrontal.

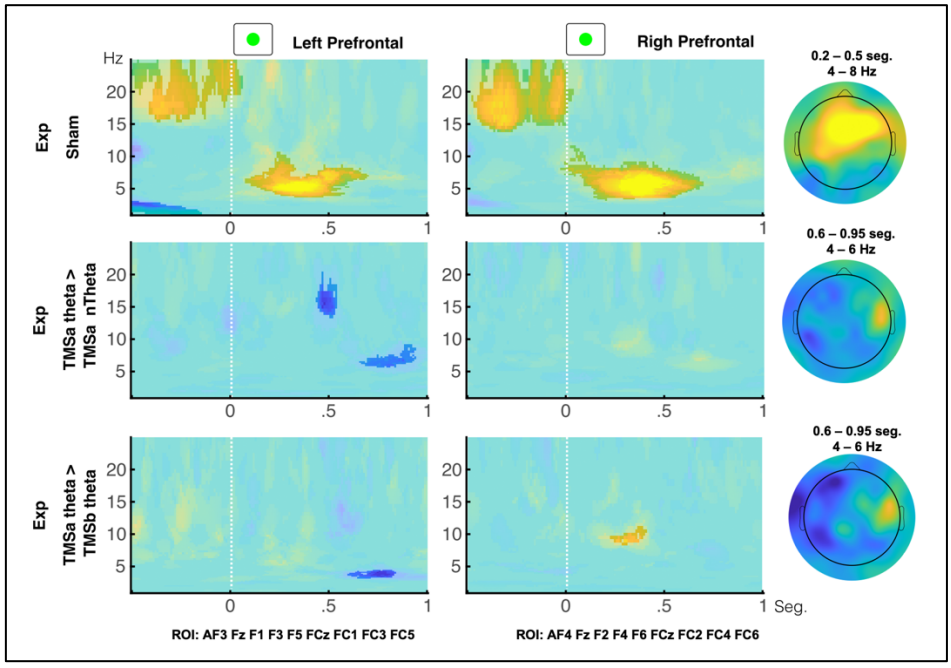

Figure 3-5: EEG-TMS experiment results. Time frequency chart (-0.5 - 1 s around go stimulus).

3.5. Discussion

The brain activity in the SFG and IFJ during the MSIT task shows the brain areas that are activated when a conflicting stimulus is approaching (proactive cognitive processing). These results are in agreement with the proposed involvement of lateral areas of the prefrontal cortex in cognitive control (Koechlin et al., 1999; Koechlin et al., 2003; Koechlin and Summerfield, 2007). Moreover, the SFG is a region implicated in different tasks including cognitive control (Briggs et al., 2020; Li et al., 2013), motor movement, working memory, and resting state (Briggs et al., 2020), and its alteration is associated with pathologies such as bipolar depression (Sun et al., 2020) and schizophrenia (Fan et al., 2022; Qiu et a., 2021). On the other hand, the IFJ is essential for executive functions (Schroeter et al., 2020) like control of action, attention, and memory (Muhle-Karbe et al., 2016), and its bilateral lesion causes dysexecutive syndrome (Schroeter et al., 2020).

In the behavioral GNG task, reaction time increased as the go sequence progressed, associated with an increase in the expectation of conflict. This slowing is a marker of cognitive control and has been documented by other researchers (Ott, 2022). In the GNG task performed with EEG-TMS, an increase in this slowing of the reaction time was observed when theta-band TMS (rhythmic TMS) was applied over the SFG. This indicates that this stimulation enhances

the expectation of conflict (proactive cognitive control) during the GNG task. In addition, evidence has shown that the use of TMS, with specific experimental designs, has improved other functions such as verbal memory (van der Plas et al., 2021) and working memory (Albouy et al., 2017; Bagherzadeh et al., 2016).

According to the electrophysiological analysis, in the period between TMS stimuli and the GNG task, theta TMS in the SFG could increase the theta activity, proving that exogenous stimulation with TMS interferes with endogenous oscillatory activity. But TMS in the IFJ could increase the delta activity. This could be explained by the fact that the network that was intervened when performing the TMS was resonating at a frequency different than theta. On the other hand, during the GNG task, theta TMS produced a negative modulation of theta activity in the left prefrontal cortex after the Go response of the task. This can be explained by the fact that by performing the TMS stimulus in the theta band, more efficient activity is achieved while cognitive control is required to execute the task, an activity that subsequently declines.

We proved that with the stimulation we are changing oscillatory prefrontal activity in the task, increasing the cognitive control on the go stimulus. This could explain the increase in the reaction time observed in the TMS behavioral analysis. TMS stimulation in the SFG modulates theta oscillations in lateral prefrontal regions during GNG Task. This may prove a causal role for theta oscillatory activity of the

lateral prefrontal cortex in expectation of conflict. The results obtained can be supported by current research, in which TMS in the left DLPFC increases proactive control (Pulopulos et al., 2020).

Considering that TMS is a safe, non-invasive, and painless technique (Malavera et al., 2014) and that can be used to selectively activate or inhibit specific cortical structures, it can continue to be used as such a tool for examining cognitive processing (Nevler & Ash, 2015). Moreover, TMS has been postulated as a therapeutic tool that could facilitate functional brain reorganization and clinical recovery in patients with nervous system disorders (Malavera et al., 2014), for example, depression (Ibiricu y Morales, 2009). For this, thanks to research, additionally it could be applied in the future for the treatment of other pathologies.

3.6. Conclusions

According to the analysis of the BOLD signal, as subjects anticipate occurrence of conflicting stimuli, more lateral prefrontal activity occurs, specifically in two areas: the SFG and the IFJ. Therefore, these areas are associated with the prediction of the occurrence of conflicting stimuli. Behavioral analysis of TMS provides evidence of expectative of conflict, specifically, in SFG theta stimulation when compared with the IFJ theta stimulation. Electrophysiological analysis shows that theta TMS stimulation modulates theta oscillations in lateral prefrontal

regions. Using stimulation, we changed oscillatory prefrontal activity during the task, increasing cognitive control on the go stimulus. This could explain the increase in the reaction time observed in the TMS behavioral analysis. Our results prove the causal role of theta oscillation in the lateral prefrontal cortex in conflict expectancy, specifically in the SFG. This activity could be used for therapeutic purposes in pathologies associated with cognitive control difficulties such as Attention Deficit Hyperactivity Disorder (ADHD). The next steps in this research project involve adding more subjects to the study and stimulating other brain areas with TMS to evaluate if it is possible to improve our proactive cognitive control by training brain activity.

4. RESEARCH 2

Effect of reward sensitivity on the outcome prediction and choice during value-based decision making.

4.1. Summary

Decision-making is a complex brain process involving learning, experience, conflict, the expectation of conflict, and the expectation of reward. Specifically, value-based decision-making refers to choosing what means the most value to us, according to the reward it means (reward sensitivity). Rewards can bias decision-making, leading to select actions other than those built internally by a predictive model, with the goal of obtaining a higher reward. How does reward sensitivity modulate the prediction and choice during value-based decision making? Here we tested the hypothesis that reward sensitivity produces a bias on prediction and choice during value-based decision making showing a dissociation between the predictive and selective model, given by an increase in BOLD activity in the ventral striatum during action selection. An investigation was conducted to study the effect of increased reward on learning and risk-taking in a group of adults by conducting two experiments: behavioral and functional magnetic resonance imaging (fMRI), during which they solved a decision-making

task. The results show that as reward increases, behaviorally the rate of learning increases, and neurobiologically the activity in the ventral striatum increases.

4.2. Introduction

We live in a complex environment where we must adapt our behavior to respond efficiently. For example, when we have to make a decision, like choosing what to have for lunch, what to wear, or a new job, we can do this because our adaptive behavior is based on specific interactions among what we predict could happen (predictive models that anticipate behavioral outcomes), what action we select based on reward (selective models), and the context in which we are (Soltani & Koechlin, 2022). The prefrontal cortex (PFC) combines these internal models to drive behavior and predict contextual changes (Soltani & Koechlin, 2022).

We make decisions all the time, either automatically or through a detailed analysis of possible options. These decisions relate to what we want to achieve and are affected by our experience, learning, assessment of courses of action, risk, and reward, among other processes. Therefore, decisions are outcomes of brain processes that incorporate experience, current context, the expectation of future outcomes (Pearson et al., 2014), the expectation of reward, and the expectation that a conflict situation will occur that must be resolved.

Value-based decision-making refers to making the choice that means the most value to us, weighing objective and subjective aspects, depending on how relevant they are to the individual. Therefore, value is an internal construct that guides our behavior. Choices based on value are related to the sensation it provokes and how much reward it provides (Fellows, 2011). Reward describes an event that produces a pleasant or positive affective experience (Gottfried, 2011), which can guide our decision-making. The value of rewards arises from multiple dimensions, among these, is motivation (Weber et al., 2018). People typically both want and like rewards, being central to goal-directed behavior (Weber et al., 2018).

This background allows us to understand that, when faced with a decision, we can be clear about the prediction and possible outcomes of each course of action. However, the potential rewards to be obtained may bias our decision, leading us to choose a course of action that, according to the prediction, is less likely to give us the expected result, but, if it does, we will obtain a greater reward, known as reward sensitivity, and refers to the degree to which the reward motivates the behavior (Kim et al., 2015). Therefore, when there are rewarding stimuli, individuals are more likely to approach them (Sutton, 2022). Moreover, punishment sensitivity refers to a behavioral inhibition system that increases our avoidance of potentially aversive stimuli (Sutton, 2022). Both mechanisms are relevant, because learning is mediated by rewards and punishments (Skinner,

1938). Thus, rewards reinforce the repetition of a behavior, and that punishment discourages it. However, it is not clear how different amounts of reward modulate value-based decision making and the underlying brain mechanisms.

In turn, it was mentioned that the expectation of obtaining a reward might generate a bias. Bias is an incorrect evaluation of the association between an exposure (action) and its effect (outcome) (Delgado-Rodríguez & Llorca, 2003). The bias can be positive or negative. A positive bias refers to giving a greater subjective evaluation to the action, leading to its effective performance. A negative bias refers to giving a lower subjective evaluation of the action, leading to not performing. Positive bias is an incorrect evaluation that can cause us to make risky decisions. Risk-taking refers to engaging in behaviors that may be high in subjective desirability (associated with high sensation, novelty, or perceived reward), but which expose us to potential injury or loss (Geier & Luna, 2009). In this case, the value of an action (magnitude of reward) is more important than its risk. Thus, making a risky decision implies making a decision with a greater likelihood of adverse outcomes.

With respect to learning, we can study how and how much individuals learn from experience and whether they incorporate that learning into their future decisions. The learning rate is an indicator of the subjects' learning, a parameter estimated from a reinforcement learning model which reflects the extent to which feedback

(result) on each trial (experience) is used to update later choices. A lower learning rate suggests that learning is guided by accumulating evidence over a greater number of trials (incorporating historical experience), rather than shifting behavior based on the outcome of any single trial, without incorporating historical experience, with a higher learning rate (Davidow et al., 2016).

The repetition of decisions, knowledge of the context, and experience also constitutes learning, which, in the future, could be incorporated and/or extrapolated it to other contexts thanks to counterfactual thinking. Counterfactuals are thoughts about how (past) reality could have been different (Van Hoeck et al., 2013). So, with the repetition of our decisions, we acquired the ability to predict when and where a reward will occur, enabling us to initiate behavioral responses prospectively (based on an expectation) in order to maximize the probability of obtaining that reward (O'Doherty, 2011).

Based on this, the research question was: How does reward sensitivity modulate the prediction and choice during value-based decision making? We tested the hypothesis that reward sensitivity produces a bias on prediction and choice during value-based decision making, showing a dissociation between the predictive and selective model, given by an increase in BOLD activity in the ventral striatum during action selection. In order to study the effect of reward sensitivity on choice during value-based decision making, two experimental

sessions were carried out (behavioral and fMRI). In each session, participants solved the same two-phase behavioral task (learning and bet, Figure 4-1 and 4-2) designed to study the brain mechanisms underlying reward sensitivity as measured by learning rate and risk.

Participants will inflate a balloon that gives them a monetary reward. But, this reward is lost if the balloon explodes (Figure 4-3). In the learning phase, participants will be able to learn the explosion threshold of a balloon through experience. The risk phase, associated with higher rewards than the learning phase, has the same explosion threshold as the previous phase so that subjects will show their attitude to risk in the face of changes in the reward magnitude. The analysis of the data will allow us to conclude whether participants are guided by their internal construct (predictive model) when making their decisions (selective model). This finding would indicate that their predictive and selective models are aligned, or whether they select an action without considering their prediction of what should occur in the environment (misaligned predictive and selective models), for example, because they are guided by the expectation of receiving a higher reward.

4.3. Methods

4.3.1. Participants

Forty-two healthy subjects (22 women, 18-34 years), who meet inclusion criteria (Appendix nº 1), participated in this research approved by the Ethics Committee of the Universidad del Desarrollo, Chile. All participants gave informed consent. Experiments were conducted in the Social Neuroscience and Neuromodulation Laboratory at the Centro de Investigación en Complejidad Social (neuroCICS) at the Universidad del Desarrollo and the Unidad de Imágenes Cuantitativas Avanzadas (UNICA) at the Clínica Alemana de Santiago.

4.3.2. Experimental design

Subjects participated in 2 experiments, including a behavioral session and an fMRI scan session. In both experiments, subjects had to solve a Risk-Learning Task associated with risk, learning, and reward (Figure 4-1), to study the effect of the reward magnitude on prediction and choice during value-based decision-making. During the behavioral session, participants played the game on a computer. Then an fMRI was performed, and subjects had to solve the same task while being scanned in the MRI machine (Figure 4-1).

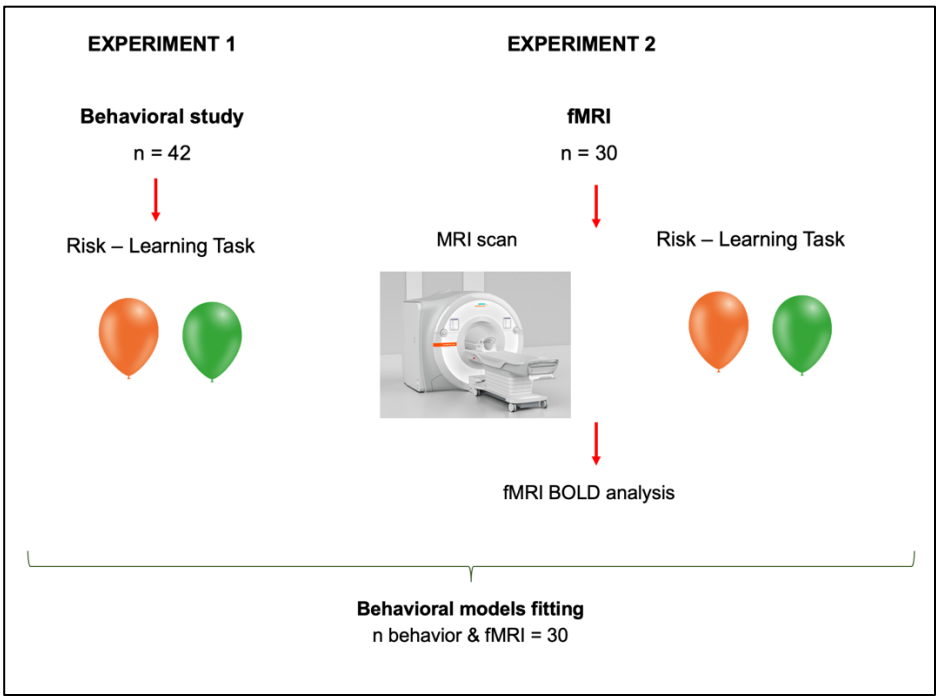

Figure 4-1: The experimental design was organized in two experimental sessions. Subjects solved a Risk – Learning Task in a behavioral and an fMRI session, according to the scheme.

4.3.3. Risk - Learning Task

The participant is presented with a balloon with the option to earn money by inflating it, by clicking on a keyboard (Figure 4-3). Each click causes the balloon to inflate and money to be added to a deposit, up to a certain threshold at which a click causes the balloon to explode. If the participant decides to cash in before the balloon explodes, he takes his money. But, if the balloon explodes, he loses

the money accumulated in that game. Therefore, each pumping offers a greater reward, but also has a greater risk.

This task consisted of 18 blocks. Each block has a learning/exploration phase (6-9 balloons) and a betting/risk phase (1 balloon, Figure 4-2). In the learning/exploration phase subjects learn, through experience, the threshold at which the balloon explodes for each block (given by a probability distribution). With this, the learning rate can be studied. The risk/bet phase consists of a game, in which the subjects must indicate beforehand how much they will inflate the balloon, and afterwards they receive feedback if they won or lost. With this, it is possible to know the attitude towards risk of the participant.

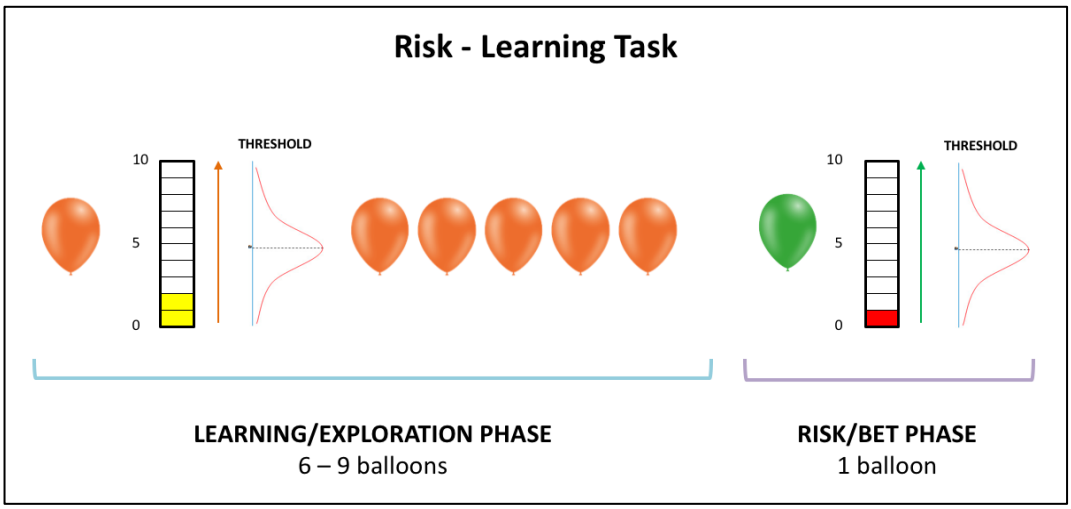

Figure 4-2: Risk-Learning Task structure. In the learning phase subjects learn, through experience, the threshold at which the balloon explodes for each block (given by a probability distribution). With this, the learning rate can be studied.

The bet phase consists of a game, in which the subjects must indicate beforehand how much they will inflate the balloon, and afterwards they receive feedback if they won or lost. With this, it is possible to know the attitude towards risk of the participant.

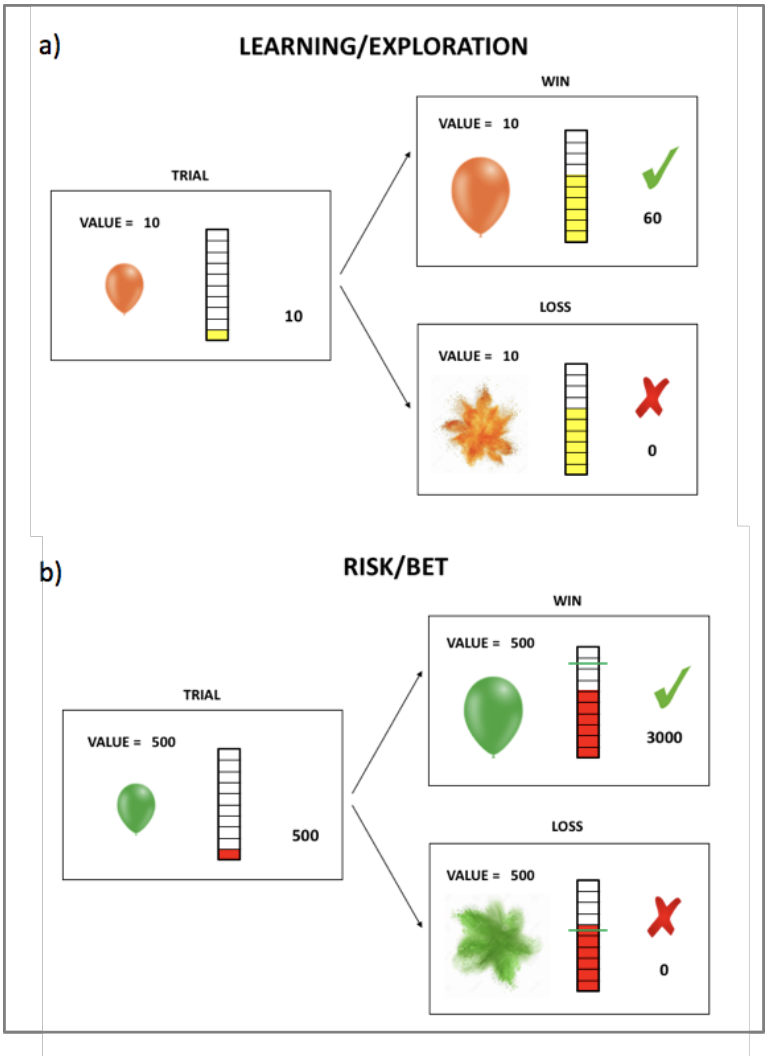

Figure 4-3: Risk-Learning Task description. In the learning phase (a) subjects learn, through experience, the threshold at which the balloon explodes for each

block (given by a probability distribution). The betting phase (b) consists of a game, in which the subjects must indicate beforehand how much they will inflate the balloon, and afterwards they receive feedback if they won or lost.

4.3.4. Anatomical Data

All participants of experiments 2 and 3 underwent a 3D anatomical MPRAGE T1-weighted and T2-weighted Magnetic Resonance Imaging scan on a 3T Siemens Skyra (Siemens AG, Erlangen, Germany). The anatomical volume consisted of 160 sagittal slices of an isotropic voxel (1x1x1 mm), covering the whole brain. The scalp and cortical surfaces were extracted from the T1-weighted / T2-weighted corrected anatomical MRI using a pipeline from the Human Connectome Project. Thus, a surface triangulation was obtained for each envelope (Fischl, 2012). The individual high-resolution cortical surfaces (~ 300 000 vertices per cortical surface) were down-sampled to ~5 000 vertices. Additionally, a five-layer segmentation based on T1-weighted / T2-weighted corrected, and T2-weighted was carried out using the algorithm implemented by the SimNIBS tool and SMP12.

4.3.5. Functional MRI Data

For the functional images, volumes of the entire weighted echo-planner T2* brains were acquired while the experimental task was executed (3x3x3 mm voxels). Participant volumes were coregistered to 2-mm standard imaging using the nonlinear algorithm implemented in FSL. The BOLD signal was analyzed using different models, including motion correction parameters.

4.3.6. fMRI imaging analysis

During the fMRI, subjects solved the Risk-Learning task. Imaging data were analyzed using one model in FSL 5.08. In this model, the activity of the reward sensibility will be isolated using different regressors (Figures 4-5 and 4-6). Second-level activation maps were calculated with FSL using a mixed-effect model (FLAME1, cluster corrected $p<0.05$, Cluster Threshold Detection (CTD) $z>3.01$).

4.3.7. fMRI behavioral analysis

Behavioral data will conform to a regression model using Matlab software. The learning rate will be adjusted using different regressors. A reward-based learning

model over subject response will be adjusted with three independent learning rates for each reward amount ($0, $10, and $100).

4.4. Preliminary results

4.4.1. Experiment 1: The learning rate increases with increased reward

In order to evaluate the learning rate associated with reward sensitivity, we adjust the learning rate for each reward amount. We found the higher the reward, the higher the learning rate (rho= 0.3012; p= 0.0485; Figure 4-4).

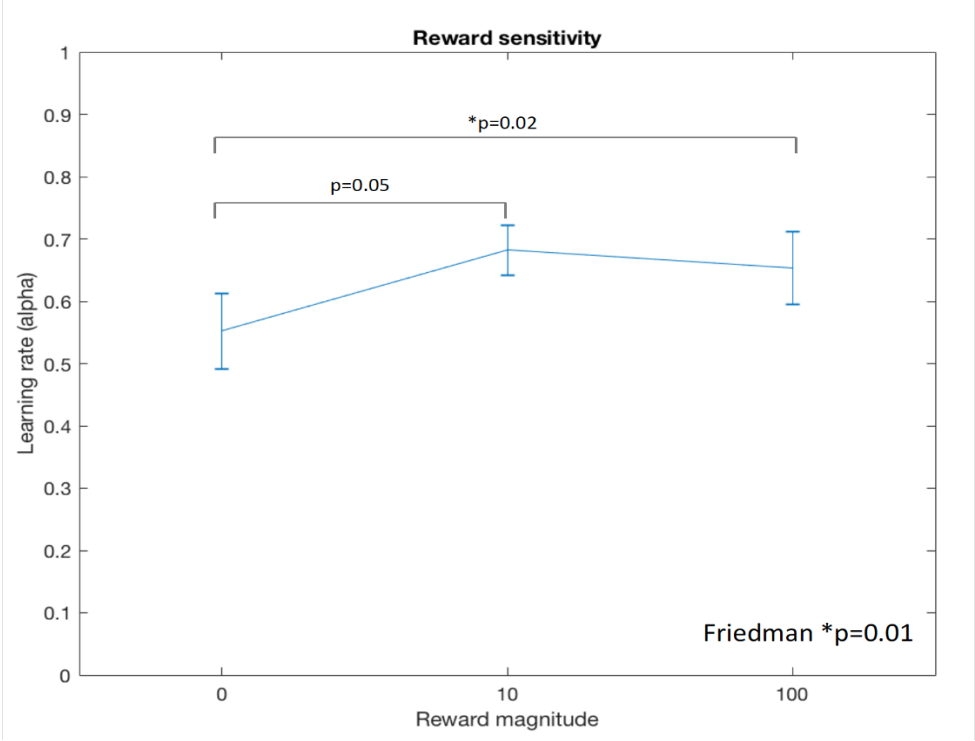

Figure 4-4: Learning rate associated with each reward sensitivity (n=18; age=18-20 years; 18 trials per subject).

4.4.2. Experiment 2: Reward sensitivity is associated with a peak activation located in the ventral striatum

In order to evaluate the brain activity associated with reward sensitivity, we subtracted the activity without reward from the different reward amounts (Model 1, contrast: $10>$0 and $100>$0; Figure 4-5). We found a peak activation located in the ventral striatum.

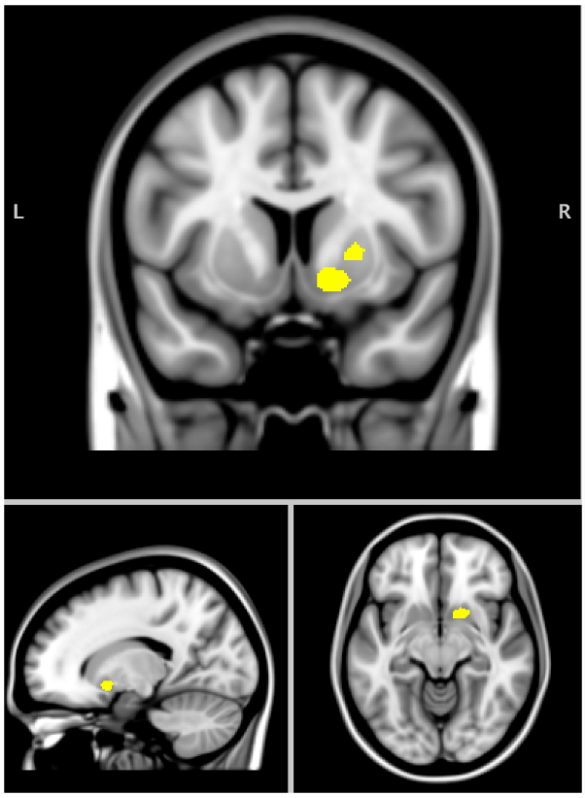

Figure 4-5: Brain activity associated with reward sensitivity (contrast: $10>$0 and $100>$0; CDT Z > 3.1; Cluster correction p < 0.05; n=4; age=18-20 years; 18 trials per subject).

4.4.3. Experiment 2: Reward difference ($100 > $10) is associated with activity in the medial posterior parietal cortex and the ventromedial prefrontal cortex

We explored the activity related to the difference of reward ($100>$10; Figure 4-6). We found activity located in the medial posterior parietal and ventromedial prefrontal cortex.

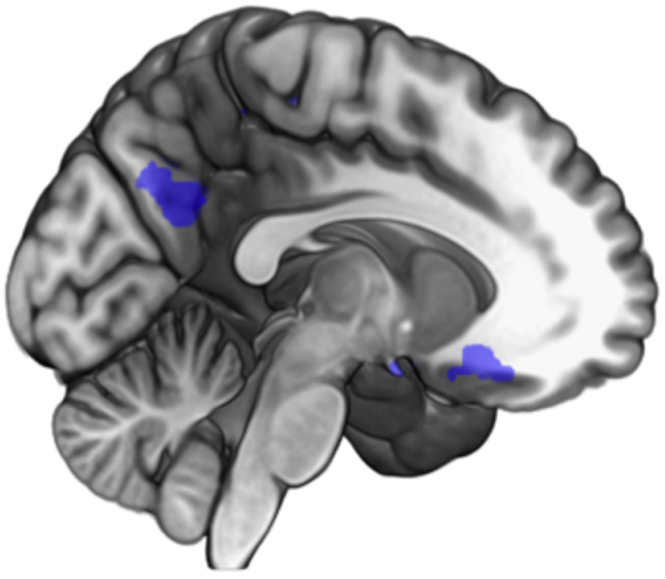

Figure 4-6: Brain activity associated with the difference of reward ($100>$10; CDT Z > 3.1; Cluster correction p < 0.05; n=4; age=18-20 years; 18 trials per subject).

4.5. Discussion

The increase in learning rate observed as reward increases indicates that participants base their decisions on current trials without incorporating history (experience). This could be explained by the fact that they are sensitive to the increase in reward and its potential gain, running the risk of losing the accumulated amount of money. Thus, an increase in monetary rewards may be associated with increased risk-taking.

While reward sensitivity could result in risky decision-making, it could also lead to positive consequences, such as greater learning (van Duijvenvoorde, 2016). Sensitivity to reinforcement seems to be related to how people learn from experience. For example, with fMRI and a probabilistic reinforcement learning task, it has been concluded that adolescents perform better on the task than adults, with a lower learning rate (Davidow et al., 2016). This learning was related to higher BOLD activity in the ventral striatum and hippocampus in adolescents, while in adults showed higher BOLD activity only in the striatum (Davidow et al., 2016).

In turn, other research has shown that, specifically in adolescents, rewards and monetary incentives can improve their performance and learning on specific tasks (Geier et al., 2010; Hallquis et al., 2018; Schwab & Somerville, 2022). This

leads to the conclusion that rewards can have different effects on learning rates depending on the context, objectives and age groups studied.

In our research, when comparing a higher reward to a lower reward, an increase in BOLD activity in the ventral striatum, a brain area associated with reward, was observed. This area has also been identified in other research during reward reception (Davidow et al., 2016; Kim et al., 2015). The activity in the medial posterior parietal cortex and the ventromedial prefrontal cortex observed in the reward difference ($100 > $10) was associated with value encoding during decision making.

The ventral striatum (VS) and ventromedial prefrontal cortex (vmPFC) are brain areas known to encode the subjective value of the decision alternatives (Pisauro et al., 2017). For example, the involvement of the VS and the vmPFC in obtaining immediate monetary rewards and estimating cumulative rewards has been evidenced (Juechems et al., 2017). Moreover, scientific evidence has indicated that the VS is a reward-processing region (Weber et al., 2018). The results obtained in our research are consistent with the mechanism identified by Weber et al., in which the PFC and the VS, flexibly encode reward dimensions depending on their behavioral relevance (Weber et al., 2018). It is necessary to keep on the analysis of the data to answer the hypothesis of this research.

4.6. Conclusions

Our results indicate an increase in the learning rate when the reward increases. This accounts that, as the reward increases, subjects become more sensitive to the immediate, without considering the learning from experience. Therefore, this sensitivity would indicate that they do not follow prediction to make decisions, as this is biased by the presence of a reward and are related to a higher expectation of reward during the game. This allows us to conclude that, even when participants learn the context of the game, their decisions are based on the expectation of obtaining a greater reward. Interestingly, this learning rate increase is related to subcortical and cortical areas related to value encoding during decision-making.

5. FINAL CONCLUSIONS

In this research, we analyzed the expectancy of conflict during conflict and value-based decision-making:

In the first study, according to our research question, we concluded that: SFG is the area of the lateral prefrontal cortex involved in the computation of the prediction of conflicting events, this frontal network seems to resonate at theta frequency, and this oscillation seems to compute the cognitive process associated with the prediction of conflicting events. Therefore, theta-band oscillatory activity plays a causal role in the expectation of conflict, and this activity can be modulated using TMS. The further guidelines of this research are to conduct specific studies to determine how these techniques can be used as part of the therapeutic strategies in people with cognitive impairment.

In the second study, with preliminary results, we concluded that the rate of learning increases as reward increases, with an increase in ventral striatal activity. A low learning rate would indicate that participants are guided by what they have learned through experience on the task; therefore, they would follow their prediction. On the other hand, an increase in the learning rate would evidence the bias to make a decision based on the expectation of obtaining a higher reward without incorporating the prediction made. Therefore, the reward

is involved in our learning and decision-making. Future steps will be to complete the analysis of the results of this research to understand how reward-sensitivity modulates the expectative of conflict during value-based decision-making. Subsequent research will include a study of reward sensitivity at different stages of development, focused on adolescence, considering that it is a developmental stage associated with a greater sensitivity to incentives and relatively weak cognitive control, which can lead them to make risky decisions.

The study of these cognitive processes is relevant because they are associated with our behavioral flexibility, so their study will be able to unpack the brain mechanism underpinning aspects of everyday life and understand how any alteration in these processes can generate pathologies.

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7. APPENDIX

Appendix Nº 1

Inclusion criteria for laboratory tests

- People between 18 and 35 years old.
- Do not take mood-stabilizing drugs.
- Not taking medicines to sleep.
- Have not had a Traumatic Brain Injury in the last 5 years.
- Not being claustrophobic.
- No metal in the body.
- No tattoos with ferromagnetic elements.
- Not having problematic drug use.
- Discuss personal and family history of neurological (epilepsy) and psychiatric (depression) diseases and evaluate participation in research.