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Electrophysiological Brain Dynamics of Visuospatial Planning

by

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"El cerebro no solo es un órgano capaz de conservar o reproducir nuestras pasadas experiencias, sino que también es un órgano combinador, creador, capaz de reelaborar y crear con elementos de experiencias pasadas nuevas normas y planteamientos." —Lev Vygotsky

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LIST OF ABBREVIATIONS

ACC	: Anterior Cingulate Cortex
BOLD	: Blood-oxygen-level-dependent
EEG	: Electroencephalogram
EFs	: Executive Functions
FDR	: False Discovery Rate
FFT	: Fast Fourier Transform
FMθ	: Frontal Midline Theta
fMRI	: functional Magnetic Resonance Imaging
FP	: Frontopolar
FPC	: Frontopolar Cortex
ICA	: Independent Component Analysis
LISAS	: Linear Integrated Speed Accuracy Score
MCC	: mid-Cingulate Cortex
MNI	: The standard Montreal Neurological Institute brain
PCA	: Principal Component Analysis
PET	: Positron Emission Tomography
PFC	: Prefrontal Cortex
PLI	: Phase Lag Index
ROI	: Region of Interest
RT	: Reaction Time
SF	: Superior Frontal Gyri and Sulci
sLORETA	: Low-Resolution Brain Electromagnetic Tomography
TOL	: Tower of London Task
wPLI	: weighted Phase Lag Inde

SUMMARY

Cognitive planning, which is the ability to develop a sequenced plan to achieve a goal, plays a crucial role in human goal-directed behavior (i.e. cognitive control). However, its neural correlates, particularly its electrophysiological dynamics, remain elusive at present. Behavioral paradigms of planning are a current challenge in cognitive neuroscience.

In this doctoral thesis, electroencephalographic (EEG) activity was recorded while twenty-seven healthy adult subjects performed a novel behavioral paradigm designed for this doctoral thesis (based on Porteus Maze and Zoo Map Task), that evaluates planning function in an ecological manner. The behavioral paradigm that we constructed was composed of a planning task and a control task. The planning task consisted of solving 36 mazes/trials which represented a zoo map. Each trial had four different periods: *i)* a planning period, where subjects were asked to plan a path to visit locations of four animals following a set of rules. After this, there was *ii)* a maintenance period. During this period, subjects had to store the planned path in their working memory. Then, during *iii)* the execution period, subjects drew the previous planned path. Finally, there was *iv)* a response period, where subjects reported the sequence of animals visited according to their planned path. The control task had the same structure, but the cognitive planning component was removed by modifying the task goal.

The behavioral results showed that the planning task was more complex and cognitively demanding than the control condition suggesting that our experimental paradigm was optimal to evaluate the planning function. Interestingly, we found differences between easy and difficult trials at the behavioral level but no differences at the electrophysiological level. This contributed to the idea that the planning task assesses more intrinsic aspects of planning reflected in theta (4-8 Hz) oscillation changes than other general cognitive demands typically present in cognitive control tasks.

EEG activity was analyzed at the time-frequency domain, by assesses induced oscillatory activity. Specifically, we hypothesized that cognitive planning will induce theta activity specifically in midfrontal electrode sites. Thus, our results showed, in agreement with our hypothesis, a progressive and sustained increase in theta band overtime during the planning period. Source analysis indicated that the origin of this induced theta activity was from specific regions within the prefrontal cortex. Specifically, in bilateral sources such as the frontopolar cortex, the anterior cingulate cortex, and the mid-Cingulate cortex. Furthermore, we found discernable associations between theta activity from regions within the prefrontal cortex and

behavioral performance. These results suggest that theta activity from the left frontopolar cortex is associated with the efficiency and accuracy of elaborating and executing plans. Whereas theta activity from the right mid-Cingulate cortex and the left anterior cingulate cortex were related to mental elaboration of a plan. Finally, widespread theta phase connectivity increases between Fz and long-distant electrode sites were found during the planning condition.

Hence, for the first time we characterized both spatial and temporal frontal-midline theta (FMθ) dynamics of cognitive planning as a marker of cognitive control, which may be coordinating information, such as visuospatial analysis and motor control preparation, through prefrontal cortex and disparate brain regions via theta phase connectivity during planning performance. The specific association between the left frontopolar cortex theta activity and planning performance may reflect the participation in elaborating a successfully self-generated plan. Furthermore, the associations between theta activity from the right mid-Cingulate cortex and the left anterior cingulate cortex with slower reaction times during the planning period may reflect attentional control engagement and conflict monitoring implementation.

Keywords: planning; frontal midline theta activity (FMθ); time-frequency analysis; prefrontal cortex; cognitive control.

RESUMEN *(español)*

La planificación cognitiva, definida como la habilidad de desarrollar un plan secuenciado de pasos conductuales para alcanzar una meta, juega un rol crucial en la conducta dirigida a meta en humanos, por ejemplo, en el control cognitivo. Sin embargo, sus correlatos neurales, en particular sus dinámicas electrofisiológicas, permanecen desconocidas hasta la fecha. El diseño de paradigmas conductuales que evalúan esta función cognitiva continúa siendo un desafío para la neurociencia cognitiva.

En esta tesis doctoral, la actividad electroencefalográfica (EEG) fue registrada mientras veintisiete sujetos adultos sanos rindieron un nuevo paradigma conductual diseñado para esta investigación (basado en el laberinto de Porteus y el Zoo Map Task, los cuales son pruebas tradicionales usadas en neuropsicología clínica), cuyo propósito buscó evaluar la función cognitiva de planificación de una forma ecológica. El paradigma conductual que diseñamos estuvo conformado por una tarea de planificación y una tarea control. A) La tarea de planificación tenía por objetivo resolver 36 ensayos/laberintos. Cada ensayo consistió en la presentación de un estímulo donde se representaba el mapa de un zoológico. Cada uno de los ensayos tenían cuatro periodos diferentes: i) un periodo de planificación, donde a los sujetos se les instruyó planificar una ruta que les permitiese visitar cuatro ubicaciones de animales al interior del mapa siguiendo un conjunto de reglas. Después de esto, le sucedió ii) el periodo de mantenimiento. Durante este periodo, los sujetos debían almacenar en su memoria de trabajo la ruta previamente planeada en el periodo anterior. Luego, durante iii) el periodo de ejecución, los sujetos dibujaron la ruta planificada sobre el mapa. Finalmente, hubo un iv) periodo de respuesta, donde los sujetos reportaron el orden de la secuencia de animales visitados de acuerdo con su plan ejecutado. B) La tarea control tuvo la misma estructura, pero el componente cognitivo de planificación fue removido al manipular el objetivo de la tarea.

Los resultados conductuales mostraron que la tarea de planificación fue más compleja y cognitivamente demandante que la condición control, sugiriendo que nuestro paradigma conductual fue óptimo para evaluar la función de planificación. Además, encontramos diferencias significativas cuando los resultados de los ensayos pertenecientes a la condición de planificación fueron separados y comparados entre ensayos difíciles versus ensayos fáciles a nivel conductual, pero no a nivel electrofisiológico. Esto contribuyó a la idea de que la tarea de planificación mide aspectos cognitivos más intrínsecos de planificación, reflejados en cambios de la oscilación theta (4-8 Hz), en lugar de demanda cognitiva en general, o esfuerzo cognitivo, típicamente presente en tareas de control cognitivo.

La actividad de EEG fue analizada en el dominio tiempo-frecuencia mediante la actividad oscilatoria inducida. Hipotetizamos que la planificación cognitiva induce actividad theta específicamente en sitios de electrodos de la línea media frontal. Por lo tanto, nuestros resultados mostraron, de acuerdo con nuestra hipótesis, un incremento progresivo y sostenido de la banda theta en el tiempo durante el periodo de planificación. Análisis de fuentes indicaron que el origen de esta actividad theta inducida provenía de regiones de la corteza prefrontal. Específicamente, desde fuentes bilaterales tales como la corteza frontopolar, la corteza cingulada anterior, y la corteza cingulada media. Adicionalmente, encontramos asociaciones diferenciables entre la actividad theta de regiones de la corteza prefrontal y el rendimiento conductual. Estos resultados sugieren que la actividad theta de la corteza frontopolar izquierda está asociada con la eficiencia y la precisión de la elaboración y ejecución de planes. Mientras que la actividad theta de la corteza cingulada media derecha y la corteza cingulada anterior izquierda estuvo asociada a la elaboración mental de un plan. Finalmente, encontramos un aumento significativo extendido de la conectividad en fase theta entre el electrodo Fz y sitios distantes de electrodos durante la condición de planificación.

Por lo tanto, caracterizamos por primera vez, tanto espacial y temporalmente, las dinámicas de la actividad theta de línea media frontal (FMθ) asociadas a planificación cognitiva como un marcador de control cognitivo el cual podría estar coordinando información, tal como análisis visoespacial y preparación de control motor, a través de la corteza prefrontal y diferentes regiones cerebrales por medio de conectividad en fase theta durante el rendimiento conductual en planificación. La relación específica entre la actividad theta de la corteza frontopolar izquierda y el rendimiento en planificación podría reflejar la participación de esta área en la correcta elaboración de un plan. Además, las asociaciones entre la actividad theta desde la corteza cingulada media derecha y la corteza cingulada anterior izquierda con tiempos de reacción más lentos durante el periodo de planificación podría reflejar el enganche de control atencional y la implementación de monitoreo de conflicto respectivamente.

Palabras clave*: planificación; actividad theta de línea media frontal; análisis tiempo-frecuencia; corteza prefrontal; control cognitivo.*

1.   INTRODUCTION

1.1.   Cognitive Control and Executive Functions

The executive control that guides our thoughts and behavior seems to be one of the most remarkable human behavior characteristics. In general terms, executive functions (EFs), or cognitive control, allude to the ability to perform goal-directed behavior (Cohen, 2017). This includes mentally elaborating possible plans, taking the time to decide before acting, solving unanticipated challenges, postponing rewards, and staying focused (Diamond, 2013). Consequently, EFs are composed by three core cognitive functions (**Figure 1**): *i)* inhibition-interference control: the capacity of inhibiting automatic behaviors and controlling the interference of distractions via selective attention; *ii)* working memory (WM): the temporary storage and manipulation of information required to perform goal-directed behavior; and *iii)* cognitive flexibility: the ability to switch between two different courses of thought or behavior (Diamond, 2013; Lehto et al. 2003). From these, higher-order EFs are constructed (Diamond, 2013). These include: *i)* reasoning: the mental process in which knowledge is applied to draw conclusions or achieve a goal (Evans, Over & Manktelow, 1993; Luria, 1973); problem-solving: searching for actions to perform the move that will best achieve the goal (Morris & Ward, 2005); and planning (Collins & Koechlin 2012, Lunt et al., 2012; Lezak, 1995). Cognitive planning (Collins & Koechlin, 2012; Sira & Mateer, 2014; Lunt et al. 2012) consists of developing a sequenced plan to achieve a goal in an organized, strategic and efficient manner (Hayes-Roth & Hayes-Roth, 1979). Planning allows imagining what the future might be, and how our behavior could affect and change the current state in turn leading us to this imagined future (Benson, 1993). However, as essential is the capacity of cognitive planning, its underlying neural mechanisms remain elusive. Understanding these mechanisms is essential to disentangling the enigma of how we are capable of goal-directed behavior, and why this ability fails given certain circumstances.
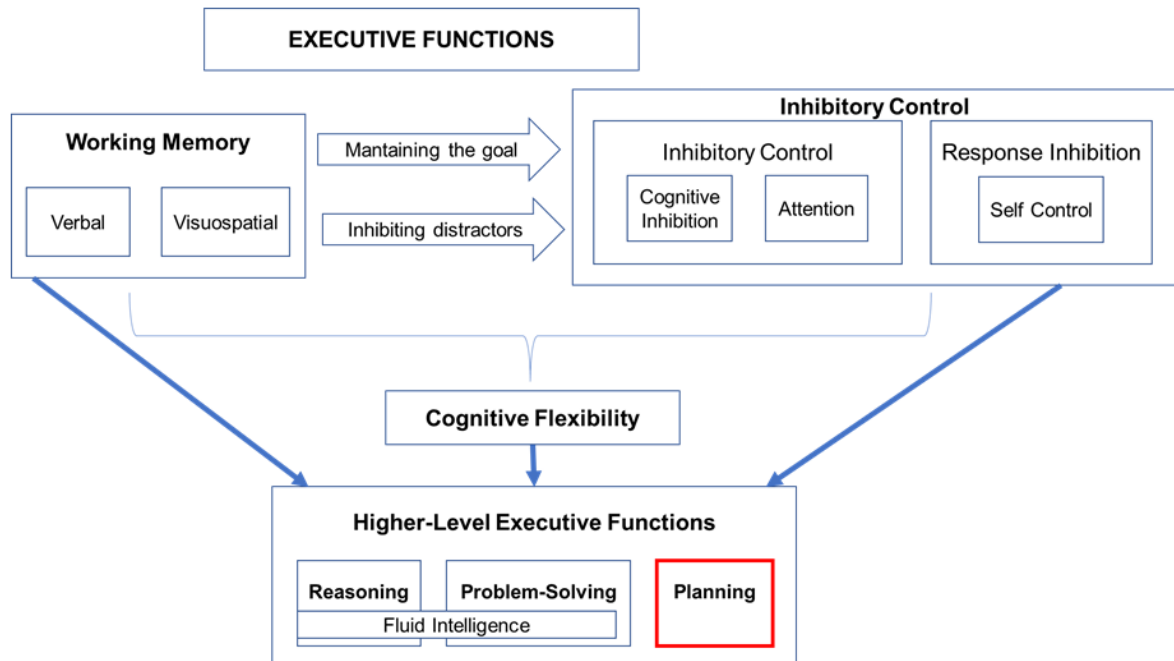
Figure 1. Executive Functions. Illustrative scheme of executive functions supporting higher order executive functions (modified from Diamond, 2013).

1.2. Neuroanatomical Basis of Cognitive Control

From an evolutionary point of view, cognitive control may have evolved from overcoming the limitations of basic adaptive behavior such as reinforcement learning (known to involve the premotor cortex and basal ganglia; Koechlin, 2014). Koechlin (2014) proposed that the evolution of cognitive control provided humans with the ability to determine between continuing with the ongoing behavioral strategy according to the external contingencies, switching to previously learned strategies, or creating new strategies. This evolutionary approach emphasizes three intrinsic characteristics of cognitive control:

1. Its *inferential* nature: selecting an appropriate action requires resolving the uncertainty associated with changes in the environment that might reflect the occurrence of known situations or new ones.

2. Its *hierarchical* nature: selecting action operates within higher-level behavioral strategies, forming abstract sensorimotor representations that adjust through reinforcement learning.

3.   Its *limited capacity* nature: selecting an optimal action leads to a limited biological possibility: monitoring the complete repertoire of learned strategies online, and comparing this repertoire whenever new information is acquired offline.

Based on this outline, neurocomputational models and neuroimaging studies, Duverne and Koechlin (2017) proposed a functional architecture of cognitive control in the human PFC (**Figure 2**).

The PFC is a cortical brain region located in front of the premotor cortex, which forms a cortico-subcortical loop with the dorsal striatum and basal ganglia, participating in learning mechanisms stimulus-action association (Doya, 2007; Horvitz, 2009). Hence, the premotor cortex participates in response to stimuli guided by stimulus-action representations. This brain region covers a substantial part of Brodmann area 6 (BA 6), extends along the precentral gyri, and is contiguous and reciprocally connected to the primary cortex and caudal PFC regions (Tomassini et al., 2007). The lateral PFC (LPFC) is reciprocally connected with the posterior association cortex (parietal and temporal regions) (Petrides & Pandya, 2009) and is located adjacent to the lateral premotor cortex. The LPFC is comprised of the inferior, middle, and superior frontal gyri (Barbas & Pandya, 1989; Pandya & Yeterian, 1996).

The caudal portion of the LPFC corresponds to BA 8, 44, and 45 (with the left hemisphere including the Broca's area) (Broca, 1861). Anterior to the caudal portion and highly reciprocally connected, is the middle LPFC which corresponds to BA 9 and 46 (Pandya & Yeterian, 1996), also known as the dorsolateral PFC (dlPFC). This region is involved in maintaining goal representation and contributes to control processes occurring in posterior brain regions (Miller & Cohen, 2001). The posterior-anterior functional organization reflects the hierarchical gradient in cognitive control. Finally, the brain region considerably more developed in humans than non-human primates is the anterior-most part of the lateral PFC corresponding to BA 10 and known as the frontopolar cortex (FPC) (Semendeferi et al., 2001; Teffer & Semendeferi, 2012). The FPC is fundamentally connected to contiguous PFC regions and there are no homologues brain regions known in the monkey PFC (Koechlin, 2011).
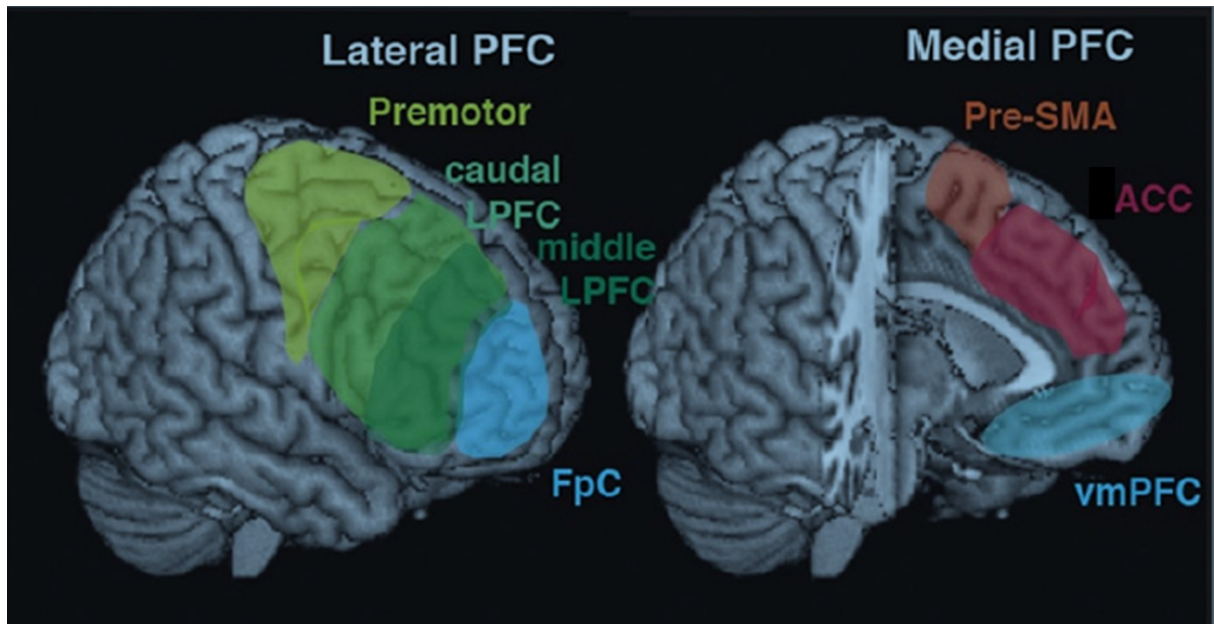
Figure 2. Human prefrontal regions involved in cognitive control. Brain model representation of the main prefrontal areas subserving cognitive control. PFC: prefrontal cortex. Premotor: lateral premotor cortex. LPFC: lateral prefrontal cortex. FpC: frontopolar cortex. Pre-SMA: pre supplementary motor area. ACC: anterior cingulate cortex. vmPFC: ventromedial prefrontal cortex (taken from Duverne & Koechlin, 2017).

The medial PFC can be divided into three regions with different roles in cognitive control. The first is the pre-supplementary motor area (pre-SMA), located adjoining the medial premotor cortex and mutually connected to the caudal LPFC (Bates & Goldman-Rakic, 1993). Next is the mid-Cingulate Cortex (MCC) located anteriorly to the pre-SMA until the corpus callosum. The MCC is densely and mutually connected anteriorly to the ACC and the middle LPFC (Medalla & Barbas, 2010). Anterior to the MCC is the ACC which participates in monitoring actions and conflict detections that demand behavioral adjustment and action re-evaluation (Quilodran, Rothe & Procyk, 2008). According to the conflict model (Cohen, Aston-Jones & Gilzenrat, 2004), ACC detects the need to increase control and coordinates sending information to dlPFC, and other brain regions. Finally, the ventromedial PFC (vmPFC), which contains the orbitofrontal cortex, can be found anterior to the ACC and has broad connections to posterior regions, to LPFC and FPC. It is involved in processing the value of action outcomes (Cavada et al., 2000).

In rodents, the PFC includes the paralimbic regions comprising the orbitofrontal cortex and the ACC (Uylings et al., 2003). In primates, the PFC evolved with the development of the LPFC regions (Fuster, 2015). In humans, the PFC evolved with the considerable development of the

FPC (Teffer & Semendeferi, 2012) and the emergence of hemispherical asymmetry (Schenker et al., 2010). This development in the PFC shows the evolution of cognitive control, with the medial, LPFC, and FPC corresponding to the emergence of inferential, hierarchical, and counterfactual dimensions of cognitive control, respectively (Koechlin, 2014).

1.3. Cognitive Psychology of Planning

Experimental cognitive psychology uses the term 'planning' to describe the organization of a sequence of actions/operations intended to achieve a certain goal (Hayes- Roth & Hayes-Roth, 1979; Scholnick & Friedman, 1987; Unterrainer & Owen, 2006) with this function widely implemented in problem-solving. The representation of this sequence of actions is called a plan (Wilensky, 1983) which can be represented internally (working memory) or externally (e.g., sticky notes, journals, etc.). There are two predominant views of cognitive psychology's planning framework: successive refinement models and opportunistic models.

1.3.1. Successive Refinement Models

These models conceive planning as a top-down hierarchical process that coordinates the order in which a series of behaviors can be executed (Miller, Galanter & Pribram, 1960; Newell & Simon, 1972). Some refinement models include problem solving within the SOAR (State, Operator, and Result) architecture (Rosenbloom et al., 1993), scripts formation (Schank & Abelson, 1977), and specific planning conceptualizations from artificial intelligence (Sacerdoti, 1974).

According to these models, plans are composed of organized subplans, which can include more subplans at the level of basic motor action (Das, Kar, & Parrila, 1996). At each level of subplans, subjects evaluate whether the goal of the subplan has been accomplished; if so, the planner continues to the next step in the sequence (Scholnick & Friedman, 1987).

1.3.2. Opportunistic Models

Opportunistic models propose that planning is a dynamic process that operates at different levels of abstraction, and in which actions taken at any level might affect decisions subsequently at higher and lower levels of abstraction (Hayes-Roth & Hayes-Roth, 1979). In

these models, decisions made at each point in the planning process can affect the opportunities and the next decisions during a plan's development. The planning process is data-driven; thus, plans are dynamics and can grow as decisions are being incorporated. Any decisions made in the past are also subject to re-evaluation. This way, planning is conceptualized as a multi-directional and revisionary process (Grafman, Spector & Ratterman, 2005).

1.3.3. Integrating Successive Refinement and Opportunistic Models

It has been shown that both successive refinement and opportunistic planning are supported empirically and explain the human planning attributes. Hence, perhaps humans plan either way depending on different factors. In some situations, a plan might be formulated in a hierarchical, top-down, and goal-directed manner (successive refinement) (Anderson, 1983), whereas in other contexts, the planning process may go between abstract and concrete decisions (opportunistic) (Pea & Hawkins, 1987; Friedman, Scholnick, & Cocking, 1987; Baker-Sennett, Matusov, & Rogoff, 1993; Dreher & Oerter, 1987).

There are also contributions from artificial intelligence literature introducing concepts such as reactive planning or dynamic world planning which considers the appearance of new information during executing a plan (Chapman, 1991). Dynamic world planning involves a less elaborated strategy with the advantage of making plans more flexible and easier to modify, which is similar to opportunistic models. In contrast, successive refinement models might require more cognitive resources (memory load, reasoning, re-planning) to correct a well-structured and hierarchized plan relative to new information.

In humans, planning behavior requires the creation of a mental representation of a goal, and the representation of the current behavior status relative to the goal to be achieved. Once these representations are created, the next step is the mental elaboration of a sequence of behaviors to achieve the goal with the subsequent motor execution of this sequence, which then leads to the transformation of the current state into the target state (Sternberg & Ben-Zeev, 2001; Anderson, 2000). Hence, the extent of plans can range from simple motor behavior (e.g. planning a sequence of key presses) (Pascual-Leone et al., 1993) to a high-demanding cognitive task (e.g. deciding on the steps required to land an airplane) (Suchman, 1987). Planning can be measured in simple and/or more complex tasks (Schwartz et al., 1991).

Thus, we can distinguish two different models according to the complexity level: simple motor planning and cognitive planning.

1.3.4. Simple motor planning behavior

A simple planned motor behavior (**Figure 3**) involves a sensorimotor interaction between the organism and its environment that culminates in an appropriate motor response (Wong, Haith & Krakauer, 2014). Wong et al. (2014) proposed that motor planning can be divided into two main domains: *i)* the perceptual domain that identifies the goal of the movement through the selection of an object and the application of task rules: what to do to that object, defining this way the motor goal. Then, *ii)* the motor domain that includes specification of the movement trajectory for the desired action, a description of how the end-effector will produce an action, and finally, a description of the full set of the joint trajectories or muscle activations required to execute the movement (respectively abstract kinematic representation, action selection, and movement specification). These processes form a single unifying framework to describe the pathway from perception to movement (Wong, Haith & Krakauer, 2014).
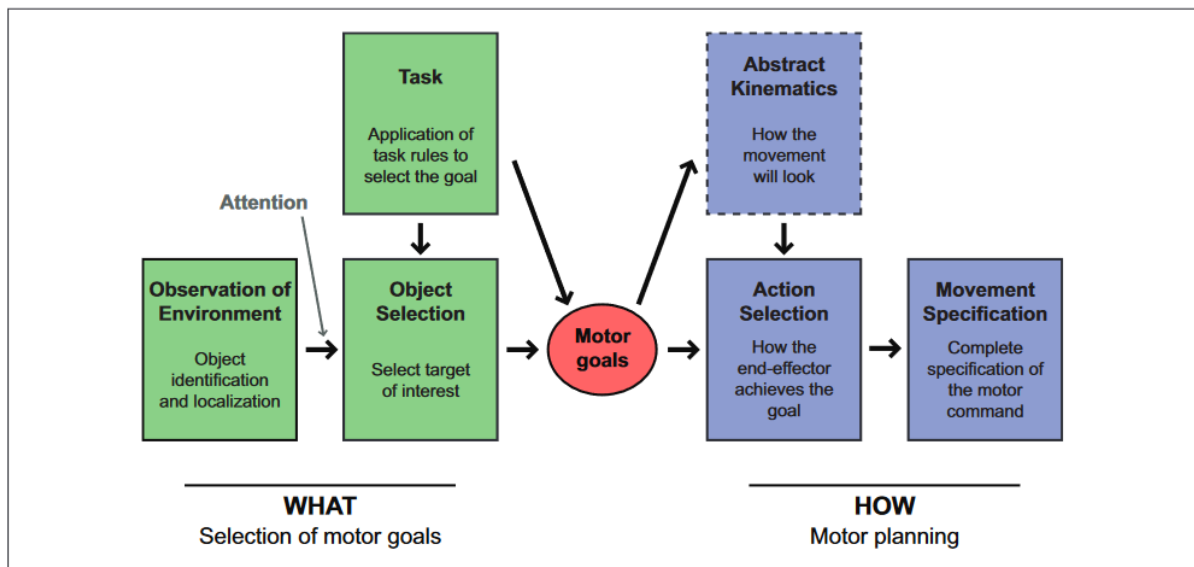
Figure 3. Simple motor planning. The process starts with the observation of the environment to identify all possible targets. The target of interest is selected using attentional processes. Additional task rules or constraints may be combined with the identified target to create a motor goal. After the motor goal is established, motor planning processes define how the movement will be produced. More complex movements may require the specification of a trajectory before the action can be selected. Finally, the complete set of motor commands necessary to produce the planned movement can be generated. This framework establishes a definition of motor planning in the context of the pathway from perception to movement (taken from Wong, Haith & Krakauer, 2014).

1.3.5. Cognitive Planning

More complex planning behavior can be divided into two major phases: *i)* a mental planning phase that involves the internal representation of a sequence of steps (i.e. plans) (Wilensky, 1983) and *ii)* a planning execution phase that involves the motor action to achieve a goal previously planned (Grafman & Hendler, 1991).

According to the *Problem Space* problem-solving theory, there may be several possible ways to achieve a goal. Therefore, specific actions are selected from a variety of optional behaviors. Some behaviors may be more efficient or appropriate than others (Newell & Simon, 1972). However, according to this theory, there are two means to solve a problem: algorithms or heuristics. The algorithms deliver a secure path to find a solution and achieving the goal, and they can define the whole range of possible options to ensure a solution. Algorithms provide complete mapping of the problem, and the solution is reduced to read the correct path of all possible behavioral states relative to the objective. However, humans do not solve problems (or plan their solutions) in this manner because they are biologically limited by their cognitive resources (Luck & Vogel, 1997). Thus, algorithms are often used by computer programs that can process all possible options. Contrarily, after creating a subjective representation of the current state relative to the goal, the most noticeable options are evaluated and selected in the case of human planning. Each time the current state changes, there is updating and monitoring of the effectiveness of sub-goals (i.e. online monitoring). Thus, it has been proposed that humans solve problems using heuristics. Heuristics implies a selective search for portions of the problem to solve, specifically those most likely to be solved, ignoring other options. This solution method optimizes cognitive resources to plan the solution of a problem but can lead to errors and does not ensure objective realization, thus the gain in efficiency is lost in effectiveness. Newell and Simon (1972) proposed that heuristics would guide operators' selection (sequenced behaviors to achieve sub-goals). The simplest heuristic approach is "repeat-state avoidance" or "backup avoidance", in which individuals prefer not to take an action that could lead them to a previous stage. Yet another heuristic is "difference reduction" or "hill-climbing" where people choose the behavior that leads them to a greater similarity between the current state and the goal state. However, the lack of flexibility of these heuristics has been criticized, because they fail in providing answers on how to proceed when subjects cannot choose an action or if the chosen action does not lead them to the expected results. The most sophisticated heuristic is the "means-ends analysis", where the subject performs a

"difference reduction" while considering what to do if the action cannot be chosen (Newell & Simon, 1972). Willingham (2008) proposed that the "means-ends analysis" heuristic may be specified as follows: *i)* Compare the current state with the goal state. If there are no differences between them, then the problem is solved; *ii)* If there is a difference between the current state and the goal state, an objective that solves that difference is set. If there is more than one difference, a goal that solves the biggest difference is set; *iii)* Return to step one with the new goal set in a fourth step if needed. Therefore, according to this heuristic, when an operator is executed and an unforeseen obstacle appears, the subject can set up a new sub-goal to remove the obstacle. This is a recursive procedure that can be repeated until the target is reached (Sternberg & Ben-Zeev, 2001), giving a solution to the previous heuristic's lack of response.

The planning process comprises a set of cognitive components. Thus, each plan consists of events, having a determined duration of time. The number of events may vary according to each plan; unforeseen events may deviate from the plan slightly or strongly. For example, a person elaborates a plan to have dinner at a friend's house. To do this, this person decides to go riding a bike, generating a plan to visit this friend which might consist of various events, e.g., preparing the bike, checking the safety equipment, establishing a route to be taken, and riding until reaching the destination. The contingencies that could disrupt a plan might be branching, which is an event that forces the person to stop at the stage of the plan was and solve the unforeseen issue. From there, the plan is resumed from where it was interrupted. In our example, branching can occur if, *en route*, the person receives a call requesting to buy some groceries on the way. This would imply deviating from the planned route to buy what is required and then returning to the same point on the route. Another type of unforeseen event can be reactive planning, which involves the unexpected introduction of a new plan event. In the example, we can consider that a part of the planned route was inaccessible due to reconstruction, which leads to taking a detour around three additional streets to reach the friend's house (Grafman, Spector & Rattermann, 2005).

Plans can be made to solve well-defined or ill-structured problems (Spector & Grafman, 1994). Resuming the example, an ill-structured problem would be to plan a route considering a general orientation from the origin to the destination, where the specific streets to reach the destination will be decided online during the trip. Contrarily, a well-defined problem would be

to plan a route by defining all the routes previously to be used beforehand (Grafman, Spector & Rattermann, 2005).
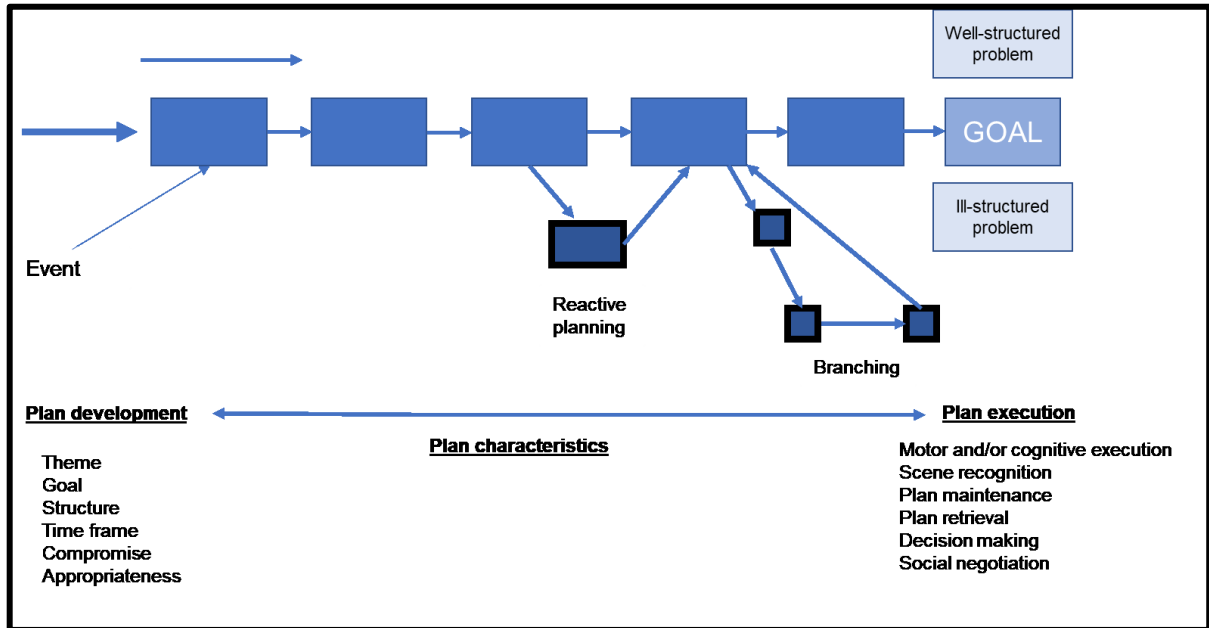
Figure 4. Components of the planning process (modified from Grafman, Spector & Ratterman, 2005).

In summary, the processes involved in planning are the production stage (plan development), where the sequence of possible actions are mentally generated, represented, stored, evaluated, and selected to be executed in a sequence of events, and the execution stage (**Figure 4**). To execute the plan, a sequence of actions is retrieved from long-term memory, loaded into working memory and performed (Gilhooly, 2005). Therefore, planning requires tight-knit operation of several cognitive components of the EFs (e.g., working memory, attentional control, response inhibition, cognitive flexibility), making the experimental manipulation and isolation of other EFs difficult (Hayes-Roth & Hayes-Roth, 1979; Tremblay et al., 1994).

1.4. Behavioral Planning Paradigms

Since planning is compromised in several psychiatric and cognitive disorders such as attention-deficit hyperactivity disorder (Barkley, 2004; Gau & Shang, 2010), major depressive disorder (Bora, Harrison, Yücel & Pantelis, 2013; Rive, Koeter, Veltman, Schene & Ruhé, 2016), bipolar disorder (Rive et al., 2016), schizophrenia (Holt, Wolf, Funke, Weisbrod &

Kaiser, 2013), frontotemporal dementias (Lima-Silva et al., 2013) as well as those due to frontal lesions (Karnath, Wallesch & Zimmermann, 1991), the implementation of proper experimental tests has been challenging. This is especially true for clinical neuropsychology, which has considerably contributed to the study of planning, specifically in the design of behavioral paradigms that allow for quantifying and characterizing normal and impaired planning performance in healthy and pathological subjects.

There are behavioral paradigms to evaluate planning performance based on semantically rich problems versus semantically impoverished problems. Semantically rich problems require some background knowledge, while impoverished problems require no specialized background knowledge. Mazes, puzzles, etc. represent the latter that healthy control subjects can usually solve within a short period. The former requires more background knowledge to resolve the problem presented effectively (e.g., chess problems, deciding medical procedures in context of clinical emergencies, etc.) (Gilhooly. 2005). In this doctoral research study, the focus is on impoverished problems because of using this approach allows us to study planning abilities and its neural correlates in the general population.

1.4.1. Tower of London Task

One of the most traditional paradigms used in neuropsychology and neuroscience to fundamentally evaluate planning (Unterrainer et al, 2004) is the Tower of London (TOL) (Shallice, 1982), a task adapted from the Tower of Hanoi (Simon, 1975), which has been used to measure processes such as organizing, working memory, inhibitory control of potential distractors, and cognitive flexibility (**Figure 5**).
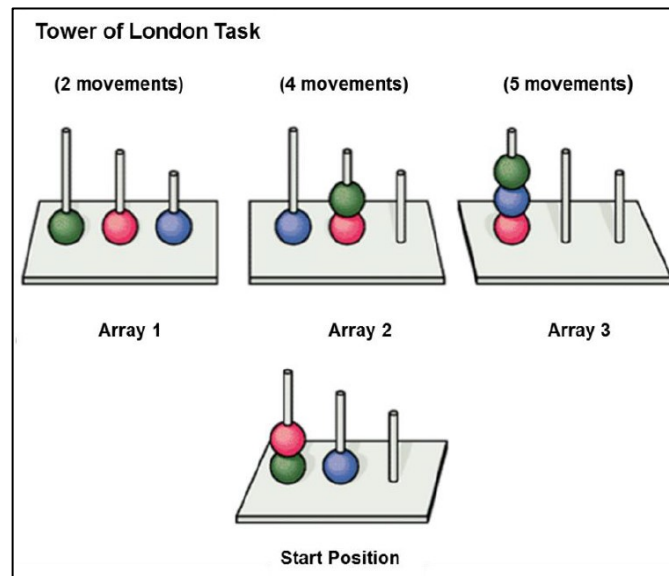
Figure 5. Tower of London Task Representation.
Above, the subject is instructed to copy different arrays following a set of rules: move a sphere one at a time, with the least possible number of moves, and as fast as possible. Below, the start position prior to executing the movements (modified from Shallice, 1982).

The TOL consists of the presentation of three spheres of different colors each (red, blue, and yellow) inserted on a device with three rods with different sizes: a large one that can carry three spheres, a medium one that can carry two, and one that can carry only one. A second device with a different distribution of spheres on different rods is presented to the subject as a model. The subject is then instructed to copy the model following some rules (see **Figure 4**). Here, the outcomes will include reaction time, number of movements made, and accuracy that will reflect the subject's planning skills. TOL can discriminate between patients with frontal lesions from controls (Shallice, 1982; Carlin et al., 2000). During this task, the problem solver plans move by assessing the difference between the current state and the goal state, and then selects or establishes a sequence of operators that minimize this difference (Ormerod, 2005). Thus, TOL has been posited as an example of a well-defined problem that demands the deployment of heuristics such as hill-climbing and means-ends analysis (Anderson, 1993; Simon & Reed, 1976). Virtual versions of TOL adapted for cognitive neuroscience research (Campbell et al, 2009) have shown that performance on this task is highly dependent on frontal lobe functioning (Colvin, Dunbar & Grafman, 2001; Owen et al., 1995).

1.4.2. Porteus Maze Task

The Porteus Maze has been widely used to study visuospatial abilities and executive functions such as problem-solving and planning in healthy control subjects and neuropsychiatric population (e.g. schizophrenia, dementia, alcoholism, ADHD) in a highly PFC-dependent visuospatial context (Krieger, Lis & Gallhofer, 2001; Peters & Jones, 1951; Gallhofer et al, 1996; Tremblay et al., 1994; Lezak, 1995). Moreover, neurological patients with fronto-medial lesions have shown performance impairment in this task with a greater number of errors (entry into dead ends) (Karnath, Wallesch & Zimmermenn, 1991). Originally, Porteus Mazes was a pencil-and-paper task (**Figure 6A**) that began with simple visual stimulus analysis. The subject had to find and draw the right way from a starting point to the exit (out of several options), following some rules such as avoiding crossing cut roads and dead-ends, and performing as quickly as possible (Porteus, 1959). Whenever a bifurcation appears while the path is being drawn, subjects make decisions in order to accomplish the goal and avoid breaking the given rules (Lis et al., 2005). As in the case of the TOL task, hill-climbing and means-ends analysis heuristics have to be used (Anderson, 1993; Simon & Reed, 1976) because subjects plan paths by assessing the difference between the current state (their place on the maze) and the goal state (the exit of the maze) and then selecting or establishing a sequence of operators (paths to draw) that minimize this difference (Ormerod, 2005). Studies using route-finding mazes have found that subjects tend to navigate mazes by using an opportunistic strategy, which depends more on the maze environment and perceptual processing. In contrast, the retrieval of a complete cognitive plan for solving the maze requires prefrontal cortex participation (Flitman, Cooper, & Grafman, 1997).

Currently, Porteus Maze has been adapted using neuroimaging techniques (Tremblay et al., 1996; Kirsch et al. 2006). Kirsch et al. studied hemodynamic brain changes during planning performance (2006) using this task. Since planning involves several cognitive components, the use of proper control conditions is crucial (Crowe et al., 2000; Krieger, Lis & Gallhofer, 2001). Interestingly, these authors used two control conditions to separate planning from other cognitive components (**Figure 6B**): a resting condition, where subjects were instructed to look passively at stimuli consisting of a non-maze pattern with a comparable physically complexity; and a pseudo-maze condition, where subjects were instructed to find an exit on pseudo-maze stimuli with no decision points (no bifurcation, thus no planning) (Kirsch et al., 2006).
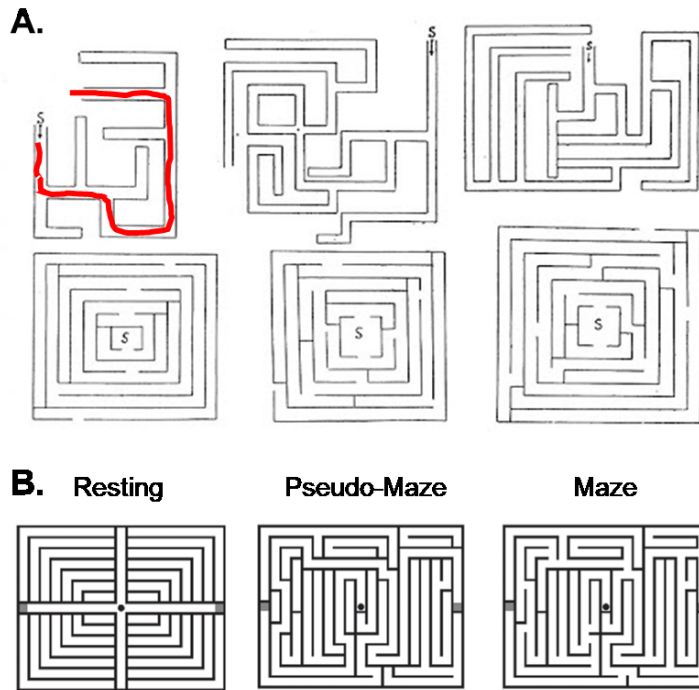
Figure 6. Porteus Maze Task. A) Original Porteus Maze. Subjects are instructed to find an exit by drawing a path starting at "S" by following a set of rules (Modified from Porteus, 1959). B) Three different Porteus Maze Task conditions adapted to be used in fMRI. On the left, the rest condition: Subjects are instructed to passively observe the stimulus. On the middle, the pseudo-maze condition: Subjects have to mentally follow the path that leads to the exit. This condition has no bifurcation. On the right, the experimental condition: Subjects are instructed to find the exit avoiding dead ends, and to make decisions whenever a bifurcation appears in their path (modified from Kirsh et al, 2006).

1.4.3. Zoo Map Task

Due to the lack of behavioral tasks with ecological validity, Wilson et al. (1996) designed the Behavioral Assessment of the Dysexecutive Syndrome battery to measure EFs (Wilson, Alderman, Burgess, Emslie & Evans, 1996). This battery includes a subtest called the Zoo Map Task which provides valid indicators of planning ability (Oosterman, Wijers, & Kessels, 2013). More importantly, this subtest has the advantage of enabling measurement of planning and organizational skills more ecologically.

The Zoo Map Task is a pencil-and-paper test consisting of planning a path to visit 6 locations out of 12 on a zoo map stimulus. The different locations are common places that are possible to find in a regular zoo, e.g., an elephant house, a lion's cage, a resting place, a coffee shop, etc. Two conditions evaluate different planning levels: *i)* the formulation condition in which subjects are instructed to plan a route to visit six locations in any order preferred but in accordance with a set of rules. Alternatively, there is *ii)* the execution condition, where subjects are instructed to visit six locations in a specific order given and following a set of rules (**Figure 7**). These two conditions provide information about planning skills on an ill-structured (formulation) and well-structured (execution) problems. The former has been presented as a

task that is a cognitively more demanding task in an open-end situation because subjects are required to develop a logical strategy to achieve the goal. Before tracing a path, a sequence of operators must be elaborated; otherwise, committing mistakes becomes very likely. On the other hand, the latter requires a lower cognitive demand because the resolution of a task that involves following an externally imposed specific strategy only requires monitoring the given formulated plan's implementation to achieve the goal (Wilson et al., 1996).
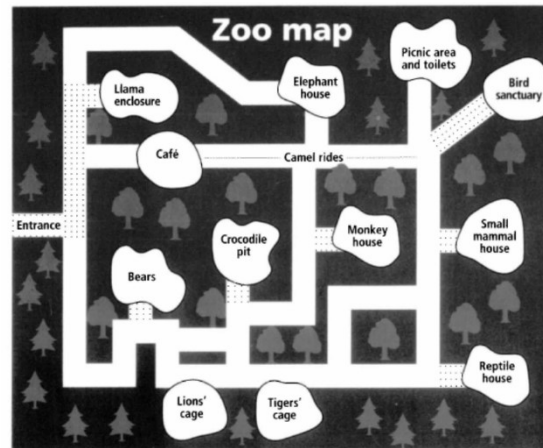
Figure 7. Zoo Map Task (taken from Wilson et al., 1996).

The performance parameters in this task are as follows: the score obtained by correctly performing the sequence, the number of errors (such as paths being used more than once, deviations, falling to draw a continuous line, visiting wrong places), and the time used to plan (mental elaboration) and drawing the planned routes (execution) (Allain et al., 2005). The performance obtained from the two conditions allows assessing the spontaneous planning ability (formulation condition) versus executing an externally imposed strategy when the structure is high (execution condition).

Zoo Map Task has been used to study planning performance in different populations. For example, Allain et al. found that older adults had greater difficulties at the formulation level than older adults (2005). Boyer et al. found that children with the inattentive subtype ADHD showed an increased latency in the time required to complete the task compared to controls (2014).

However, proper performance on this task does not depend only on the planning skills, but also on several cognitive functions. Oosterman, Wijers and Kessels examined whether the

planning domain was a better predictor on this particular task in a sample of neurological and psychiatric patients (e.g. patients with traumatic brain injury, cerebrovascular disease, stroke, intracranial tumor, epilepsy, neurodegenerative disease, depression, and anxiety disorder), as compared to planning and other cognitive domains (episodic memory, processing speed, and inhibitory control) evaluated on other neuropsychological tests (2013). These researchers argued that multiple independent cognitive predictors could be identified if multiple functions are essential for planning performance. These predictors may, then, be used to determine whether there is an overlap of cognitive functions in neuropsychological tests. They found that the Zoo Map Task was the best predictor of planning as compared to other tests, and this is a valid indicator of planning ability, especially in the number of errors (visiting wrong places), in the patient population (Oosterman, Wijers & Kessels, 2013).

1.4.4. Ecological behavioral paradigms

Typically, behavioral paradigms used in cognitive neuroscience research are presented in lab-based sensory deprived settings using oversimplified stimuli, to avoid confounding factors that might interfere in the understanding of cognitive phenomena as much as possible (Miotto & Morris, 1998; Zaki & Ochsner, 2009; Shamay-Tsoory & Mendelsohn, 2019). For this reason, the brain mechanisms of several cognitive functions, including social cognition and high-order cognitive functions such as planning, is lacking.

There are two main limitations in studies using such artificial tasks, *i)* the person-dependent factor, which establishes that artificial tasks may limit the active role of the participants in paradigms affecting their sense of agency and embodiment; *ii)* the situation-dependent factor, which states that the artificial context where participants perform on tasks might engage different mechanisms than what a real-life context would demand (**Figure 8**) (Shamay-Tsoory & Mendelsohn, 2019). As a result, current cognitive neuroscience trends encourage and promote experimental designs with greater ecological validity, since this might bring more extrapolatable findings to understand the brain mechanisms underlying human cognition (Caine, 2005; Kingstone et al., 2002; Zaki & Ochsner, 2009).
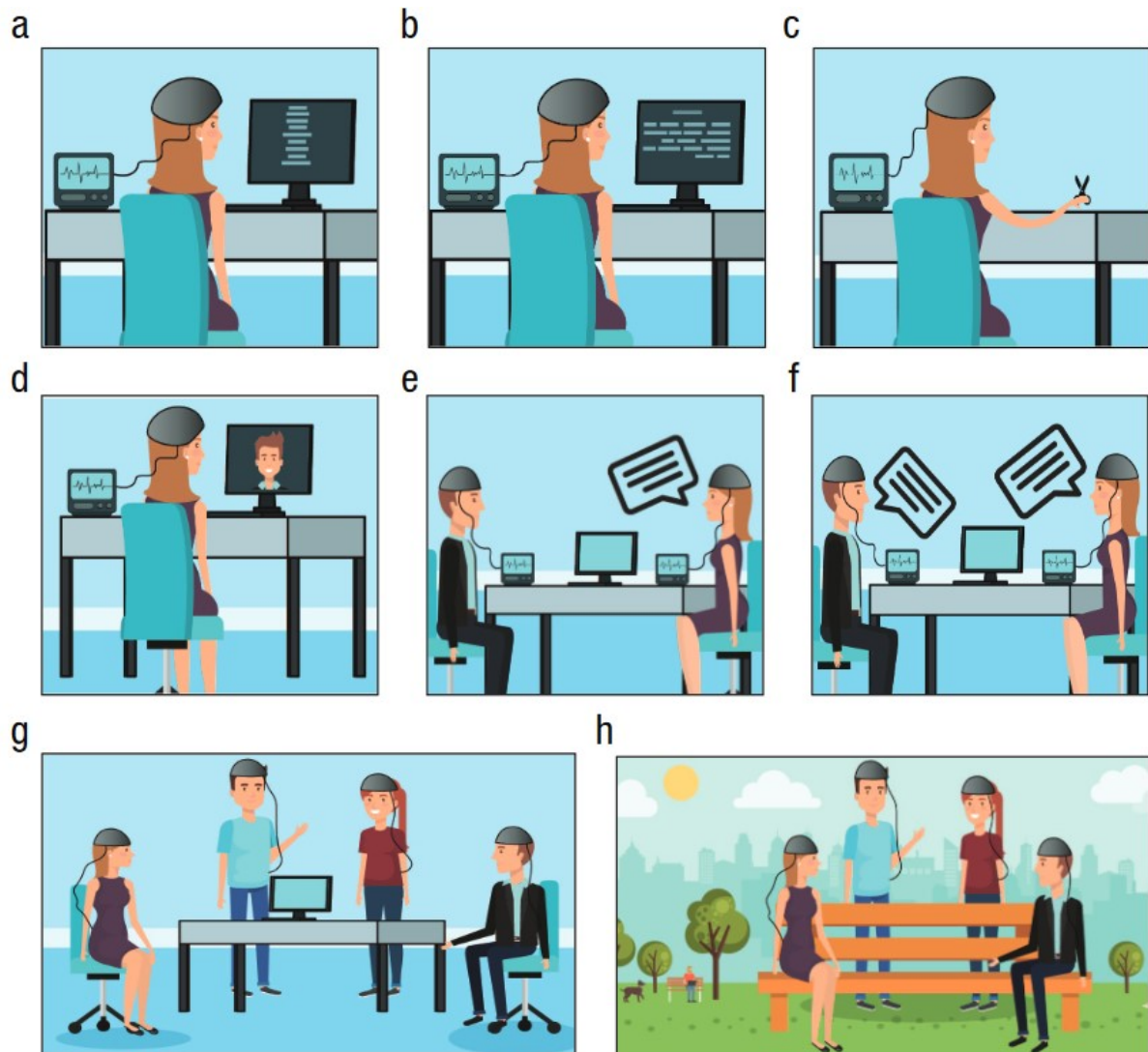
Figure 8. Experimental Settings in Cognitive Neuroscience. a) A traditional lab-based setting for evaluating human cognition, showing a deprived environment with artificial tasks such as memorizing a decontextualized word list (situation-dependent limitation). The participant cannot affect the situation (person-dependent limitation). b) The task involves meaningful stimuli (e.g., reading a story) but the participant cannot affect the situation (situation dependent). c) The participant is able to interact with an object, but the context is limited. d) There are artificial social stimuli presented on a screen. e) Lab-based unidirectional interactions. f) Dyadic bidirectional interactions: the participant may exchange information and receive feedback from another subject. The context is limited (situation-dependent limitation). g) Multi-brain interactions allowing assessment of group dynamics in the lab. h) Real-life multidirectional interaction: Participants interact as part of a group and the situation is evaluated in a naturalistic condition (taken from Shamay-Tsoory & Mendelsohn, 2019).

1.4.5. A Novel Planning Task

Taking these factors into account, in this doctoral thesis we have designed a behavioral paradigm based on the Zoo Map and Porteus Maze Tasks that allow the measurement of the planning function in a controlled setting. There are several trade-offs in our design. While our novel planning task sticks to a deprived lab-based setting, the task is enriched with meaningful stimuli and goals. The behavioral paradigm was composed of a planning task that demands the performance of a daily life situation divided into four different periods present in cognitive planning: *i)* a planning period, where subjects were asked to plan paths to visit different locations on a map while monitoring whether the plan being elaborated follows a set of rules; *ii)* a maintenance period, where subjects had to store the planned path in their working memory. This was followed by *iii)* the execution period, where subjects drew the previously planned path while monitoring and controlling its correct execution. Finally, there was *iv)* a response period, where subjects reported the sequence of animals visited according to their planned path. This paradigm uses different stages to measure different parameters that account for the planning capacity, including the display of its different components involved (including working memory, attentional control, visuospatial analysis, among others) in a way that is more analogous to real-life situations, since planning paths on maps is a common daily activity. Furthermore, to control confounding factors, the paradigm considers a control task with the same structure and psychophysical stimuli as the planning task and demands the implementation of cognitive components that also emerge during cognitive planning (working memory, attentional control, and visuospatial analysis). The only exception here is elaborating a plan per se, since the control task has a different goal. This allows for adequate isolation of the cognitive planning factor for contrasting the parameters of both behavioral performance and electrophysiological signals.

1.5. Neural Correlates of Planning

Neuroimaging studies have provided valuable evidence about the critical role of the prefrontal cortex (PFC) in cognitive control, including planning. The most traditional paradigm used in those studies to evaluate planning is the Tower of London Task (TOL) (Shallice, 1982; Unterrainer et al., 2004) which has helped to demonstrate the involvement of the dorsolateral PFC (dlPFC) (Nitschke et al., 2017), the mid-Cingulate cortex (MCC), the ACC, and the

superior parietal lobe, among other brain regions (Kirsch et al., 2006; Newman, Carpenter, Varma, & Just, 2003; Owen, Doyon, Petrides & Evans, 1996).

First evidence in the literature were provided in a set of studies using PET and the TOL paradigm. These studies shown that the dlPFC is involved during planning activity (Morris et al., 1993; Owen et al., 1996; Baker et al., 1996; Dagher et al., 1999). For instance, Owen et al. (1996) evaluated regional cerebral blood flow (rCBF) changes associated with the execution of a planning task while subjects performed TOL under different levels of complexity. Significant increases in rCBF were observed in the left mid-dorsolateral frontal cortex during the planning condition (**Figure 9A**). Using the same technique and behavioral paradigm, Dagher et al. (1999) assessed relative rCFB changes associated with planning conditions of different complexities, and found that only the dlPFC, ACC, and the caudate nucleus co-varied its rCBF according to the complexity of the task (**Figure 9B**).
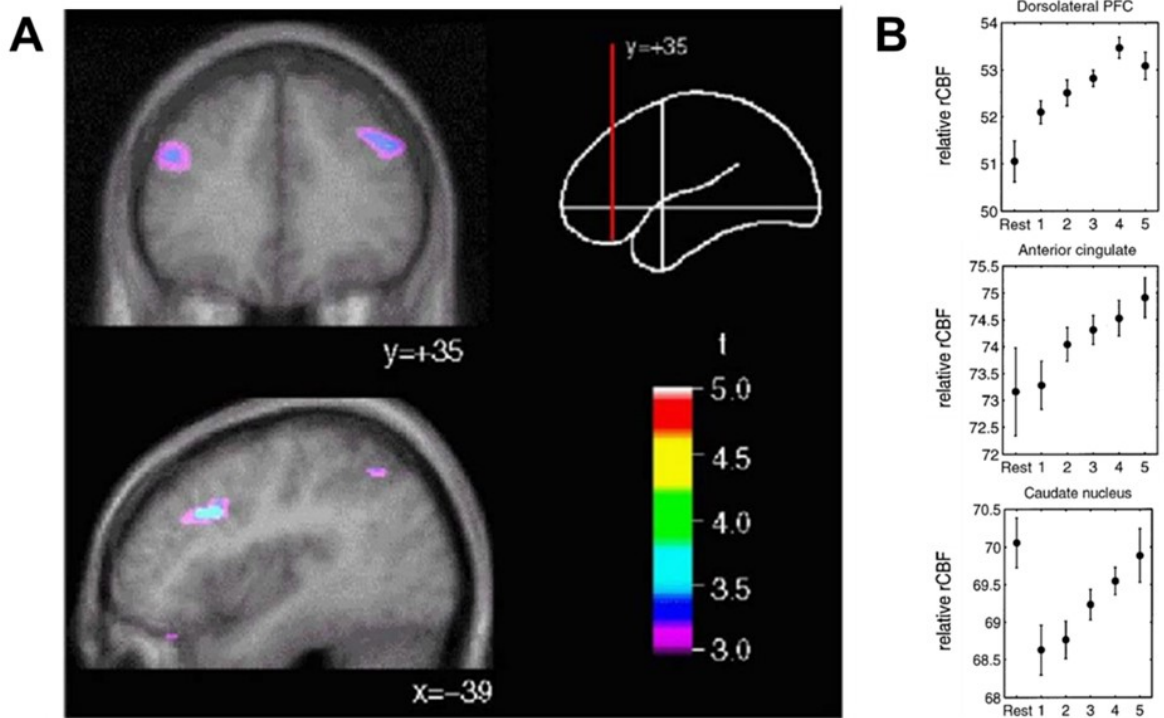
Figure 9. Brain Areas Involved in Planning. A) Activation in the mid-dorsolateral frontal cortex during planning function using the Tower of London Task and PET (taken from Unterrainer & Owen, 2006; adapted from Owen et al., 1996). B) Brain areas involved in planning complexity: rCBF changes in dlPFC, the ACC, and caudate nucleus were correlated to task complexity (measured by Tower of London Task) suggesting that they are involved in highly demanding planning (taken from Dagher et al, 1999).

Another set of evidence comes from studies using fMRI, which also found increased in blood oxygenation level-dependent (BOLD) signal, mainly in dlPFC while performing planning in a TOL paradigm (Lazeron el al., 2000; Newman et al., 2003; van den Heuvel et al., 2003). Particularly, Lazeron et al. (2000) demonstrated bilateral activation in dlPFC, the ACC, and parietal regions during planning. Furthermore, Newman et al. (2003) compared brain activation while performing the TOL with three levels of complexity (easy, moderate, and difficult). Bilateral dlPFC and Superior Parietal Lobe exhibited an increase in BOLD signal with increased in complexity (**Figure 10**). Moreover, van den Heuvel et al. (2003) found that planning correlated with an increased BOLD signal in the dlPFC, striatum, and the parietal regions. Interestingly, increasing task complexity correlated only with activity in the left FP cortex (**Figure 11**). This region has been shown to be involved in third-order higher cognitive functioning: temporarily holding an ongoing goal in mind while first completing intermediate tasks or subgoals (Burguess, Quayle & Frith, 2001; Baddeley, 1996).
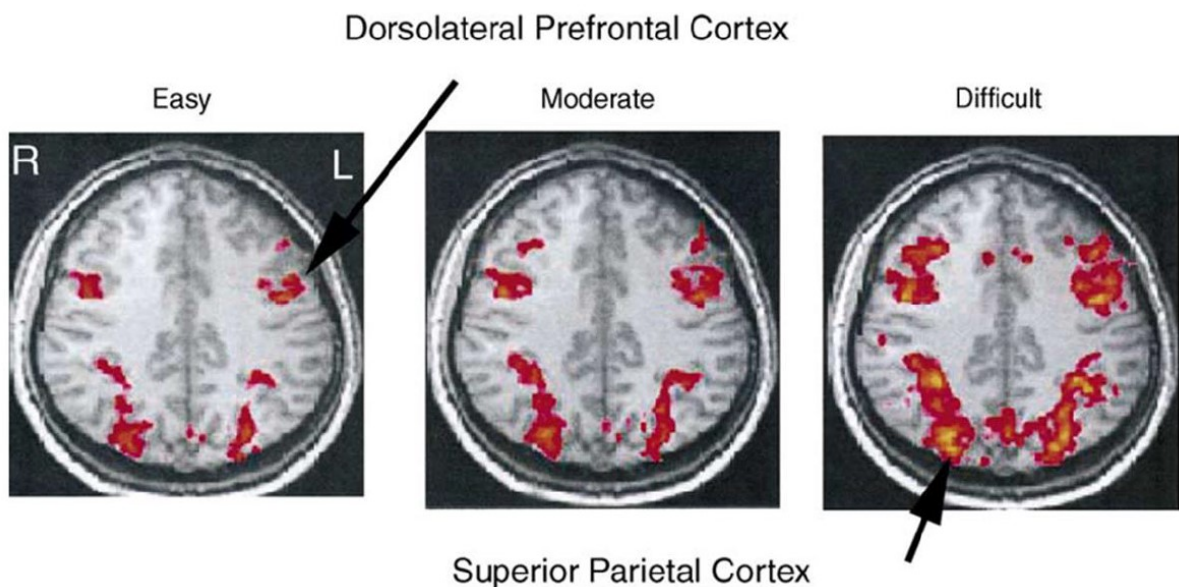
Figure 10. Dorsolateral Prefrontal Cortex and Superior Parietal Cortex Involved in Planning Complexity. BOLD activity patterns for each complexity level in a Tower of London task paradigm. On the left, the easy condition, in the middle the moderate condition, and on the right the difficult condition. BOLD activity increases according to the task complexity in the dlPFC and the superior parietal cortex (taken from Newman, 2003).
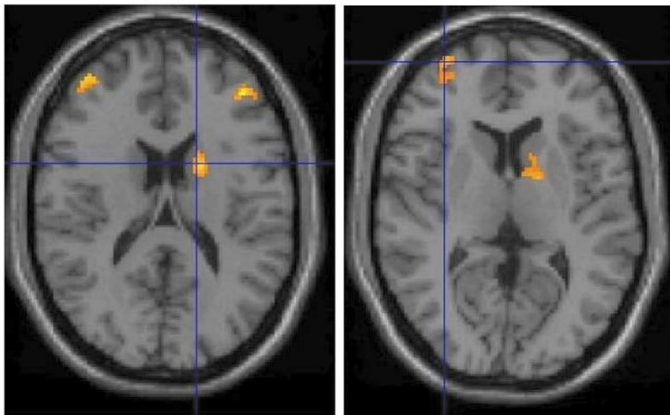
Figure 11. BOLD signal increases in bilateral dorsolateral prefrontal cortex and right caudate nucleus (left), and left frontopolar cortex and right pallidum (right), correlating with increased task complexity (taken from van den Heuvel et al., 2003).

Other studies using different behavioral paradigms have also shown the implication of the dlPFC in planning function. For instance, using fMRI and a Porteus Maze paradigm, Kirsch et al. (2006), found BOLD increases in dlPFC, ventrolateral PFC, and the dorsal part of the parietal lobe (**Figure 12**). However, determining the relative cognitive contributions of these different regions involved in planning has long been a subject of debate.

Although several studies mentioned above were conducted before the introduction of correction methods (such as multiple comparisons, double-dipping, etc.) in the neuroimaging research (Woo, Krishnan & Wager et al., 2014; Eklund, Nichols & Knutsson, 2016), over the past few years evidence that supports the PFC involvement in planning function has been provided (Milla et al., 2019; Kaller el al., 2015; Korn & Bach, 2018; Javadi et al., 2017; Spiers & Gilbert, 2015; Brown et al., 2016; Balaguer et al., 2016) . For instance, using fMRI and a virtual subway task where subjects were asked to plan paths, Balaguer el al. (2016) found that plans are represented hierarchically over contexts as well as states. These hierarchical plans are encoded in the caudal prefrontal cortex (the bilateral anterior premotor region and the dorsomedial PFC) (Balaguer el al., 2016; Holroyd and Yeung, 2012). Additionally, Milla et al. (2019) showed associations between planning performance and oxygenated hemoglobin changes in PFC during a Tower of Hanoi paradigm using functional near-infrared spectroscopy. Furthermore, Kaller et al. (2015) found that the strength of the left and the right mid-dlPFC connectivity was critical in predicting interindividual differences in planning performance across different stages of adulthood. Moreover, Korn and Bach (2018) using fMRI demonstrated that sequential decision-making implemented by planning may emerge from the

integration between heuristic and optimal policies, implemented by controllers in the medial prefrontal cortex.

Figure 12. BOLD increases during maze and pseudo-maze completion superimposed on a standard model brain comparing each condition with the others: maze > rest (a), pseudo-maze > rest (b), and maze > pseudo-maze (c) (taken from Kirsch et al., 2006).

1.5.1. Functional Contributions of the Anterior Cingulate Cortex and the Mid-cingulate Cortex in Cognitive Control

The ACC and the MCC are engaged by tasks that demand cognitive control. Numerous meta-analyses of the neuroimaging literature have confirmed the involvement of the ACC (Nee et al., 2007), and the MCC (Botvinick, Cohen & Carter, 2004; Niendam et al., 2012; Ridderinkhof et al., 2004; Shackman et al., 2011) in control-demanding tasks, and these have been supported by evidence of a causal relationship between the ACC (Shenhav et al., 2013; Metzler-Baddeley et al., 2012), the MCC (Tolomeo et al., 2016), and cognitive control.

Particularly, the ACC has been proposed to play a key role in several aspects of performance monitoring and cognitive control, such as error and conflict detection, as well as predicting errors among other functions (Brown, 2017). **Figure 13** summarizes conflict models that have been proposed over the years using Stroop tasks.
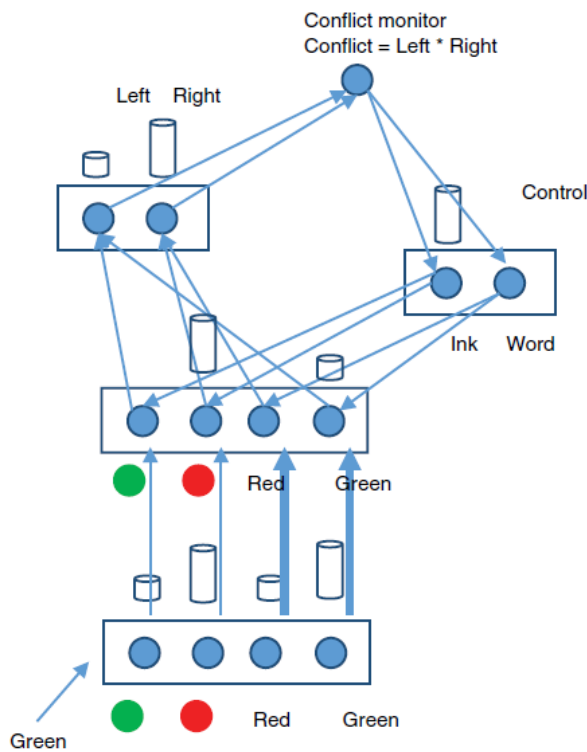
Figure 13. Conflict model of the Stroop task. The Stroop task consists of naming the color of the ink used to write a word stimulus while ignoring its semantic meaning. Whenever the subject is presented with an incongruent stimulus, the cognitive representations of the left and right responses are activated. The conflict model states that the ACC detects the activation of two incompatible responses before a conflictive stimulus. Conflict = Left response activation level * Right response activation level (Botvinick et al., 2001). Detecting a conflict increases the control signals that lead the network to execute the correct response according to the rules provided for performing the task correctly (taken from Brown, 2017).

Another group of studies has posited that the cingulate cortex is highly involved in attention to task-relevant stimuli (Posner & DiGirolamo 1998; Dreher & Berman 2002; Weissman et al. 2005). Dissociating the functional role of narrowed and parcellated brain regions has proven to be difficult and controversial, since cognitive functions are active and exerted in a concerted manner (Orr & Weissman, 2009; Kirsch et al., 2006). Along these lines, Orr & Weissman (2009) designed a cross-modal attentional cueing task for fMRI to investigate regional specialization in the cingulate cortex for processes that increase attention to relevant stimuli and those that detect response conflict (**Figure 14A**). Activity in the MCC was associated with an increase in attention to relevant stimuli, correlated with reaction times of orienting attention to those stimuli. A similar increase in the dlPFC has also been observed during driving attention towards relevant stimuli. On the other hand, the ACC activity was associated with detecting response conflict produced by irrelevant stimuli (**Figure 14B-C**). Findings in this study support a

differentiated role of the MCC and the ACC in cognitive control and provide insights about their putative role during higher cognitive processes such as planning.
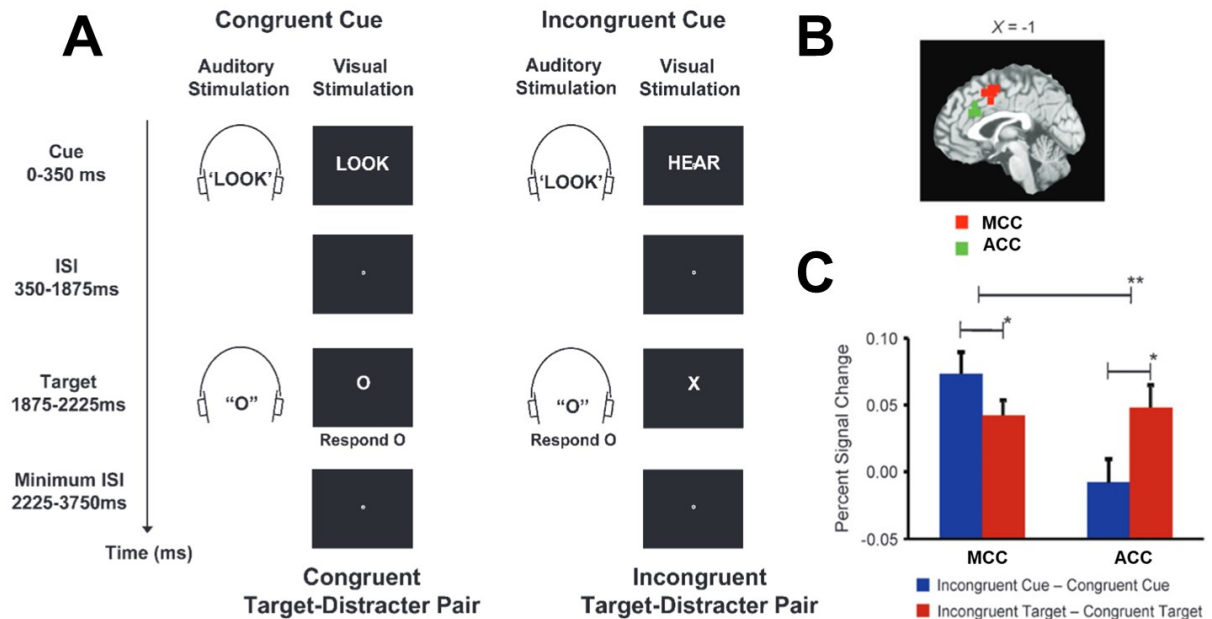
Figure 14. Functional dissociation for cognitive control in the cingulate cortex. A) Cross-modal attentional cueing task. In each trial of this study, a word cue (''Look'' or ''Hear'') was visually presented on a black screen instructing participants to attend to either the visual letter (''X'' or ''O'') or the auditory letter (''X'' or ''O'') of a possibly upcoming audiovisual target-distracter letter pair. The visually word cue presented at the beginning was accompanied by the presentation of an irrelevant, binaurally auditory word that also indicated either "Look" (Congruent cue condition, top left) or "Hear" (Incongruent cue condition, top right). After a brief interval (ISI), an audiovisual target-distracter letter pair was presented. The distracter letter was either congruent to the target letter (Congruent target-distracter condition, left) or incongruent to the target letter (Incongruent target-distracter condition). Participants were instructed to press one button if the cued target letter was an X and a different button if it was an O, as quickly as possible without making mistakes, using the index and middle fingers of their right hand. Researchers used two trial types to distinguish brain activity associated with cues (attentional process) from activity associated with targets (response conflict detection process). To isolate activity related to cues, they included "cue-only" trials in which only the cue was presented (33% of all trials). To isolate activity related to targets, they included "cue-plus-target" trials in which a cue was followed by a target (66% of all trials). Using a mixture of cue-only and cue-plus-target trials they could distinguish neural activity for cues from activity for targets. B) Sagittal view showing the ACC (green) and the MCC (red) on an MNI-normalized brain. C) Activity elicited by cue congruency and target congruency in the MCC and in the ACC. In the MCC, there was greater activity specific to cue congruency than to target congruency. In turn, there was an opposite effect in the ACC. A single asterisk shows p< .05. Two asterisks denote p< .005. Error bars represent S.E.M. (modified from Orr & Weissman, 2009).

1.5.2. The Frontopolar Cortex and Planning

Numerous brain lesion and functional neuroimaging studies have suggested that the frontopolar cortex (FPC), the most anterior part of the frontal lobes (**Figure 15A**), is involved in complex cognitive processes underlying reasoning, planning, and working memory, thus, forming the apex of the executive system (Koechlin & Hyafil, 2007). Activation in the FPC has been shown during several EF tasks. This includes the Tower of London task, which as mentioned before, measures planning function (Baker et al., 1996); the Raven's Progressive Matrices Test, which provides a non-verbal estimate of fluid intelligence (Prabhakaran et al., 1997); the Wisconsin Card Sorting Test, which measures cognitive flexibility (Berman et al., 1995; Goldberg et al., 1998; Nagahama et al., 1996); as well as inductive and probabilistic reasoning tasks (Goel et al., 1997; Osherson et al., 1998); and tasks with cognitive branching/multitasking (**Figure 15B**), where achieving goals in many tasks requires holding information about a pending task in short-term memory while alternative subtasks are being completed (Dreher et al., 2008). Patients with FPC lesions show no significant impairments on formal neuropsychological tests of perception, language, and intelligence. However, they appear markedly impaired in cognitive branching (Dreher et al., 2008), and decision-making in open-ended and ill-structured situations, which often occur in everyday life (Burgess, Dumontheil & Gilbert, 2007). Typically, these events are where the correct way of behaving is under-specified: there are many possible courses of action, and what constitutes success has to be self-determined (Burgess, 2000; Burgess et al., 2000; Goldstein, 1993).
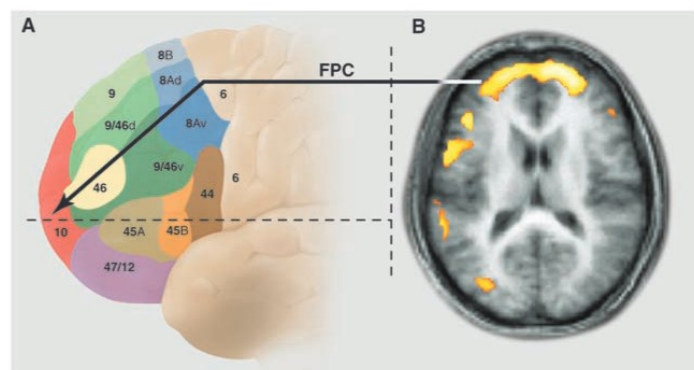
Figure 15. The human frontopolar cortex. (A) The FPC corresponds to the lateral Brodmann Area 10 (in red), the most rostral portion of the human prefrontal cortex (Pandya & Yeterian, 1996). (B) FPC activation observed using functional magnetic resonance imaging (fMRI) on a horizontal brain slice (dashed line indicates approximate localization) in multitasking behavior where subjects postponed the execution of a task to perform another task first (Koechlin et al., 2000).

Another cohort of studies that evaluated the function of the medial FPC in monkeys has demonstrated its role in monitoring the relevance of current and alternative goals. During reception of reward after successful self-generated response, the FPC in monkeys showed increased activity as compared to other PFC areas (Tsujimoto & Genovesio, 2017; Tsujimoto, Genovesio & Wise, 2010). Moreover, Mansouri et al. (2015) studied the effects of bilateral lesions in the FPC of monkeys on their ability to perform an adapted version of the Wisconsin Card Sorting Test (WCST) under different conditions. It was found that the FPC lesions cause no impairment in behavioral measures related to the working memory of rules, selective attention to the current rule, inhibition of a previously relevant rule, or assessment of the behavioral outcome to shift between abstract rules. On the other hand, lesions augmented the ability to remember relevant rules after meaningful distractions (presentation of rewards at random moments), or the need to execute a secondary task. These results may be pointing to the specialized role of the FPC in disengaging executive control from the current task and redirecting attention to novel sources of reward to explore new opportunities/goals. This, in turn, also points to a functional dissociation between the FPC and other prefrontal areas (Mansouri et al., 2015).

Additionally, the results obtained under the WCST condition that presented a secondary task (involving cognitive branching) suggest that non-lesioned monkeys are unable to hold relevant information, and simply restart the previous task after completing or exploring other options or sources of rewards. In contrast, cognitive branching is an inherent aspect of goal-directed behavior for human cognition (Mansouri et al., 2017). Humans with lateral FPC lesions exhibit impaired performance in tasks that demands cognitive branching. This suggests that the integrity of the lateral FPC, a region that seems to have no homolog in the monkey brain (**Figure 16**) (Neubert et al., 2014), is necessary to perform tasks requiring maintaining a primary goal in mind while processing secondary goals.
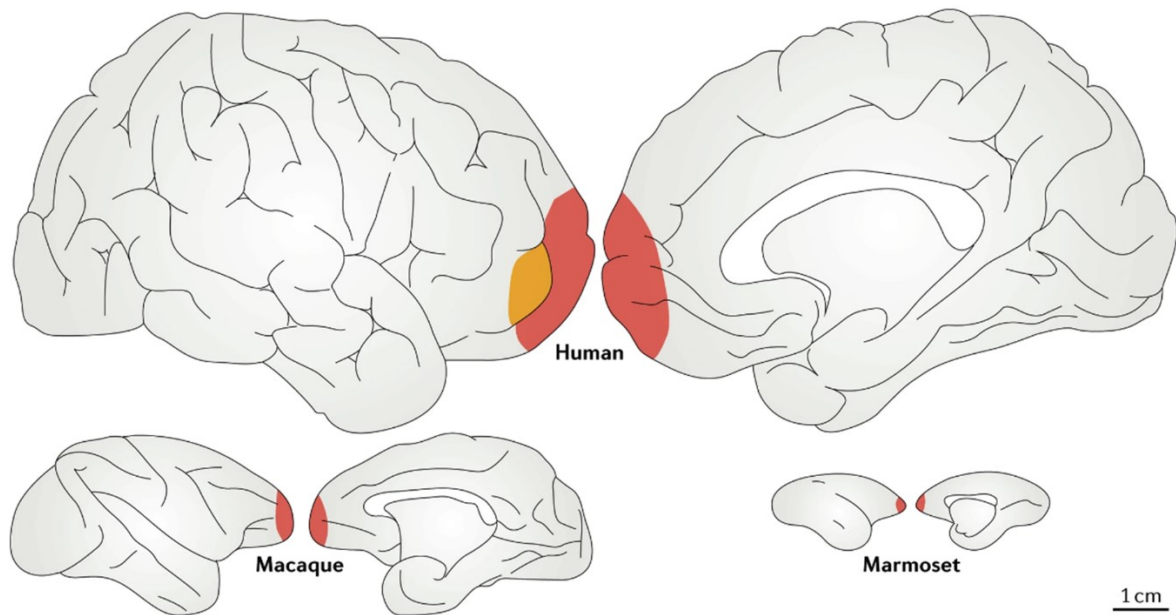
Figure 16. Neuroanatomy of the frontopolar cortex. The frontopolar cortex (BA 10) is shown in lateral (left) and medial (right) views of the right hemisphere in three species of primates. The extent of FPC is colored in red. In the human brain, yellow indicates the lateral part of the FPC, which is hypothesized to support functions such as cognitive branching, that monkeys are less capable of performing (Neubert et al., 2014; Koechlin 2014). Taken from Mansouri et al., 2017.

Considering the studies mentioned above, Mansouri et al. (2017) proposed a functional model of the FPC in monkeys (**Figure 17**). The model states that the PFC participates in exploitation mode of behavior, which consists of maximizing the value that can be obtained from an ongoing task or goal (Boschin, Piekema & Buckley, 2015; Mansouri et al., 2015), for instance, a monkey engaged in grooming a peer for a long time to receive social rewards. In the case of humans, we may imagine working at a specific job in a well-structured setting, allocating our cognitive resources to solve pre-determined challenges to achieve a goal and benefitting from this known source of reward. In such scenario, the FPC may be activated to participate in an exploration mode of behavior, monitoring the environment for alternative goals and its potential as a new source of reward, facilitating the disengagement of the ongoing behavior to allocate the cognitive resources to one of those alternative tasks (Boschin, Piekema & Buckley, 2015; Mansouri et al., 2015). Following the example, in the case of a monkey engaged in grooming a peer, it is essential to reallocate cognitive resources to other potentially relevant tasks such as cues of a predator, sources of food or other social opportunities (Mansouri et al., 2015). In the case of humans, if a promotion is offered during the current job, we might monitor and evaluate this new potential and advantageous source of reward before making a decision.
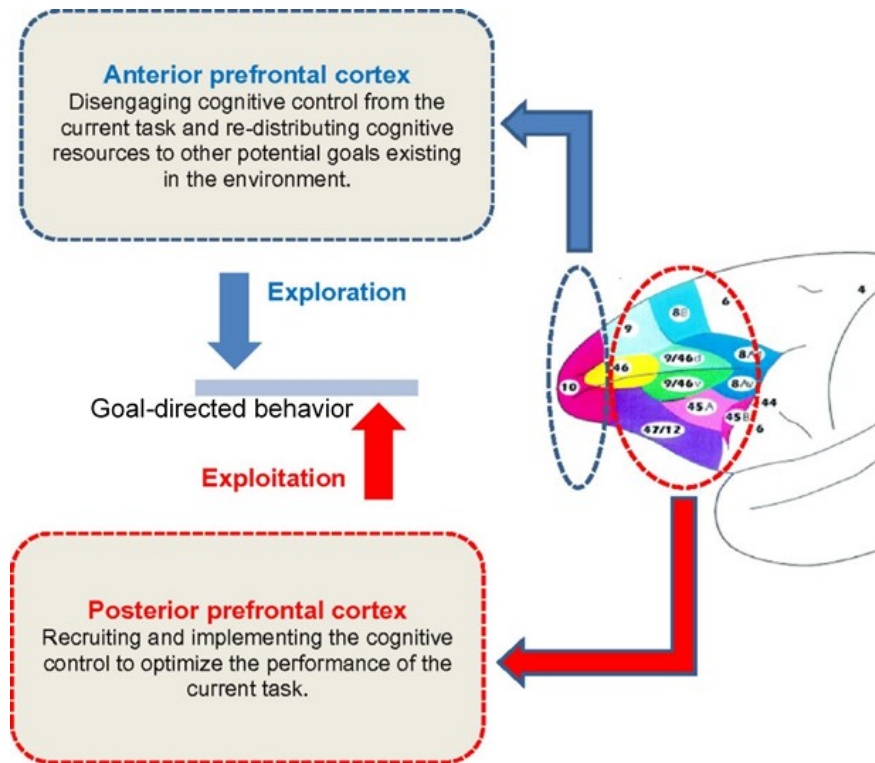
Figure 17. Functional role of the frontopolar cortex in monkeys. Mansouri et al. (2015) proposed that FPC (Brodmann Area 10, in blue) and posterior parts of the PFC (including dorsolateral and ventrolateral PFC, orbitofrontal cortex, Brodmann Area 8 within the peri-arcuate region and the ACC) have complementary but dissociable roles in adjusting the distribution of cognitive control. In this model, there is a balance between the 'exploitation' drive from the posterior parts of the PFC and the 'exploration' drive from the FPC that limits the focus on the current task and redistributes some cognitive resources to other potential goals (taken from Mansouri et al., 2015).

The idea of the function of the FPC in distributing attentional and executive resources away from an ongoing default behavior may explain the critical involvement of the human FPC in a variety of cognitive functions such as mind-wandering, planning, abstract reasoning, multitasking and cognitive branching, as these require changing from an ongoing behavioral option to another one considering multiple learned behavior options or exploring new ones.

There have been studies that combine computational modelling, behavioral tests and evidence from the fMRI technique to propose a new model that explains cognitive arbitration processes between exploitation and exploration modes of behavior (**Figure 17-18**). According to this model, there is a basic system (mediated by the medial FPC) that monitors the ongoing behavior's relevance online and triggers undirected exploration whenever this ongoing behavior is considered irrelevant. The relevance of the ongoing behavior is based on the

possible subsequent outcomes and the presence of contextual cues that have been previously built and stored in long-term memory. The second (mediated by the lateral FPC) is a system that monitors the relevance of different alternative behaviors online. These behaviors were previously learned when they were considered relevant by the basic system while using them as ongoing behavior but were subsequently considered irrelevant. This system allows replacing the ongoing behavior with one of these alternative behaviors when the former is no longer considered relevant by the basic system (**Figure 18**). This model integrates the two systems carried on by the medial and the lateral FPC, accounting for human sequential choices in uncertain, changing, recurrent or open-ended environments (Koechlin, 2011; Koechlin et al., 1999; Donoso, Collins & Koechlin; 2014; Koechlin, 2014; Wan, Cheng & Tanaka, 2016).

Additionally, fMRI studies in humans show that monitoring the relevance of behaviors based on expected outcomes is associated with anterior prefrontal activations: the medial PFC showed engagement when monitoring the ongoing behavior and the lateral PFC when monitoring alternative behaviors (Koechlin, 2011; Koechlin et al., 1999; Donoso, Collins & Koechlin; 2014). This latter engagement has been seen in the FPC region previously identified as subserving cognitive branching (Koechlin, 2011; Koechlin et al., 1999; Donoso, Collins & Koechlin; 2014), and may have no homologue in monkeys (Neubert et al., 2014).
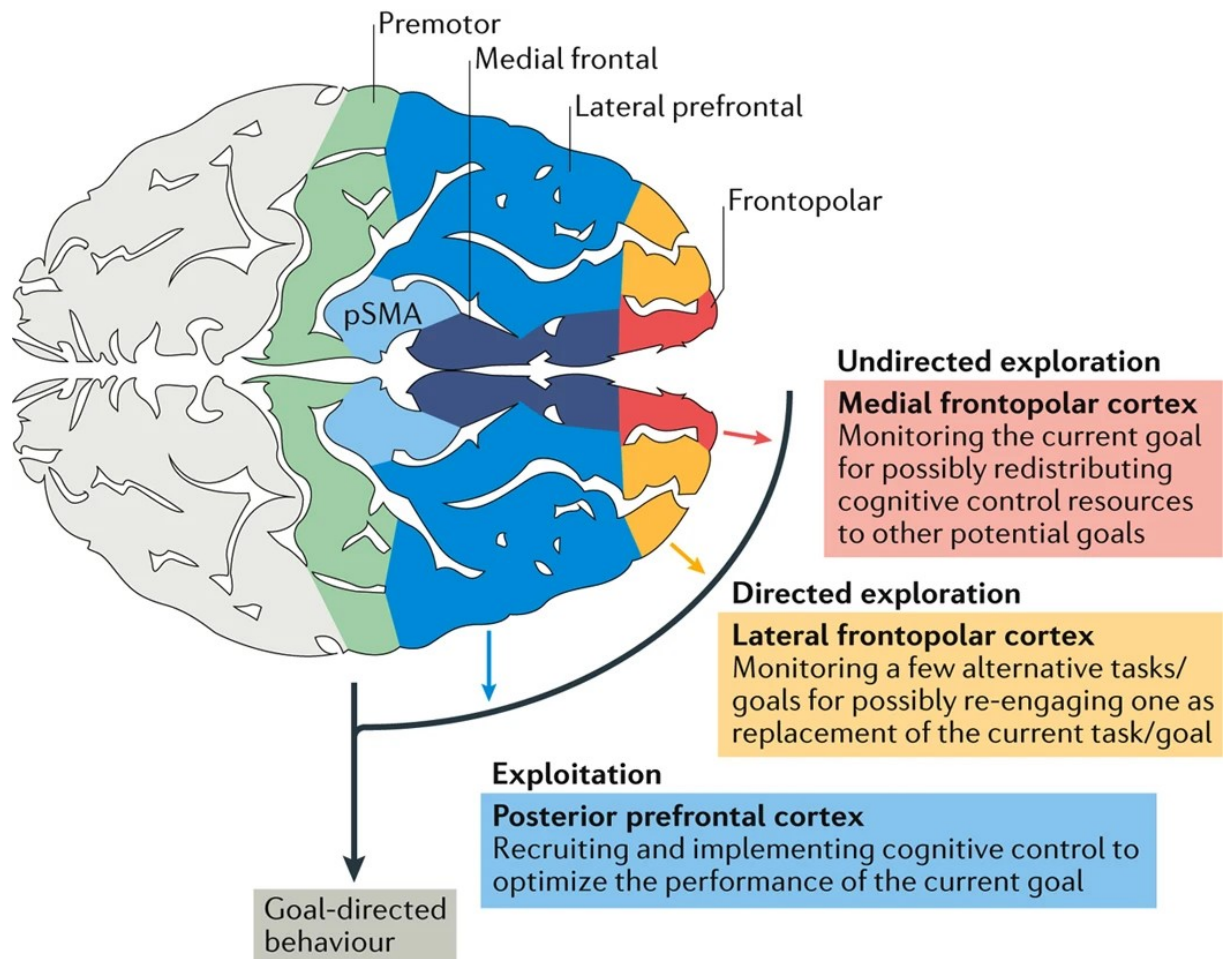
Figure 18. Functional role of the frontopolar cortex in humans. Mansouri et al. (2015) proposed that the monkey FPC evolved in humans through the development of a lateral FPC region. In both monkeys and humans, the medial FPC (in red) is mainly involved in undirected exploration which consists of monitoring the relevance of the ongoing behavior/current task and regulating the allocation of cognitive sources away from this current behavior or goal according to the context (internal and external contingencies). In humans, the lateral FPC (in yellow) is associated to directed exploration which consists of monitoring the relevance of a few alternative tasks, behaviors, or goals, and the opportunity to reallocate cognitive resources towards one of these. In both monkeys and humans, the posterior prefrontal cortex (in blue) is involved in exploitation which consists of controlling the execution of the current task or goal according to the context in which the subject is behaving. pSMA: pre-supplementary motor area (taken from Mansouri et al., 2015).

In the context of planning in humans, the medial FPC may activate while monitoring the relevance of elaborating a determined sequence of steps to achieve a goal (undirected exploration). Alternatively, the lateral FPC might activate when the plan made was deemed irrelevant by the medial FPC, and a few alternative strategies, behaviors, subplans are being evaluated to replace the ongoing sub-plan (directed exploration).

1.6. Frontal Theta as a Marker of Cognitive Control

Over the past decade, numerous studies investigated oscillatory neural dynamics and their role in cognition and behavior. These studies have asseverated that cognition in general, and cognitive control, might result from frequency-specific interactions of specialized and widely distributed cortical regions (Siegel et al., 2012; Fries, 2005; Fries, 2015). This approach emphasizes the rhythmic nature of the brain activity to coordinate large-scale cortical dynamics to underpin cognitive processing and goal-directed behavior (Thut; Miniussi, & Gross, 2012; Fröhlich & McCormick, 2010). Extensive evidence has demonstrated that cognitive processing exhibits rhythmic oscillations whose neural patterns have been associated to perception (Spaak, de Lange, & Jensen, 2014), attention (Fiebelkorn, Saalmann & Kastner, 2013; Landau & Fries, 2012; Song et al., 2014), decision-making (Wyart, Nobre & Summerfield, 2012), memory reactivation (Leszczyński, Fell & Axmacher, 2015), working memory (Onton et al., 2005), and other cognitive control functions (Cavanagh & Frank, 2014). There have been described several oscillatory mechanisms that may guide goal-directed behavior, in general terms, oscillations via transient large-scale frequency-specific networks support cognitive processing (Siegel et al., 2012; Siegel, Buschman & Miller, 2015; Weisz et al., 2014). For instance, recent findings have revealed that specific frequency bands oscillations could reflect a feedback mechanism to control spiking activity providing a temporal reference frame to control and coordinate cortical excitability and spike timing to produce behavior (Buzsáki & Draguhn, 2004; Cohen, 2014; Yuste, 2015; for a review Helfrich & Knight, 2016). This large set of evidence raises how the PFC encodes planning task contexts and other related behaviorally relevant rules. Cognitive control and the means to perform goal-directed behavior have long been thought to be supported by oscillatory patterns of activity in the PFC, which selectively bias the neural activity in distant brain regions and control the flow of information in large-scale neural networks (Miller & Cohen, 2001). Moreover, it has been proposed that regions that exhibit local synchrony also are more likely to participate in inter-regional activity (von Nicolai et al., 2014; Sweeney-Reed et al., 2015; Voytek et al., 2015). In particular, cortical theta-band oscillations, measured by EEG scalp, it has been posited as a candidate mechanism by which neurons could compute and communicate top-down control across broad networks to exert control (Cavanagh & Frank, 2014). Theta band activity in humans reflects high-level cognitive processes, such as memory encoding and retrieval, working memory retention, novelty detection, decision-making, and realizing the need for top-down control (Raghavachari, 2006; Jacobs et al., 2006; Onton et al., 2005; Itthipuripat et al., 2013).

1.6.1. Frontal Midline Theta Activity

Cavanagh and Frank (2014) described two sequential mechanisms of control processes: *i)* realizing the need for control, and *ii)* ways by which that control may be instantiated.

The realization of the need for control may be conveyed by FMθ activity whose sources are from medial PFC. These FMθ activities have been described as event-related potential (ERP) components that reflect mPFC-related control processes elicited by a variety of situations, such as novel information (Cavanagh et al., 2012; Mas-Herrero & Marco-Pallarés, 2014; Folstein & Van Petten, 2008), conflicting stimulus–response requirements (Cohen & Donner, 2013), error feedback (Walsh & Anderson, 2012), and errors detection (Luu, Tucker & Makeig, 2004) (**Figure 19**).
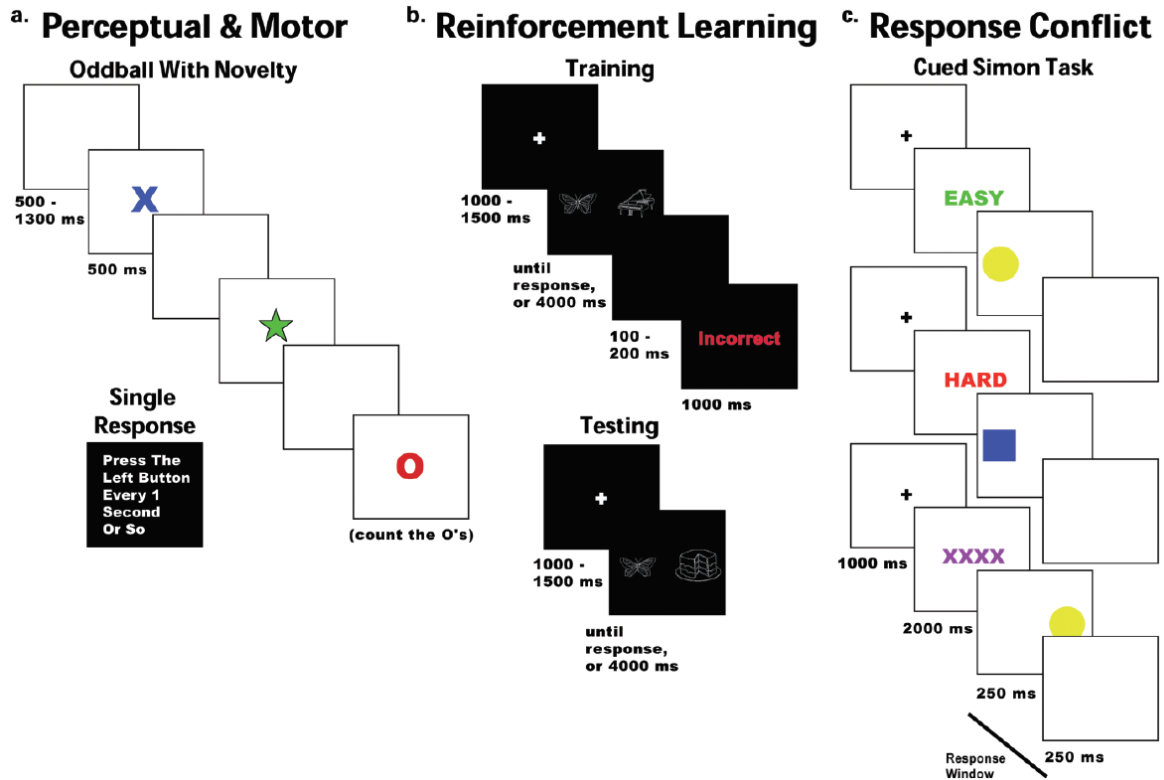
Figure 19. Examples of three cognitive control tasks. A) Oddball task with standards ("x" letter, ~72% occurrences), nontarget novel shapes (star, ~14% occurrences), and targets (circle, ~14% occurrences). Also, endogenously generated single button pushes were completed between oddball blocks. B) Reinforcement learning task. During training, participants learned to choose one item in each pair of stimuli that was reinforced more often. During testing, participants had to choose the better stimulus, leading to high conflict (win–win or lose–lose) and low conflict choices (win–lose). C) Response conflict task. Informative (Easy, Hard) or noninformative (xxxx) cues were followed by congruent or incongruent spatial cues requiring a rapid response (yellow circle for left response, blue square for right response). Taken from Cavanagh, Zambrano-Vazquez & Allen, 2012.

Each of these paradigms and their elicited ERP components share a need for increased cognitive control (novelty, conflict, punishment, and error) and their EEG responses share a common spectral signature in the theta band located in frontal midline electrodes (Itthipuripat Wessel & Aron, 2013; Cavanagh et al., 2012; Hanslmayr et al., 2008; Cavanagh, et al., 2009; Cohen et al., 2009; Cavanagh et al., 2010; Cohen & Cavanagh, 2011; Cohen & van Gaal, 2013; Nigbur et al., 2012; Van de Vijver, et al., 2011; Van Driel et al., 2012; Narayanan et al., 2013; Anguera, J. et al., 2013; Smit et al., 2005), specifically they exhibit an oscillatory pattern of phase reset and power enhancement in this particular frequency band (Cavanagh et al., 2012) (**Figure 20**).
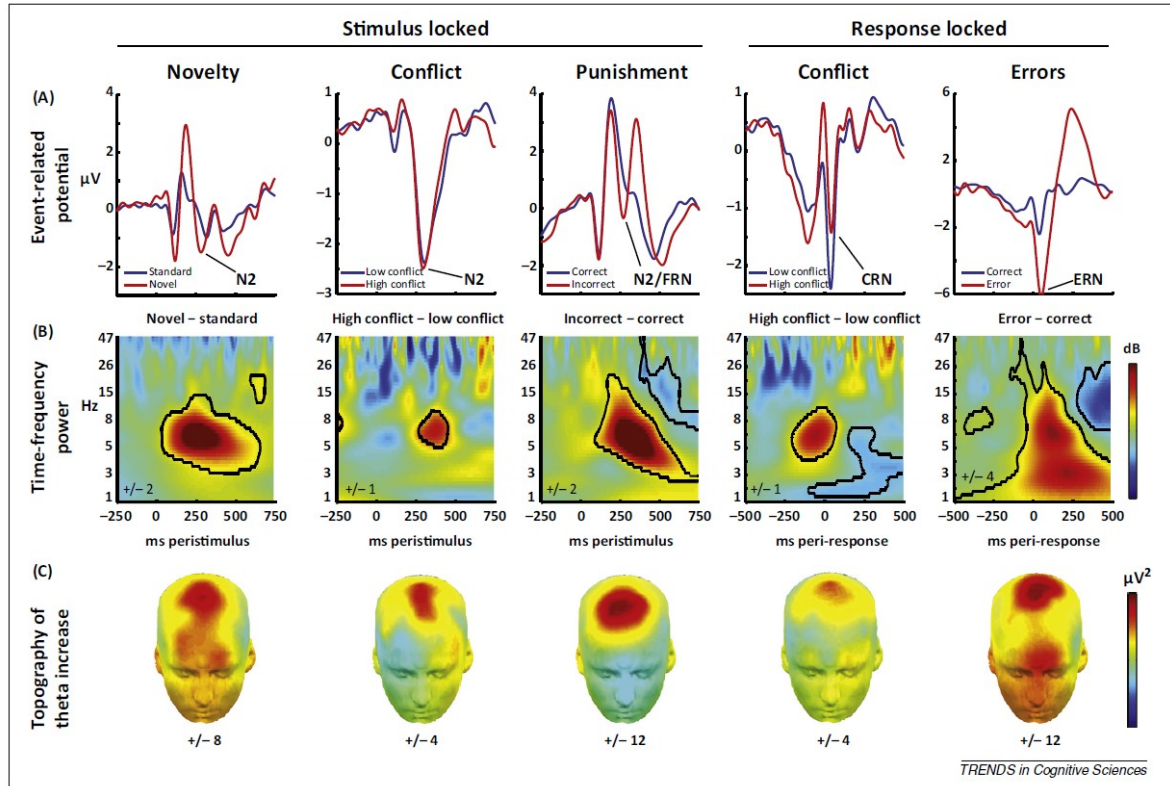
Figure 20. Events associated to Cognitive Control evoke a similar spectral signature on the scalp. A) N2: an ERP component elicited by novelty or stimulus–response conflict. Feedback-related negativity (FRN): a similar N2-like component elicited by external feedback signaling an incorrect response. Correct-related negativity (CRN): a mandatory component evoked by motor responses and enhanced by response conflict. Error-related negativity (ERN): a massive ERP component evoked by motor commission errors. B) Time-frequency charts showing a common significant increase in theta band power to novelty, conflict, punishment, and error (outlined in black). C) Scalp topography of event-related theta activity. The distribution of theta power bursts is consistently maximal over the frontal midline electrodes (Taken from Cavanagh & Frank, 2014).

Despite the low spatial resolution of the EEG technique, there is extensive evidence using source analyses (Hanslmayr et al., 2008; Gehring et al., 1993; Walsh & Anderson, 2011; Yeung, Botvinick & Cohen, 2004; Cohen & Ranganath, 2007), concurrent EEG and fMRI (Debener et al., 2005; Hauser et al., 2014), and invasive EEG recordings in humans (Wang et al., 2005) as well as in monkeys (Tsujimoto et al, 2010; Womelsdorf et al., 2010a; Womelsdorf et al., 2010b), revealing that these FMθ activities are generated by the mid-cingulate cortex (MCC) (**Figure 21A**).
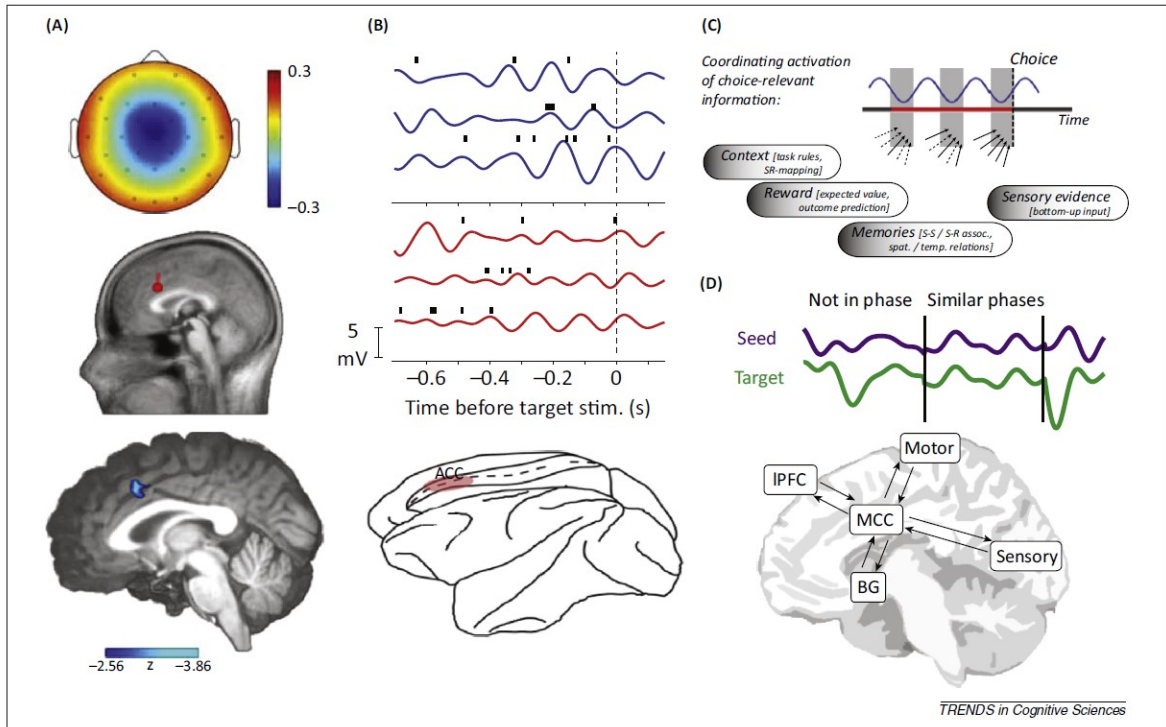
Figure 21. Theta as a biophysical mechanism for organizing local and distal neurocomputational functions. A) In humans, source analysis of FMθ evoked by errors has been localized to midcingulate cortex (MCC) based on dipole source modeling (red) and concurrent hemodynamic activity (blue) (Debener et al., 2005). B) Theta activity recorded from the rostral cingulate sulcus (in red) in rhesus macaques during performance of an antisaccade task. Greater theta power on anti- versus pro-saccade trials was associated with stronger spike-field coupling in the theta rhythm, showing how that local theta activity from MCC provides a temporal window for coincident neural activities that contribute to adaptive control (Womelsdorf, et al., 2010; Johnston et al., 2007). C) FMθ is thought to reflect the synchronization of goal-relevant information around critical decision points, such as action selection. In this example, theta activity coordinate inputs across cortical areas (arrows), particularly at the trough of the oscillation (gray bars). Action selection is likely to be executed when these sources of choice-relevant information (context, reward, memory, etc.) are successfully integrated (solid arrows) (Nácher et al., 2013). D) Theta band phase consistency is thought to reflect the instantiation of transient functional networks (purple and green traces). For instance, intersite theta band phase consistency following signals of cognitive control have been observed between sources modeled in MCC, lateral prefrontal cortex (lPFC), motor areas, and sensory cortex. Theta activity may also implement communications between MCC and the basal ganglia (BG). Taken from Cavanagh & Frank, 2014.

These theta dynamics are thought to act as temporal templates for organizing medial PFC neuronal processes (**Figure 21A-C**), which are then enhanced following events indicating a need for increased control (Cavanagh et al., 2012). Collectively, these observations reinforce the theory that FMθ reflects a common mechanism, a lingua franca, for implementing adaptive control in a variety of contexts involving uncertainty about actions and outcomes (**Figure 21C-D**), as might be the case in the context of planning, and specifically in the behavioral paradigm

that we proposed. While different cognitive control mechanisms have been described in different contexts, higher cognitive functions such as planning, and their temporal and neural properties remain unrevealed. Under this context, using a novel and experimental ecological paradigm, the present doctoral thesis attempts to answer whether the implementation of cognitive planning induces FMθ activity originating in the PFC, which sources, via theta activity, are critical for exerting planning.

1.6.2. Theta Phase Connectivity

Cavanagh and Frank (2014) proposed that this common theta activity may indicate how the need for control is biophysically realized and communicated to other brain regions as well as suggest that these phenomena are aspects of a common high-level process. The traditional hypothesis of neural communication through coherence has suggested that brain areas that exchange information synchronize their activity in distinct narrow frequency bands (Fries, 2015). Over the past decade, multiple findings have suggested that different spectral signatures do not occur in isolation but are functionally coupled through phase - amplitude or phase to phase synchrony (Canolty & Knight, 2010; Fell & Axmacher, 2011), and this constitutes a key mechanism to coordinate the spatio-temporal organization of neural networks. For instance, phase angle changes over time reflect membrane potentials of wide neuronal population oscillating (Wang, 2010), and the enriched spatio-temporal correlation structure of the brain might permit effective cortical computation and information transfer (Siegel et al., 2012; Fries, 2015; Hipp et al., 2012). In other words, synchronization can create time windows for dividing cortical populations (Nadasdy, 2010), which can separate processes of information received and transferred (Buzsáki & Draguhn, 2004; Buzsáki, 2010). Neuronal populations can be prone to interact, exchange information, and modulate synaptic plasticity if they are engaged in a determined frequency because this way they can be more or less likely to be excited as a function of the population oscillation (Fries, 2005; Fell & Axmacher, 2011). Moreover, it has been proposed that brain regions exhibiting local synchrony have more chances to participate in long-distance inter-regional communication (Sweeney-Reed et al., 2015; von Nicolai et al., 2014). Specifically, it has been shown that increased theta power is related to enhanced coupling between single neuron spikes and the phase of the population theta cycle (**Figure 21B**). This spike-field coherence is present in both rat (Nadasdy, 2010) and monkey cingulate cortex (Womelsdorf et al., 2010). Importantly, Womelsdorf et al. (2010) proposed that midfrontal theta phase-synchronization may organize neural processes during

critical decision points where choice-relevant information is integrated to perform action selection (**Figure 21C**). The theta phase synchrony established from the medial PFC suggests a mechanism where signals of cognitive control produce communication between distant brain regions in various situations (Cavanagh & Frank, 2014; Fries, 2005) (**Figure 21D**).

Anatomically, the medial PFC, specifically the MCC is strongly interconnected to cortical (local and long-distance areas) and subcortical areas in a hub-like manner, including FP cortex and lateral PFC (Cohen, 2011, Rolls, 2019; Morecraft & VanHoesen, 1993; Cavada et al., 2000), thus, local medial PFC large-amplitude theta-band might provide a temporal organization scheme for coordinating distal communication of information when control is demanded (Buzsáki, & Draguhn, 2004; Uhlhaas et al, 2010). Theta phase synchrony between frontal midline and distal electrode sites has been observed during a variety of cognitive control functions that also evoke FMθ activity (Hanslmayr et al., 2008, Cavanagh et al., 2009; Cohen et al., 2009; Cohen & Cavanagh, 2011; Cohen & van Gaal, 2013; Nigbur et al., 2012; Van de Vijver et al., 2011; Van Driel et al., 2012; Narayanan et al., 2013; Anguera et al., 2013) (**Figure 22**).
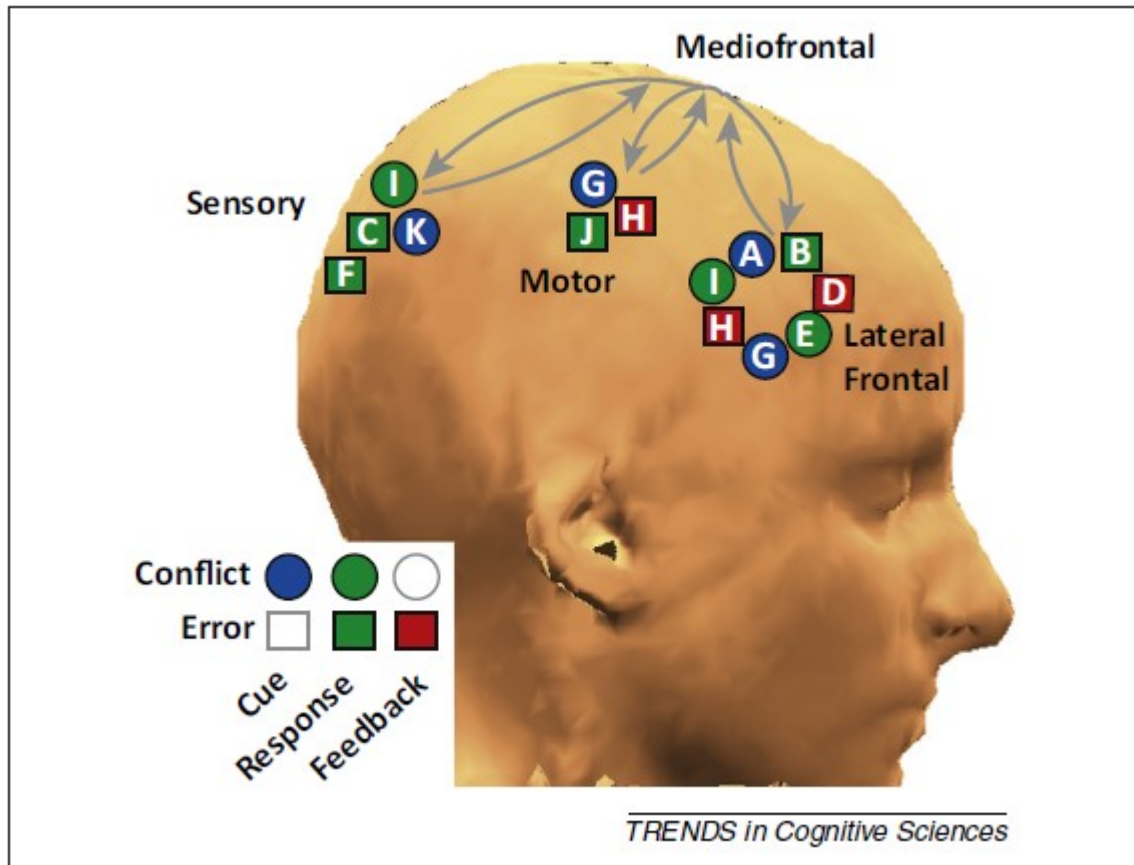
Figure 22. Theta phase synchrony between midfrontal and varied electrode sites during cognitive control functions. Eleven studies (A–K) found theta phase synchrony between midfrontal sites and areas including lateral prefrontal cortex (goal or attention reorientation), motor cortex (motor preparation/response) and sensory cortices (to enhance sensory processing). References: A (Hanslmayr et al., 2008), B (Cavanagh et al., 2009), C (Cohen et al., 2009) D (Cavanagh et al., 2010), E (Cohen & Cavanagh, 2011), F (Cohen & van Gaal, 2013), G (Nigbur et al., 2012), H (Van de Vijver et al., 2011), I (Van Driel et al., 2012), J (Narayanan et al., 2013), and K (Anguera et al., 2013). Taken from Cavanagh and Frank (2014).

A similar pattern has been observed in intracranial recordings from monkeys (Phillips et al., 2014). However, the dynamic interplay between EEG oscillatory activity and the planning function remains unknown.

1.7. Summary of the Theoretical Background

Taking the theoretical background together, we consider that several core PFC regions might be involved in different cognitive planning processes during planning, as a high-order cognitive function. During planning, a sequenced step of subgoals are generated to achieve a goal (Unterrainer & Owen, 2006). To reach this, the dlPFC may participate in the maintenance and representation of the goal along with the manipulation of external generated information

(Christoff & Gabrieli, 2000). While elaborating the plan, the ACC could monitor the ongoing behavior and performance to adjust in case of errors as reported in Quilodran, Rothe and Procyk (2008). Whereas the MCC contributes to increasing attention to relevant stimuli (Orr & Weissman, 2009). Furthermore, following Mansouri et al. model (2017), the FPC may be involved in distributing executive resources away from the ongoing behavior to explore different alternative subgoals to achieve the main goal of the plan (performing branching and multitasking functions). The medial FPC might be evaluating the relevance of the ongoing behavior, whereas the lateral PFC may be involved in the monitoring and manipulation of the self-generated plans along with redirecting cognitive resources to novel sources of subgoals to achieve the planned goal, which is maintained and represented (Christoff & Gabrieli, 2000; Mansouri et al.,2017) (**Figure 23**).

■ **Dorsolateral PFC**
Maintenance of goal representation and contributes to control processes occurring in posterior brain regions (Miller & Cohen, 2001); working memory load/planning complexity (Owen et al., 1996; Newman 2003); monitoring and manipulation of externally generated information (Christoff & Gabrieli, 2000).

■ **Anterior Cingulate Cortex**
Participates in monitoring actions and conflict detections that demands behavioral adjustment, action re-evaluation (Quilodran, Rothe & Procyk, 2008); error prediction (Brown, 2017).
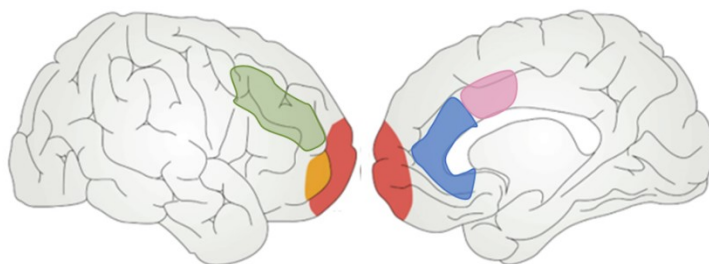
■ **Mid-Cingulate Cortex**
Attentional control; increasing attention towards relevant stimuli, correlates with reaction times of orienting attention to stimuli (Orr & Weissman, 2009).

■ **Lateral Frontopolar Cortex**
Temporarily holding an ongoing goal in mind while first completing intermediate tasks or subgoals (Burguess, Quayle & Frith, 2001; Baddeley, 1996); Dreher et al., 2008); monitoring and manipulation of internally **self-generated plans/decisions** (Christoff & Gabrieli, 2000; Burgess, 2000; Burgess et al., 2000; Goldstein, 1993); disengaging executive control from the current task and redirecting attention to novel sources of reward in order to explore new opportunities/goals (Mansouri et al., 2015)

■ **Medial Frontopolar Cortex**
Undirected exploration: monitors the relevance of the ongoing behavior online for possibly redistributing cognitive control resources to other potential goals (Mansouri et al., 2015).

Figure 23. Putative functional role of PFC regions during planning. Modified illustration from Mansouri et al., 2017.

Additionally, during cognitive control functions, it has been established that frontal midline theta may act as a biophysical candidate that reflects a signature for cognitive control

implementation, which establish communication and coordination in theta phase trough other brain regions. However, the electrophysiological dynamics, its fine temporal and neural properties of the planning function remain unknown. Under this context, the present doctoral thesis research attempts to explore the temporal dynamics of theta oscillation to answer whether cognitive planning implementation induces a FMθ activity originating in PFC regions (such as the FPC, ACC, MCC), and whether exerts cognitive control via theta phase connectivity between frontal and disparate brain regions reflected by long distant theta phase synchrony electrodes sites, using a novel and ecological experimental paradigm. Thus, we hypothesize that frontal theta activity could be a physiological mechanism of temporal dynamics, reflecting cognitive planning processes at the amplitude and the phase level (Buzsáki & Draguhn, 2004).

2. HYPOTHESIS AND OBJECTIVES

2.1. Hypothesis

Cognitive planning implementation induces a frontal midline theta activity originating in the PFC and exerts cognitive control via theta phase connectivity between the PFC and disparate brain regions.

2.2. General Objective

Determine whether the cognitive planning implementation induces FMθ activity originating in the PFC, and whether exerts cognitive control via theta phase connectivity between midfrontal and long distant electrode sites, using a novel and ecological paradigm.

2.2.1. Specific Objectives:

STUDY 1: Theta Activity from Frontopolar Cortex, mid-Cingulate Cortex and Anterior Cingulate Cortex Shows Different Role in Cognitive Planning Performance.

2.2.1.1. Design a visuospatial planning cognitive task adapted to be coupled with both an eye movement recording system (Eye-Tracker) and electrophysiological signal recording systems (EEG).

2.2.1.2. Determine the behaviorally characterization of visuospatial planning by reaction time, accuracy response, and LISAS (see methods section).

2.2.1.3. Establish the neural correlates of visuospatial planning, specifically by the time-frequency analysis, and the temporal profile of the frontal theta oscillatory activity along its brain sources.

2.2.1.4. Determine a correlation between planning performance and frontal theta activity.

STUDY 2: Frontal Theta Phase Connectivity during Cognitive Planning.

2.2.1.5. Establish the inter-regional communication dynamics by determining the phase synchrony level in theta frequency band between midfrontal and long distant electrodes sites of oscillatory brain activity associated to planning behavior.

2.2.1.6. Determine a correlation between planning performance and frontal theta phase activity.

2.3. Experimental predictions:

STUDY 1: Theta Activity from Frontopolar Cortex, mid-Cingulate Cortex and Anterior Cingulate Cortex Shows Different Role in Cognitive Planning Performance.

2.3.1. Behavioral performance

2.3.1.1. Visuospatial planning requires a greater cognitive demand than the evaluation period of the control task, which is reflected on a greater reaction times and lower correct response accuracy rate.

2.3.2. Electrophysiological activity

2.3.2.1. Visuospatial planning induces frontal midline theta activity from PFC.

2.3.2.2. Behavioral performance of planning correlates with a power increase of frontal theta activity.

STUDY 2: Frontal Theta Phase Connectivity during Cognitive Planning.

2.3.2.3. Theta phase large-range synchronization between midfrontal and long distant electrode sites are associated to planning performance.

2.3.2.4. Behavioral performance of planning correlates with a midfrontal theta phase synchronization increase.

<u>Summary of experimental predictions</u>: We expect that the cognitive control implementation during planning is expressed by a significant theta power increase in frontal midline electrodes during the planning period as compared to the control condition, where theta power will slightly increase. Additionally, we expect that sources of this theta activity will be the PFC regions such as the ACC, the MCC, and the Frontopolar Cortex (FP). The ACC and MCC have shown to be involved in conflict monitoring and attentional control processes, respectively (Orr & Weissman, 2009). Thus, we predicted positive correlations between theta activity and behavioral parameters that reflects difficulty in task, i.e. longer latencies of response during the planning period. Further, we expect that theta activity from FP, which has been shown to participate in generation and monitoring of internally generated stimuli (Christoff & Gabrieli, 2000), will correlate with behavioral aspects that reflect better performance in the task such as the percentage of correct responses or more efficient reaction times during the execution of the plan. Finally, in line with the evidence shown in cognitive control research, cognitive planning performance will be correlated to theta phase large-range synchronization, reflecting inter-regional communication between midfrontal and long distant electrode sites.

3. STUDY 1: Theta Activity from Frontopolar Cortex, mid-Cingulate Cortex and Anterior Cingulate Cortex Shows Different Role in Cognitive Planning Performance.

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Highlights

- A novel and ecological task was designed to evaluate planning function.

- A progressive and sustained increase of FMθ over time was induced by planning.

- Theta activity in core executive regions correlated with behavioral performances.

- Frontopolar theta activity was associated with quicker RT during plan execution.

- Theta activity from the MCC/ACC were associated with longer RT during planning.

ABSTRACT

Cognitive planning, the ability to develop a sequenced plan to achieve a goal, plays a crucial role in human goal-directed behavior. However, the specific role of frontal structures in planning is unclear. We used a novel and ecological task, that allowed us to separate the planning period from the execution period. The spatio-temporal dynamics of EEG recordings showed that planning induced a progressive and sustained increase of frontal-midline theta activity (FMθ) over time. Source analyses indicated that this activity was generated within the prefrontal cortex. Theta activity from the right mid-Cingulate Cortex (MCC) and the left Anterior Cingulate Cortex (ACC) were correlated with an increase in the time needed for elaborating plans. On the other hand, left Frontopolar cortex (FP) theta activity exhibited a negative correlation with the time required for executing a plan. Since reaction times of planning execution correlated with correct responses, left FP theta activity might be associated with efficiency and accuracy in making a plan. Associations between theta activity from the right MCC and the left ACC with reaction times of the planning period may reflect high cognitive demand of the task, due to the engagement of attentional control and conflict monitoring implementation. In turn, the specific association between left FP theta activity and planning performance may reflect the participation of this brain region in successfully self-generated plans.

Keywords: planning; frontal midline theta frequency band (FMθ); prefrontal cortex; frontopolar cortex, mid-cingulate cortex; anterior cingulate cortex; cognitive control.

3.1. INTRODUCTION

Cognitive control or executive functions are a theoretical construct that includes a wide range of higher-order cognitive functions associated with goal-directed behavior (Lezak, 1995; Shallice, 1991; Stuss, 1992; Zwosta, Ruge & Wolfensteller, 2015; Cooper, 2010). One of these functions is planning (Collins & Koechlin, 2012; Sira & Mateer, 2014; Lunt et al. 2012), which consists of the ability to develop a sequenced plan to achieve a goal in an organized, strategic and efficient manner (Hayes-Roth & Hayes-Roth, 1979). Planning allows imagining what the future might be and how our behavior could affect and change the current state leading us to this imagined future (Benson, 1993). The extent of plans can range from simple motor behaviors (e.g., planning a sequence of key presses) (Pascual-Leone et al., 1993) to a highly demanding cognitive task (e.g., deciding on the steps required to land an airplane) (Suchman, 1987). Planning behavior can be divided into two major phases: *i)* a mental planning phase that involves elaborating an internal representation of a sequence of steps (plans) (Wilensky, 1983) and *ii)* a planning execution phase that involves the motor action to achieve a previously planned goal (Grafman & Hendler, 1991). Thus, planning can be measured in simple and/or more complex tasks (Schwartz et al., 1991). Typically, in the context of higher-order cognitive processes, planning requires the operation of several components of the executive functions (e.g., working memory, attentional control, response inhibition) making the experimental manipulation and its isolated measurement difficult (Hayes-Roth & Hayes-Roth, 1979; Tremblay et al., 1994).

Neuroimaging studies have provided valuable evidence about the critical role of the Prefrontal Cortex (PFC) in cognitive control, including planning. Several studies have suggested a relevant implication of the dorsolateral PFC (Nitschke et al., 2017; Morris et al., 1993; Owen et al., 1996; Baker et al., 1996; Dagher et al., 1999; Newman, 2003; Kirsch et al., 2006), the Frontopolar cortex (FP) (Braver & Bongiolatti, 2002; Baker et al., 1996; Christoff & Gabrieli, 2000), the mid-Cingulate Cortex (MCC), and the superior parietal lobe, among other brain regions (Kirsch et al., 2006; Newman, Carpenter, Varma, & Just, 2003; Owen, Doyon, Petrides & Evans, 1996) using behavioral paradigms such as Tower of London (Shallice, 1982; Unterrainer et al., 2004) or Porteus Maze (Porteus, 1959; Gallhofer, Bauer, Lis, Krieger, & Gruppe, 1996; Krieger, Lis, & Gallhofer, 2001; Lee et al., 2007; Lezak, 1995; Peters & Jones, 1951; Tremblay et al., 1994). However, the ecological validity (i.e., the extent to which a task reflects natural, every-day life conditions) of the tasks mentioned above is limited, because in order to control confounding factors, paradigms become more artificial and may have less

predictive validity (Miotto & Morris, 1998; Burgess, Simons, Coates & Channon, 2005; Oosterman, Wijers, & Kessels, 2013; Campbell el al., 2009). To address this problem, some ecological tasks analogous to real-world planning situations have been proposed (Miotto & Morris, 1998; Burgess et al., 2005). Noticeably, Wilson et al. designed the Behavioral Assessment of the Dysexecutive Syndrome battery (Wilson, Alderman, Burgess, Emslie & Evans, 1996) to measure executive functions including a subtest called Zoo Map Task that provides a valid planning ability indicator (Oosterman, Wijers, & Kessels, 2013). Importantly, this subtest provides planning and organizational skills measurement in a more ecological manner. In the present study, in order to evaluate the cognitive planning function, we used an adaptation of Porteus Maze and Zoo Map Task paradigms designed for this study. This behavioral paradigm was composed of a daily life situation divided in four different periods present in cognitive planning: *i)* a planning period, where subjects were asked to plan a paths to visit different locations on a map while monitoring whether the plan being elaborated follows a set of rules; *ii)* a maintenance period, where subjects had to store the planned path in their working memory. Then, *iii)* the execution period, where subjects drew the previously planned route while monitoring and controlling the correct execution. Finally, there was *iv)* a response period, where subjects reported the sequence of animals visited according to their planned path. This paradigm allows measuring different parameters that account for the planning capacity using different stages, including the display of its different components involved (working memory, attentional control, visuospatial analysis, among others) in a manner more analogous to real-life situations, since planning paths on maps is a common daily activity. Furthermore, to control confounding factors, the paradigm considers a control task that has the same structure, the same or similar psychophysical stimuli as the planning task. It demands the implementation of cognitive components that also emerge during cognitive planning (working memory, attentional control, and visuospatial analysis), except the elaboration of a plan per se, since it had a different goal. This allowed adequate isolation of the cognitive planning factor for contrasting the parameters of both behavioral performance and electrophysiological signals.

While the precise brain regions involved during planning are accessible by imaging studies that use fMRI or PET, its fine temporal and neural properties remain elusive. In this study, we address this issue by analyzing neuronal oscillatory activity. We hypothesize that FMθ could be a physiological mechanism of temporal dynamics, reflecting cognitive planning processes (Buzsáki & Draguhn, 2004). Over the past 15 years, there has been an active focus on FMθ

activity using scalp EEG assessment, which has been associated closely with several cognitive control functions such as working memory and attentional control. These studies have shown that when subjects engage in processes characterized by goal-directed influence, there is an increase in frontal theta activity (Cavanagh & Frank, 2014; Deiber et al., 2007; Green & McDonald, 2008; Onton, Delorme, & Makeig, 2005; Summerfield & Mangels, 2005; White, Congedo, Ciorciari, & Silberstein, 2012; Raghavachari et al., 2006). Furthermore, FMθ has been posited as a candidate mechanism through which cognitive control might be biophysically performed (Cavanagh & Frank, 2014). However, the dynamic interplay between EEG oscillatory activity and the planning function remains unknown. Under this context, using a novel and experimental ecological paradigm, the present study attempts to answer whether the implementation of cognitive planning induces FMθ activity originating in the PFC, whose sources, via theta activity, are critical for exerting planning.

We hypothesize that the cognitive control implementation during planning is expressed by a significant theta power increase in frontal midline electrodes during the planning period as compared to the control condition, where theta power slightly increases. Additionally, we expect that sources of this theta activity are the PFC regions such as the Anterior Cingulate Cortex (ACC), the mid-Cingulate Cortex (MCC), and the Frontopolar Cortex (FP). The ACC and MCC have shown to be involved in conflict monitoring and attentional control processes, respectively (Orr & Weissman, 2009). Thus, we predict positive correlations between theta activity and behavioral parameters that reflect difficulty in task, i.e., longer latencies of response during the planning period. Finally, we expect that theta activity from FP, which has been shown to participate in generation and monitoring of internally generated stimuli (Christoff & Gabrieli, 2000), correlates with behavioral aspects that reflect better performance in the task such as the percentage of correct responses or more efficient reaction times during the execution of the plan.

3.2. MATERIALS AND METHODS

3.2.1. Participants

Data was collected from twenty-seven right-handed healthy adults (13 females) between 19 to 38 years old (mean age = 27.81, standard deviation (SD) = 4.58 years). The sample size was calculated using G*Power 3.1.9.2 software (http://www.gpower.hhu.de/) considering the statistical Wilcoxon signed-rank test, an effect size of 0.7, alpha value of 0.05, and a power of

0.95 (Faul, Erdfelder, Lang & Buchner, 2007). No participant reported neurological or psychiatric disorders according to the International Neuropsychiatric Interview, Spanish version adapted (Ferrando, Bobes, Gibert, & Soto, 2000). All participants had a normal or corrected-to-normal vision. They were paid CLP$10,000 (approximately USD$15.76 or €13.30) for their participation. The bioethics committee of the Faculty of Medicine of Pontificia Universidad Católica de Chile approved procedures, and all participants signed an informed consent form before the beginning of the study (research project number: 16-251).

3.2.2. Experimental Design and Procedure

We created a planning task paradigm based on Zoo Map Task (Wilson et al., 1996) and Porteus Maze (Porteus, 1959) programmed in the Presentation Software® by Neurobehavioral Systems (Version 18.0, www.neurobs.com, Neurobehavioral Systems, Inc., Albany, CA) and stimuli were designed using open source SVG tool Inkscape (www.inkscape.org). Using an eye-tracking system (EyeLink 1000 Plus, www.sr-research.com, SR Research, Mississauga, Ontario, CA), we were able to provide participants with real-time on-screen feedback of their eye movements during the task. Simultaneously, we registered the participants brain activity using a scalp EEG system.

The experiment was composed of two conditions: a planning condition and a control condition, each of which included four different periods (see below). These conditions were constructed with a similar structure that allowed control of confounding factors and perceptive components involved in the task and thus, help improve the specific assessment of the processing involved in cognitive planning. Stimuli were projected on an ASUS VG248QE 24" LCD monitor located 82 cm away from the subject.

3.2.2.1. Planning Condition

The planning condition consisted of 36 trials each with a distinct gray-scale maze that represents a zoo map, preceded by three seconds of a central fixation cross as a baseline. Inside the maze were a gateway and several paths leading to locations of four animals (**Figure 1A**). Trials were pseudo-randomized. The planning condition was composed of four different periods: planning, maintenance, execution and response (**Figure 2A**).

Planning period: Subjects were instructed to find a path to complete a sequence of visits to all four animals (in any order) according to the following set of rules: (1) Plan the path as fast as possible within a maximum of 10 seconds, (2) Start from the gateway and conclude the path at the fourth animal visited, (3) Do not pass through the same path or corner twice, (4) Do not

cross a dead end, (5) Do not cross a path perpendicularly. The planning period was over once the subject pressed a button from a joystick whenever they finished planning or if they exceeded the maximum time. Reaction time (RT) was recorded for further analyses.

A. Experimental Condition   **B.** Control Condition
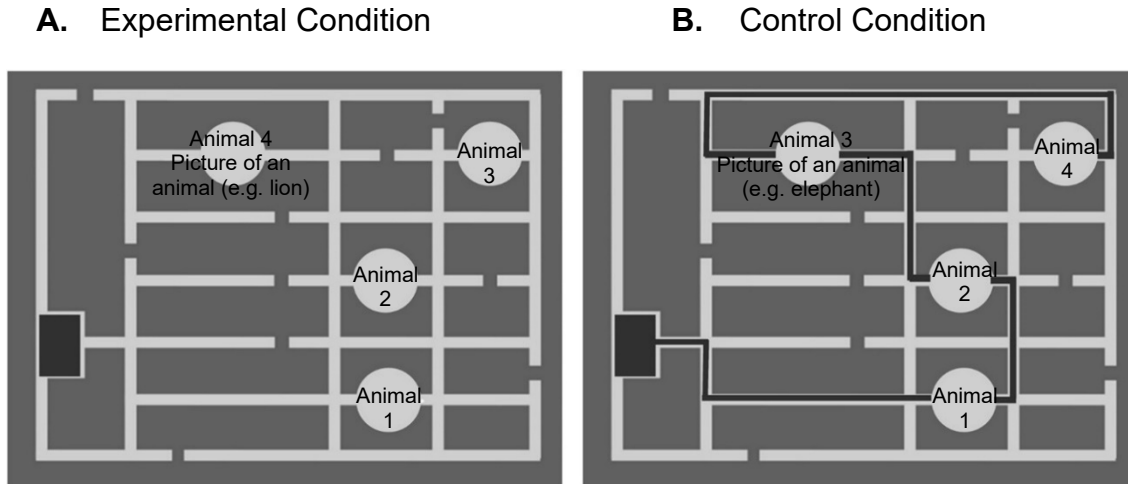
Figure 1. Stimuli of Planning and Control Condition. Illustrative example of the task stimuli is shown. Each stimulus consists of a zoo map with a starting gate, four images of animals located along the maze and different paths that may or may not lead to their locations. During the experimental condition (A) subjects had to plan a path from the gate passing through all animal locations, considering a set of rules. On the other hand, for the control condition (B) a marked line indicating an already existing path was shown (black line*). Here, subjects were instructed to look at this path and figure out whether the rules were followed or not. *The black line presented here is for illustrative purposes. The real marked path was a slightly darker line with low contrast controlled by illuminance (see methods section 2.2.2.) in order to keep the mazes presented in the planning and control conditions as similar as possible. Animals inside of circles were pictures of animals.

Maintenance period: Here, a shifted fixation cross was presented by three seconds. The position of the fixation cross indicated the start position (gate) of the zoo map in order to facilitates the execution of the trace for the next period (see below). During this period, subjects retained in their working memory the plan elaborated in the previous period. Also, this period serves to delimitate the end of the planning period and the beginning of the execution period as an inter-trial interval.

Planning execution period: In this period, the maze was shown again, and subjects were instructed to trace their previous planned path using their gaze through an online eye movement feedback given and registered by the eye-tracker system. Calibrations of the eye-tracker were made at the beginning of the experiment and after every five trials completed. Subjects had a maximum time of 10 seconds to trace the planned path but once they crossed

the fourth animal visited, they could finalize by pressing a button. Their RTs were saved for further analysis.

Planning response period: After 10 seconds or upon button press at the end of the execution period, the maze disappeared and only the animals remained on the screen in the same spatial location in which they appeared in previous periods. Additionally, there were four yellow circles at the bottom of the screen. Subjects were asked to insert the animals in each circle following the same order in which they visited them during the execution period. Then, subjects got feedback based on the feasibility of the traced sequence (thumbs-up or thumbs down when the answer was either correct or incorrect, respectively). Paths performed during the execution period were reconstructed offline using the eye-tracker data, then accuracy responses of the traced and planned paths were calculated and used for further analyses (see Supplementary **Figure S1**). Thus, the main goal of the response period was to provide online feedback in order to allow participants monitoring their performance during the task, as well as to keep the motivation to perform the task properly given the rewarding effects of performance feedback (Drueke et al., 2015).

Consequently, the behavioral features used to measure planning performance were the RT during the planning period (the time that subjects needed to figure out how to solve the maze following the rules) and the RT during the execution period (the time that subjects needed to execute the planned trace), and their accuracy, i.e., whether the traced path was feasible or not.

A. Planning Condition

Sample Trial

3 s

Planning
< 10 s

Maintenance
3 s

Execution
< 10 s

Response

Thumbs-up
or
Thumbs-down

Feedback

B. Control Condition

Sample Trial

3 s

Evaluation
< 10 s

Maintenance
3 s

Execution
< 10 s

Response

?

Thumbs-up
or
Thumbs-down

Feedback

Figure 2. Experimental Design. A) Representative planning condition trial. Planning trial started with a fixation cross presented for 3 seconds. Subjects were then instructed to plan a path visiting all the four animal locations with a maximum time of 10 seconds, following a set of rules (previously explained). Afterward, a shifted fixation cross was shown. Once the maze appeared again, subjects had to execute the trace planned in the previous planning period using their gaze with a visual feedback (given by an eye-tracker system) that delineated their gaze movement in real-time (dark line) with a maximum time of 10 seconds. Then occurred the response period where the subjects had to indicate the sequence made during execution by arranging the animals in the chosen order with a joystick. Based on their response, subjects received feedback (thumbs-up when correct and thumbs-down when incorrect). B) Representative control condition trial. A fixation cross appeared for 3 seconds. Next, subjects were instructed to look at an existing traced path (dark line) and evaluate whether it followed the rules or not. Next, a shifted fixation cross appeared again after which the maze reappeared. This time subjects had to replicate the already traced route having the same visual feedback as the execution planning period. Next came the response period where they had to answer if the traced sequence followed the previously stated rules or not by pressing a joystick button. Based on their response, subjects received feedback.

3.2.2.2. Control Condition

Our novel planning task mainly demands the execution of visuospatial planning function, but also requires visuospatial analysis and working memory to some extent (Wilson et al., 1996; Oosterman et al., 2013). In order to control confounding factors, a control task with all the cognitive and perceptual functions needed to solve the planning task was designed, removing the component that elicits the planning function.

The control task had the same structure as the planning task. It consisted of the same 36 distinct mazes. But, each of these presented an already traced path in a slightly darker color

with low contrast. This was to keep the psychophysical features of the planning and the control conditions as similar as possible. The illuminance data was measured using a lux-meter positioned in the same chinrest used by the subjects, at the same distance from the screen. No differences in illuminance was found between stimuli of each condition (Planning task stimuli: n = 42, mean = 6.8 lux, SD = 0.14, SEM = 0.02. Control task stimuli: n = 42, mean =6.8, SD = 0.14, SEM = 0.02, unpaired-samples t-test, t (82) = 1.50, p = 0.1397). The traced paths of each maze could either followed the rules or not (**Figure 1B**). Trials were pseudo-randomized. This control task also included four periods: control, maintenance, execution, and response periods (**Figure 2B**).

Control period (guided sequences): Subjects were instructed to look at the mazes which had a traced path from the entrance visiting all four animals. Subjects had to evaluate the traced path and verify whether the sequence followed the rules or not. First, a fixation cross appeared for three seconds. The subject then had 10 seconds to evaluate the traced path. Same as the planning task, subjects could press a joystick button whenever they finished, and the RT was saved for further analyses.

Maintenance: A shifted fixation cross was presented by three seconds. The position of the fixation cross preceded the location of the maze entrance to facilitate the gaze tracing (same as planning condition). In this period, subjects stored in their working memory whether the marked path seen in the previous period followed the rules.

Control execution period: Subjects had 10 seconds to follow the traced path again, overlapping their gaze with the traced path. Once they reached the fourth animal, they could finalize the trial by pressing a button and the RT here was recorded as well.

Control response period: During this period, a question mark appeared, and subjects were asked to answer whether the sequence was correct or not using joystick buttons and the accuracy response was saved. Finally, the feedback was presented, the same as in the experimental condition.

For both the planning and the control condition, subjects were orally instructed by the experimenter using visual aid before starting each condition. Instructions included examples of how to solve the planning and the control condition, respectively. For the control condition, examples of how to evaluate the paths without using any planning strategies (for instance, looking for rule violations of the paths drawn, such as identifying drawings using the same path twice, crossing a dead-end, etc.) were provided. Afterward, a training session of six trials was

held for each condition to ensure subjects got familiar with the experiment setup and the goal of each trial condition. Furthermore, after each trial the experimenter asked the participants what strategies they implemented to solve the trial. Then, they received oral feedback about their performance and strategy to make sure that subjects evaluate the paths drawn in the control condition to avoid planning a new path.

3.2.3. EEG Data Acquisition

Electroencephalography brain activity was recorded using a scalp EEG Biosemi® System (www.biosemi.com) consisting of sixty-four scalp electrodes placed following the 10/20 system, and eight external electrodes. Four external electrodes measured electro-oculography (EOG) activity, two were used for electrocardiogram (EKG), and two for mastoids which were used for referencing later during signal pre-processing. All electrodes were placed according to standard anatomical references (Keil et al., 2014) and referenced to CMS and DRL active electrodes during acquisition. The data was sampled online with a rate of 2048 Hz.

3.2.4. Data Analyses

3.2.4.1. Behavioral Data Analysis

Behavioral data were analyzed using custom scripts from MATLAB 8.0 (The MathWorks, Inc., Natick, Massachusetts, United States), SPSS version 22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, version 22.0. Armonk, NY: IBM Corp.), and GraphPad Prism version 8 for Windows (GraphPad Software, La Jolla California USA, www.graphpad.com). All behavioral analyses were conducted using the accuracy (percentage rate of incorrect and correct responses) from each condition (the planning and the control condition), and the RT (the average of time spent solving the mazes and evaluating marked paths, and all execution periods) of the first two periods of each condition: the planning period, the planning execution period, the control period, and the control execution period. Additionally, we calculated the RT of each period considering the correct trials only.

Since each condition had two RTs measures and one accuracy outcome, we decided to use an index that can give an integrated measure that accounts for both the RT and the accuracy for each period. This index allowed us to later evaluate the association between electrophysiological signal (theta activity) and behavioral performance properly (see below in 2.4.3. section). Thus, as a new behavioral parameter, we used a performance index that is based on a linear combination of reaction time (RT) and proportion of errors (PE) called the

Linear Integrated Speed-Accuracy Score (LISAS) (Vandierendonck, 2018) and is defined as follow:

$$LISAS = RT_j + PE_j \times \frac{S_{RT}}{S_{PE}} \qquad (1)$$

In the above equation, RT_j represented the participants correct RT (in ms) average of the participants in condition j, PE j represented the participant's accuracy (in proportion of error) in condition j, S_{RT} is the overall correct RT standard deviation of the participant, and S_{PE} is the overall PE standard deviation of the participant. This equation renders a weighted measure of RT and PE. Thus, an estimate of RT corrected for the number of errors was obtained as a balanced combination of speed and accuracy, which can be interpreted as RT adapted for the percentage of incorrect responses. Hence, LISAS can be considered an integrated index of performance (Vandierendonck, 2018) and it has been proven to be useful when it is known that RT and accuracy might be related or might be the expression of similar or the same cognitive processes (Vandierendonck, 2017, Vandierendonck 2018). To evaluate this, we performed Spearman's rho correlation between RT and accuracy for both the planning and the control conditions (using RT of each period).

To evaluate the internal consistency of the task we computed a Cronbach's Alpha coefficient using RT of each period as input. Additionally, in order to evaluate homoscedasticity, the Levene Test was conducted. D'Agostino & Pearson Omnibus Normality Distribution Test was also conducted in order to choose the proper statistic test in each comparison (parametric or non-parametric). Afterward, depending on the data normality Wilcoxon signed-rank test or matched-paired t-test were performed to compare the difference of the different parameters of behavioral performance between condition periods. These comparisons were conducted to evaluate whether the planning component present in the planning condition was more cognitive demanding than the control condition, and further to find out whether the planning task and the control condition are optimal to evaluate cognitive planning.

Finally, in order to analyze planning with different complexity levels, trials were divided considering the number of valid solutions, being those trials with more than 5 possible solutions considered as 'easy' (18 trials) and those with equal or less than 5 possible solutions considered as 'difficult' (18 trials). Then, the accuracy and RTs of the planning and the planning execution period were compared between 'easy' and 'difficult' trials using matched-paired t-test.

3.2.4.2. Electrophysiological Data Analyses

3.2.4.2.1. Signal Preprocessing

The EEG data pre-processing pipeline was carried out using EEGLAB toolbox codes (Delorme & Makeig, 2004), EYE_EEG extension (Dimigen, Sommer, Hohlfeld, Jacobs, & Kliegl, 2011), and the ADJUST plugin (Mognon, Jovicich, Bruzzone, & Buiatti, 2011).

Eye movement activity recorded from eye-tracker was synchronized with EEG recordings allowing us to observe the occurrence of fixation, saccades, and blink events, improving the quality of the visual inspection. Co-registration was ensured with shared TTL trigger pulses that were sent from the presentation display computer to the eye-tracker computer during the whole experiment. The sampling rate was downsampled to 1024 Hz and re-referenced to average of electrodes on mastoids. Then, a zero-phase finite impulse response (FIR) filter was used for high-pass filtering, with a high-pass cut-off frequency of 1 Hz and a low-pass cut-off frequency of 40 Hz. The EEG signal was segmented into 36 trials per condition, time-locked to the onset of planning and control periods as epochs of interest. Each trial consisted of 1 s before the start of the maze presentation (as a baseline) and 4 s after the planning or control period, respectively. Subsequently, a second segmentation time-locked to the end of planning and control periods was generated. These epochs consisted of 4 s before the end of planning and control periods, and 1 s of maintenance. These windows length was chosen due to the time to perform each period in the planning and control condition is variable, thus we used the first and the last 4 s of planning and control periods as adequate and sufficient to analyze the oscillatory dynamics without overlapping the first period over the execution period.

Thereafter, Logistic Infomax Independent Components Analysis (ICA) algorithm (Bell & Sejnowski, 1995) was used to identify and remove artefactual components from EEG data. Artefactual components associated with eye movements were rejected based on their covariance with simultaneously recorded eye movement data. This was done using saccade-to-fixation variance ratio criterion between 10 ms pre- and post-saccade (Plöchl, Ossandón, & König, 2012). Additionally, other artefactual components associated to EMG, electrode movement or non-brain-related components were identified by visual inspection. All rejected independent components were also visually validated by inspecting the topographies, spectra, and activations over time.

Finally, noisy channels identified by visual inspection and by automatic channel rejection using kurtosis criterion (5 z-score as threshold) were interpolated using spherical interpolation.

3.2.4.2.2. Time-Frequency Decomposition

EEG time-frequency analysis was carried out using short-time Fast-Fourier Transform (FFT) for frequencies ranging from 1-40 Hz using a window length of 250 ms and a time step of 5 ms. The time-frequency charts were then z-score normalized to the baseline (-1 to -0.1 s).

Thereupon, electrode Fz was selected for further analyses due to: *i)* The strong increase in theta frequency band seen in frontal midline electrodes (including Fz electrode) shown in topographic maps, and *ii)* the Fz electrode is widely used in frontal midline theta/cognitive control studies (Onton, Delorme & Scott Makeig, 2005; Gartner, Grimm & Bajbouj, 2015; Wang, Viswanathan, Lee & Grafton, 2016). The Pz and Oz electrodes were chosen as controls because they are non-frontal midline electrodes. Afterward, statistical comparisons of time-frequency charts betweeb both conditions, for Fz, Pz, and Oz electrodes, were made through a non-parametric cluster-based permutation test for paired samples, with a *p* value < .05 at the group-level. The probability of observing a statistically significant effect was calculated using Monte Carlo method with 1000 random draws. The statistic value chosen to perform the permutation test was the maximum statistic value of the cluster (Maris & Oostendveld, 2007).

Theta frequency band (4–8 Hz) from these two different segments was averaged along its whole epoch respectively: 0 to 4 seconds (first four seconds of planning/control) and -4 to 0 seconds (last four seconds of planning/control). Then, averaged theta activity was compared between conditions using a matched-pair t-test or Wilcoxon signed-rank test.

Besides, to analyze the temporal dynamics of theta activity, power in the 4-8 Hz range was averaged across trials by subject. Time profiles of theta band activity for both conditions and the selected electrodes were then compared using Wilcoxon signed-rank test (match-paired, 88 ms steps of non-overlapping windows) and corrected by False Discovery Rate (FDR).

All time-frequency analyses were made using self-written scripts in MATLAB R2014a and R2018b and Statistics Toolbox 8.1 (The Mathworks, Inc., Natick, Masachussets, United States).

3.2.4.2.3. Source Reconstruction Analyses

Source localization analyses were performed using the open access Brainstorm toolbox (Tadel, Baillet, Mosher, Pantazis, & Leahy, 2011), which is documented and freely available for download online under the GNU general public license (http://neuroimage.usc.edu/brainstorm).

Once we observed that there were significant differences in both periods: the first four seconds and the last four seconds between planning and control period, we selected the first four seconds for further analyses. Thus, sources were estimated over the preprocessed EEG signal of the first four seconds of planning (1-40 Hz range, filtered and cleaned) using Standardized Low-Resolution Brain Electromagnetic Tomography (sLORETA) (Pascual-Marqui, 2002). The parameters chosen to perform sLORETA were the minimum-norm imaging method, and the symmetric Boundary Element Method (symmetric BEM) using OpenMEEG toolbox (Gramfort et al., 2010). sLORETA algorithm was conducted on the default anatomical MNI template implemented in Brainstorm ("Colin27") using the default electrode locations for each subject.

We conducted two types of source analysis with different purposes. First, in order to estimate the brain sources of theta activity observed in the scalp electrodes, a bandpass filter between 4-8 Hz was applied over the preprocessed signal. Theta frequency band was selected as a band of interest due to: *i)* There is extensive evidence supporting FMθ as a biophysical mechanism of cognitive control implementation (Cavanagh & Frank, 2014), *ii)* the theta band power increase in midline frontal electrodes observed during visualization of topographic maps, and *iii)* because of the significance difference observed in the planning condition as compared to the control condition in the time-frequency charts and the time profile slices from Fz electrode. Consequently, a z-score normalization was applied using -1000 to -10 ms pre-trial onset as baseline. Then, we averaged the theta activity between 1 and 4 seconds as a time span of interest. The criterion used to select this range of time was based on the theta activity dynamics observed in topographic maps time slices, the time-frequency charts and the time profile slices whose significant increased activity started after 500 ms (see results section). Lastly, averaged space sources were compared between conditions using non-parametric permutation sign test using Monte Carlo Sampling (1000 randomizations) (Tadel et al., 2011).

Second, in order to determine regions of interest (ROIs) associated to planning, cortical areas were labeled according to Destrieux Atlas available in the FreeSurfer Package in Brainstorm

toolbox (Destrieux, Fischl, Dale & Halgren, 2010), and ROIs were bilaterally selected based on *i)* significance differences between conditions in permutation tests as well as *ii)* high theta frequency band increase in the planning condition alone, and *iii)* evidence reporting prefrontal cortex regions involved in cognitive control functions (Orr & Weissman, 2009; Christoff & Gabrieli, 2000). These regions included bilateral superior frontal gyri (SF), bilateral transverse frontopolar gyri and sulci (FP), bilateral ACC, and bilateral MCC (Supplementary **Table S1**). Using the previous preprocessed EEG signal (1-40 Hz range, filtered and cleaned) Principal Component Analysis (PCA) was conducted for each ROI's activity and the first mode of the PCA decomposition for each ROI was selected. A spectral estimation using a short-time FFT was performed as indicated in the Time-Frequency Decomposition section and compared between left and right ROI using a non-parametric cluster-based permutation test (Maris & Oostendveld, 2007) following the same procedure and using the same parameters described above at the channel-level. Afterward, each bilateral region presenting no differences between left and right was extracted again as one bilateral time series: SF, ACC, MCC, and then represented in time-frequency charts and compared between conditions. Furthermore, time-frequency charts obtained according to the complexity level of the planning task (easy versus difficult trials) were compared for each ROI. Since the dorsolateral PFC has been described as a crucial region for planning performance and working memory (Nitschke et al., 2017; Barbey, Koenigs & Grafman, 2013), this brain region was also considered for analyses.

To compare the time profile of theta band across conditions, activity from selected ROIs was band-pass filtered between 4-8 Hz and Hilbert Transform was applied to obtain the instantaneous amplitude (Le Van Quyen et al., 2001) using Signal Processing Toolbox from MATLAB software (MathWorks). In order to avoid edge effects created by the band-pass filter, each end of the signal was mirrored using a length of 512 samples before applying the Hilbert Transform. Afterward, the signal was z-scored (using -1000 to -10 ms as baseline) and averaged across trials by subject. Finally, each ROI source activity was compared between conditions using Wilcoxon signed-rank test (matched-pairs, 1 s of non-overlapping windows) and corrected by FDR.

3.2.4.2.4. Correlations between Theta Activity and Behavior

In order to test whether there is a relationship between frontal theta activity and planning performance, the eight ROIs source time-series were first z-score normalized by baseline. Then, a window from 1 to 4 seconds after planning/control onset was selected as a period of interest based on relevant theta activity dynamics observed in time-frequency results.

Moreover, based on the extensive evidence of theta activity increase in the ACC and the MCC (Cavanagh & Frank, 2014; Cohen, 2014) canonically associated to slower performance (typically greater RTs) indicating the employment of cognitive control (Gratton et al., 1992; Rabbitt & Rodger, 1977) in a variety of cognitive control functions (Cavanagh et al., 2017; Munneke et al., 2015; van Driel et al., 2015; Frank et al., 2015; van Driel et al., 2017; Cohen, 2016), we chose the bilateral ACC and MCC to evaluate whether their theta activity correlated with slower RT. Additionally, we sought to analyze specific segments of time intervals within the 1 to 4 s window. Thus, we used two additional non-overlapped windows of 1 second each at the second and the third second after the trial onset. We sought to evaluate whether there were specific time intervals with associations with RTs during the planning period. To do this, we selected late time intervals of interest based on the time dynamics of theta activity whose significant increases can be seen between 2-4 s after trial onset.

Subsequently, the source signal was decomposed in the frequency domain (1-40 Hz) using the multitaper method implemented with Chronux toolbox (Bokil et al., 2010) for each period and ROI. Next, the theta frequency band (4-8 Hz) was averaged, and two measures of theta power were calculated: *i)* Δ theta, which was obtained by subtracting the control period theta power ($\theta_{control}$) from the planning period theta power ($\theta_{planning}$), and *ii)* the relative increase in theta activity, which is the ratio of the Δ theta (Δ θ) and the control theta activity ($\theta_{control}$):

$$\Delta\theta = \theta_{planning} - \theta_{control} \qquad\qquad (2)$$

$$Relative\ Increase\ in\ Theta = \frac{\Delta\theta}{\theta_{control}} \qquad\qquad (3)$$

These two parameters provide information of the theta activity increase in the planning condition with respect to the control condition.

On the other hand, we calculated two behavioral parameters: *iii)* Δ LISAS Planning, which is the subtraction between LISAS Planning and LISAS Control, and *iv)* Δ LISAS Planning Execution, which is the subtraction between the LISAS Planning Execution and LISAS Control Execution:

$$\Delta LISAS_{planning} = LISAS_{planning} - LISAS_{control} \qquad\qquad (4)$$

$$\Delta LISAS_{planning\ execution} = LISAS_{planning\ execution} - LISAS_{control\ execution} \quad (5)$$

These behavioral parameters provide information of the behavioral performance during planning with respect to control condition.

Finally, Spearman's rho correlations were performed using the electrophysiological and behavioral parameters calculated and then corrected by FDR across the total number of tests.

3.2.4.2.5. Analysis of Theta Phase Synchrony

To identify theta phase synchrony communication within the PFC brain regions, we first computed individual time-resolved phase-locked activity for each ROI source using the weighted Phase Lag Index (wPLI) (Vinck et al., 2011) as implemented in the Fieldtrip toolbox (Oostenveld et al., 2011). We performed this analysis for frequencies ranging from 1 to 40 Hz using a Hanning multitaper time-frequency transformation and a non-overlapping window length of 100 ms for the epoched trials between -1 to 4 seconds locked to the trial onset of the planning and the control period. Thereupon, the theta band (4-8 Hz) was extracted and the time-resolved wPLI was z-score normalized to the baseline (-1 to -0.1 s). The wPLI was chosen because of its lack of sensitivity to zero phase-lag interactions. Then, we compared time-resolved wPLI values between conditions using Wilcoxon signed-rank test (matched-pairs, 250 ms of non-overlapping windows) and FDR corrected.

3.2.4.3. Eye Movements analyses

The saccade amplitude and the saccade peak velocity from the whole trial and from 0 to 3.75 seconds of the planning and the control condition were extracted using EYE_EEG toolbox (Dimigen et al., 2011) and then compared using Wilcoxon signed-rank test or matched-paired t-test depending on whether data were normally distributed. The window between 0 to 3.75 seconds was selected to control for potential differences in eye movements that might be present at delays around 3.75 seconds, in which the control condition subjects were close to finishing the trial, and their eye movements were expected to stop. Additionally, the coherence between Fourier EEG power at electrode Fz and saccade rate was evaluated as described in Sato and Yamaguchi (2008). The power-saccade rate coherence values from the first four seconds after trial onset were compared between conditions using Wilcoxon signed-rank test.

3.3.   RESULTS

3.3.1. Behavioral Results

All behavioral features analyzed showed a normal distribution according to D'Agostino & Pearson Omnibus Normality Test except values of accuracy for the control condition. Supplementary **Table S2** shows a summary of the normality distribution test results.

3.3.1.1.   Reliability

The internal consistency of each task period (the planning, the control, the planning execution, and the control execution period) was excellent according to the categories of reliability proposed by George and Mallery (2003). The Cronbach's alpha coefficient ranged between .95 and .97 (Supplementary **Table S3**) for RTs as input. These results suggest that each task period has a consistent set of trials indicating high task reliability.

3.3.1.2.   Performance

Table 1 shows a summary of the most relevant descriptive statistics. Variability analysis by the Levene Test showed homogeneity in variance (Supplementary **Table S4**).

Table 1. Behavioral descriptive data for each parameter

Parameters	Descriptive Statistics*			
	Mean	Median	SD	SEM
Planning RT	8.85	9.15	1.15	0.22
Planning Execution RT	6.33	6.29	1.11	0.21
Accuracy Planning	85.70	88.89	7.69	1.48
Control RT	6.81	6.57	1.50	0.29
Control Execution RT	5.71	5.55	0.99	0.19
Accuracy Control	95.68	97.22	4.77	0.92
LISAS Planning Index	9281	9779	938.2	180.6
LISAS Planning Execution Index	6927	6912	1341	258.2
LISAS Control Index	7117	7023	1466	282.1
LISAS Control Execution Index	5923	5725	1033	198.7
Planning RT 'easy'	8.55	8.86	1.40	0.27
Planning RT 'difficult'	8.97	9.41	1.07	0.21
Planning Execution RT 'easy'	5.83	5.65	1.22	0.24

Planning Execution RT 'difficult'	6.55	6.68	1.08	0.21
Accuracy Planning 'easy'	89.92	94.44	7.55	1.45
Accuracy Planning 'difficult'	81.48	83.33	10.56	2.03

SD = Standard deviation; SEM = Standard error of the mean; RT = Reaction Time; LISAS = Linear Integrated Speed-Accuracy Score. *Values of RT are presented in seconds. Values of accuracy are the percentage of correct responses. Values of LISAS are presented in milliseconds.

Furthermore, RTs of different periods were evaluated and compared. The RT of the planning period in comparison to the control period was significantly greater (**Table 1**, Supplementary **Table S5**, **Figure 3A**). The same was observed when the RT of the planning execution period was compared to the execution control period (**Table 1**, Supplementary **Table S5**). This reflected that the planning condition was cognitively more demanding than the control condition. Furthermore, the planning period was also more time consuming than the planning execution period (**Table 1**, Supplementary **Table S5**, **Figure 3B**). Similarly, the RT during the control period was significantly greater than the RT of the execution control period (**Table 1** and Supplementary **Table S5**). In terms of response accuracy, subjects were less accurate during the planning condition as compared to the control condition (**Table 1**, Supplementary **Table S5**, **Figure 3C**) which may also reflect that the planning condition is more complex leading the subjects to perform less accurately.

To analyze whether there is a relationship between RT and response accuracy, we performed Spearman's rho correlation between these behavioral parameters. We found that only the RT of the planning execution period was correlated with the accuracy of the planning condition (Supplementary **Figure S2**, **Table S6**), showing that both may appertain to the same cognitive process.
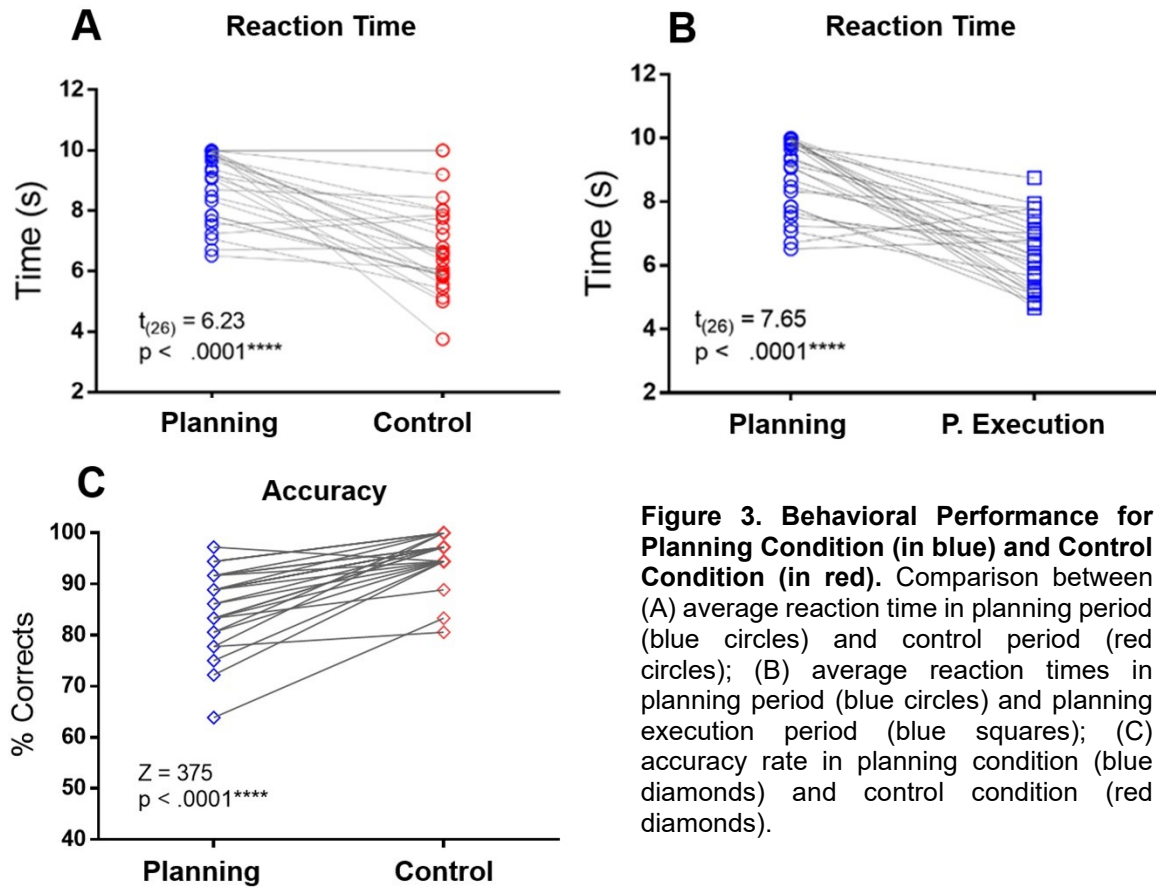
Figure 3. Behavioral Performance for Planning Condition (in blue) and Control Condition (in red). Comparison between (A) average reaction time in planning period (blue circles) and control period (red circles); (B) average reaction times in planning period (blue circles) and planning execution period (blue squares); (C) accuracy rate in planning condition (blue diamonds) and control condition (red diamonds).

Since the RT of the planning execution period and the accuracy of planning are related, we used LISAS to obtain an index that represents the RT corrected for the number of errors (Vandierendonck, 2017; Vandierendonck, 2018). The correlation effect was also present when we used LISAS of the planning execution period (Supplementary **Figure S2, Table S6**), suggesting that LISAS of this period might reflect the association between RT and accuracy as well. Similar effects observed in the behavioral performance comparisons between conditions were obtained when the LISAS performance index was compared to intra and inter-condition (Supplementary **Table S5**).

Additionally, the complexity levels of planning were analyzed. We found there were statistically significant differences between the 'difficult' and the 'easy' level in accuracy and RTs for both the planning and the planning execution period (**Table 1**, Supplementary **Table S5**, **Figure S3).** The 'difficult' level showed greater RTs in the planning and the planning execution period

compared to the 'easy' level, respectively. Moreover, accuracy for the 'difficult' level was lower than the 'easy' level. These results suggest that separating trials according to the number of valid solutions can discriminate easy trials from the difficult trials.

Collectively, once the planning component was successfully extracted from the control condition, all these behavioral results indicate that the planning condition (both the planning and the planning execution period) is more cognitively demanding. This was expressed by higher RT and lesser accuracy during the planning condition. Therefore, the task conditions, specifically their neural correlates, can also be compared to each other.

3.3.2. Electrophysiological Results

3.3.2.1. Frontal Midline Theta Activity

Global theta activity was calculated as follows: Topographic maps from the averaged theta frequency power of the whole epochs (the first and the last four seconds of the planning period and the control period, plus 1 s of their respective maintenance period) across the subjects were visualized. Global theta activity corresponding to the planning period showed a local increase in the frontal midline electrodes (Fpz, AFz, Fz, FCz) in the first 4 seconds, the last four seconds, and the maintenance period, respectively as compared to their control period counterpart where there was not an apparent increase in theta band power. The planning effect was computed as the power subtraction between planning and control periods and showed an increase in theta power that stays consistent in frontal midline electrodes for the planning period (**Figure 4A,** Supplementary **Figure S4**).
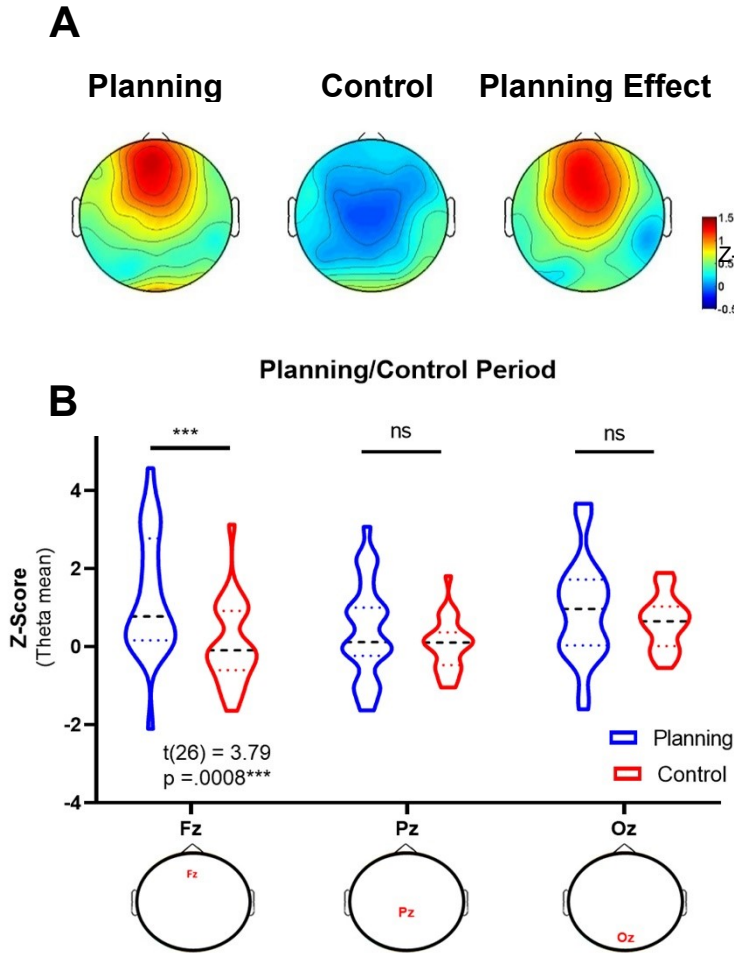
A

Planning **Control** **Planning Effect**

Figure 4. Global FMθ activity during the first 4 seconds of planning. A) Scalp representation of average theta frequency band power across all subjects, normalized to z-score during the planning period (left), the control period (middle) and for the planning effect (right). Left: During the planning period, subjects showed an increase in theta frequency band power located mainly in frontal midline electrodes. Middle: Control period showed no evident increase in the theta frequency band. Right: Planning Effect (power subtraction between periods) illustrates the increase in theta frequency band in frontal midline electrodes. Color bar indicates z values between -0.5 to 1.5. B) Fz average theta band power (left) for all 27 subjects during the first 4 seconds of planning (blue) in comparison to the control period (red) exhibited a significant greater power. In contrast, Pz and Oz did not present significant differences between periods. (see Supplementary **Table S7** and **Table S8**).

B

Planning/Control Period

$t(26) = 3.79$
$p = .0008$***

To analyze whether this observed increase in global FMθ activity during the whole epochs were significant, the averaged theta frequency band during the first and the last 4 seconds of planning for Fz electrode from the planning period were compared to the control period respectively. Global FMθ activity from Fz electrode during planning showed a significant increase in comparison to global theta activity during the control period in both epochs. However, no significant differences between conditions were found for non-frontal midline electrodes used as controls: Pz and Oz (**Figure 4B**, Supplementary **Table S7-S8**).

Afterward, in order to assess the temporal dynamics of FMθ we observed topographic maps corresponding to specific time points of averaged theta band power (750, 1750, 2750 and 3750 ms). As time progress, a sustained increase in the FMθ activity for the planning period is observed. While theta activity during the control period seems absent (**Figure 5A**). Time-frequency analysis of electrodes Fz, Pz, and Oz for the first and last four seconds of planning

revealed increases in low-frequency bands, most importantly a progressive increase in the theta band (4-8 Hz) that starts after 1 second of the planning period onset. This effect was absent in the control period. Time-frequency charts were assessed using a cluster-based permutation test confirming a significant difference between conditions. Clusters suggested differences in the theta band power between periods for Fz, Pz, and Oz electrodes (**Figure 5B**, Supplementary **Figure S4-S8**). Furthermore, negative clusters suggested a power decrease in both alpha and beta ranges during the planning condition when compared to the control condition in Fz electrode (**Figure 5B, Figure S4**), which might be reflecting working memory processes (Lundqvist et al., 2011; Lundqvist et al., 2018) and motor planning preparation as it has been shown in motor control studies (Fairhall, Kirk & Hamm, 2007; Doyle, Yarrow & Brown, 2005). At the beginning of the control period there was a broadband activity specific for this condition. This activity could have been showing evoked activity, an early error detection and/or task-specific evaluation processes which did not affect our analysis and interpretations since the focus of this study and the main comparisons were on late cognitive process (**Figure 5B**). Additionally, the frequency of interest showed a non-significant increase in this early period (0 to 1 second after trial onset) for both conditions as shown later (**Figure 6A**).
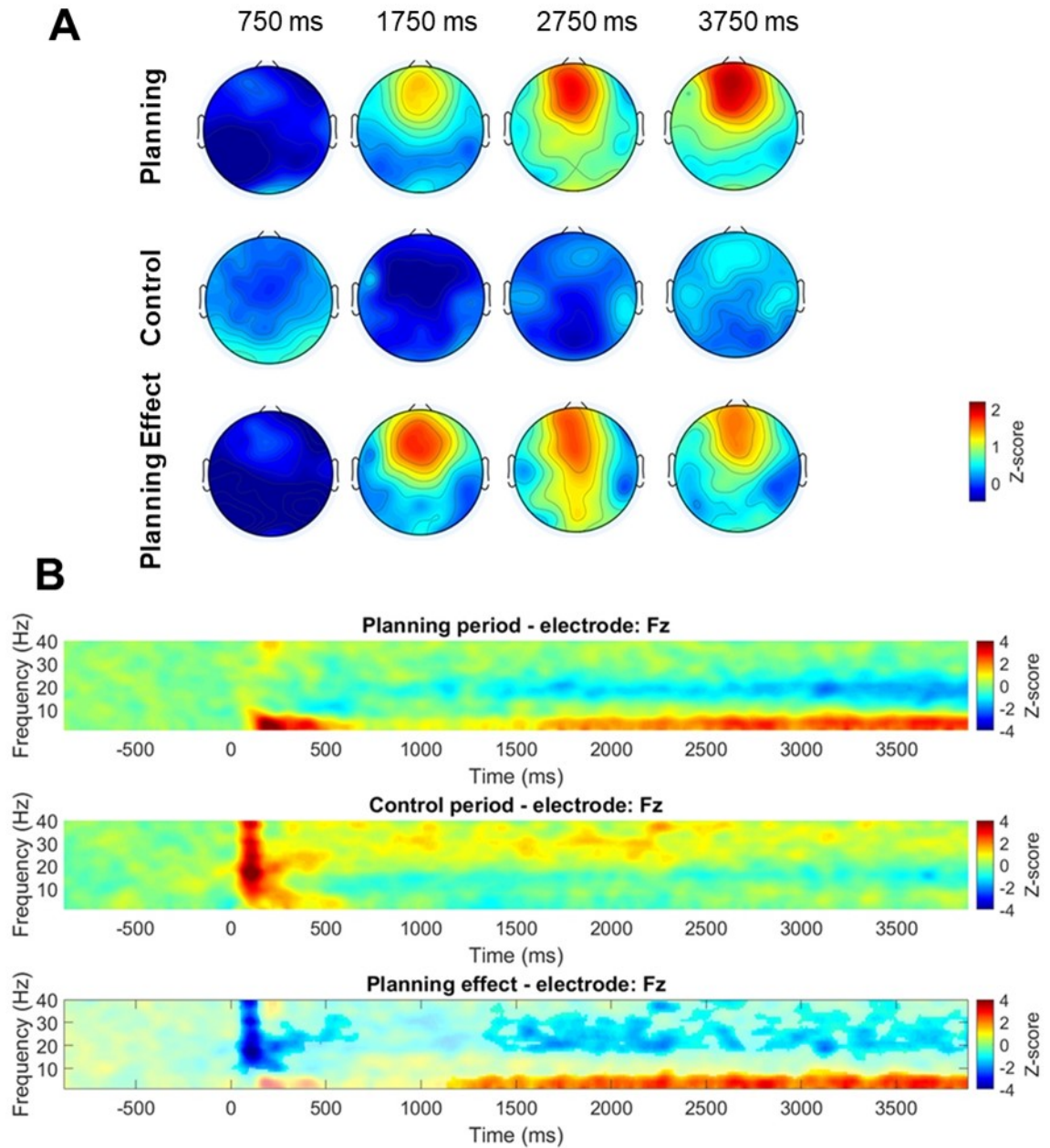
Figure 5. FMθ temporal dynamic of topographic maps and Time-Frequency charts of Fz electrode. A) Figure shows the temporal dynamic of theta activity in topographic maps. Different time points are shown in topographic scalp maps. We observed a progressive increase in the frontal midline theta frequency band across time while subjects were planning paths (the planning period) and not when they were evaluating them (the control period). Each topographic map shows theta frequency power normalized to z-score averaged over all trials for all 27 subjects at a specific time point. Color bar indicates indicates z-score units between -0.5 to 2.2. B) Top: Time-frequency plot for the planning period showing a marked increase in theta band power with time. Middle: Time-frequency plot for the control period. Bottom: Planning effect computed as the subtraction between planning and control period. Non-significant pixels are shown lighter in the plot. Color bar indicates z-score units between -4 to 4.

In order to better characterize the temporal dynamic of the increase in theta frequency band, we then averaged the power between 4-8 Hz for both conditions, obtaining the average band power of theta band over time. We found that the increase in theta activity was significantly greater for the planning period for Fz electrode starting 1 second after the trial onset until subjects stopped planning (**Figure 6**). However, this effect was absent for non-frontal midline electrodes: Pz and Oz electrodes (Supplementary **Figure S9-S10**). This was seen in both time windows: the first four seconds (**Figure 6A**, Supplementary **Figure S9A-S10A**) and the last four seconds of planning and control period (**Figure 6B**, Supplementary **Figure S9B-S10B**). Interestingly, a remarkable increase in theta band was found during the maintenance period of the planning condition, which may reflect storing of the plan in working memory to execute it on the next period (**Figure 6B,** Supplementary **Figure S4**).
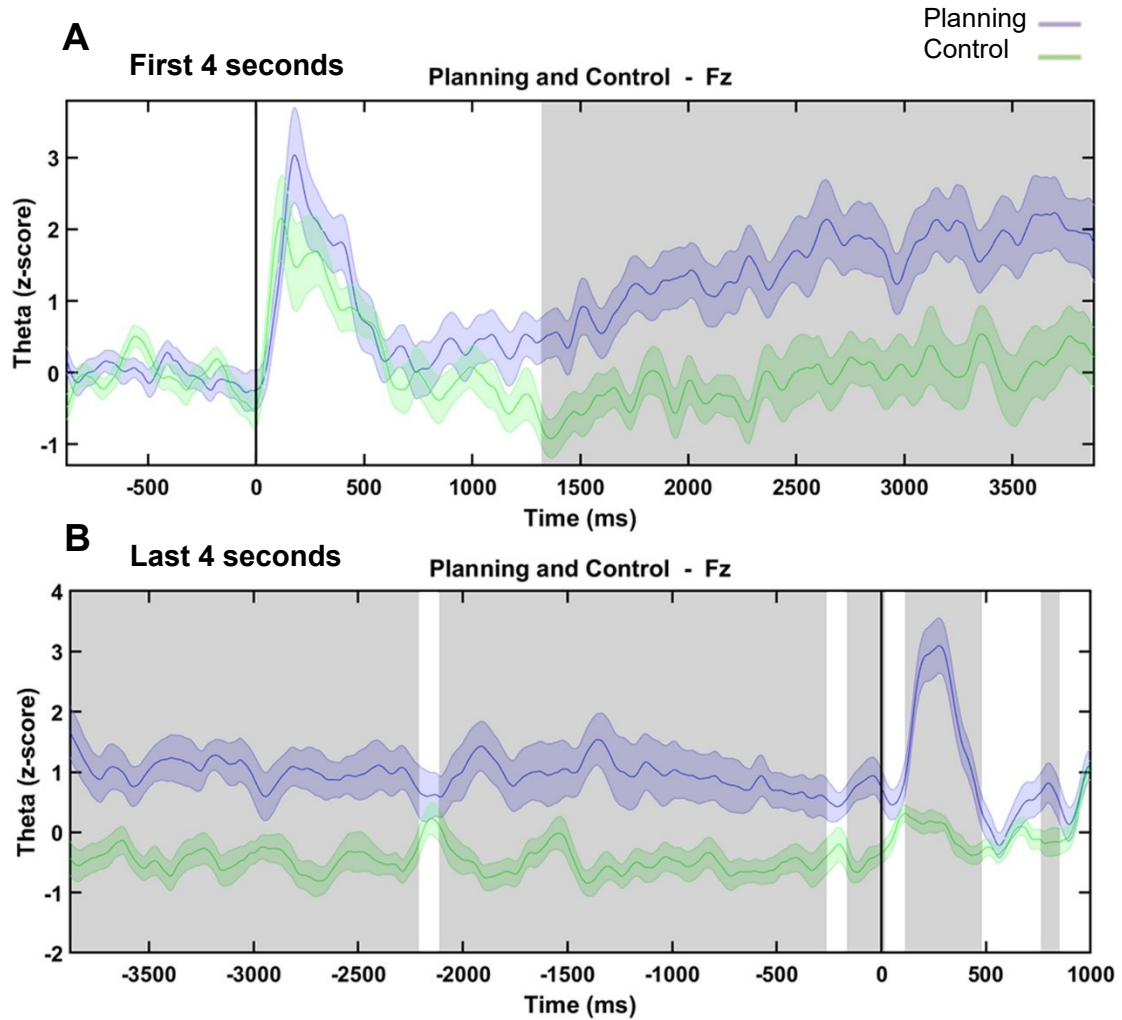
Figure 6. Time Theta Frequency Slices of Fz. A) Fz first 4 seconds of planning (purple) and control (green) period showing a significant and progressive increase of theta activity starting after 1 second of planning onset compared to the control period. B) Fz last 4 seconds of planning showing a sustained and significant increase during planning. At 0 the trial ends and starts the maintenance period. In this period there is a transient and remarkable increase of theta activity for the planning condition, which may represent the working memory load of the plan previously elaborated to be executed on the next period. Gray shaded areas show statistically significant differences according to a non-overlapping moving window with steps of 88 ms of Wilcoxon signed-rank test comparison, FDR corrected. Shaded regions represent 95% confidence intervals.

3.3.2.2.   Source Reconstruction Results

In order to localize the sources, we visualized the whole brain model template and cortical activations for both conditions. We found a specific activation in prefrontal areas for planning (bilateral FP, bilateral ACC, and bilateral MCC), and right-occipital and right-temporal activations for the control period (Supplementary **Figure S11**). However, significant differences between conditions were found in the PFC (the bilateral SF, the bilateral ACC, and the bilateral MCC) (**Figure 7**) being higher for the planning period. Furthermore, to analyze the time frequency domain we performed spectral estimation of ROI time series. ROI time series were calculated using the first mode of the PCA decomposition of all the signals from a ROI. Time-frequency charts were then obtained by using a short-time window FFT. Subsequently, time-frequency charts were compared between bilateral ROIs and periods using non-parametric cluster-based permutation tests (**Figure 8**, Supplementary **Figures S12-S15**).
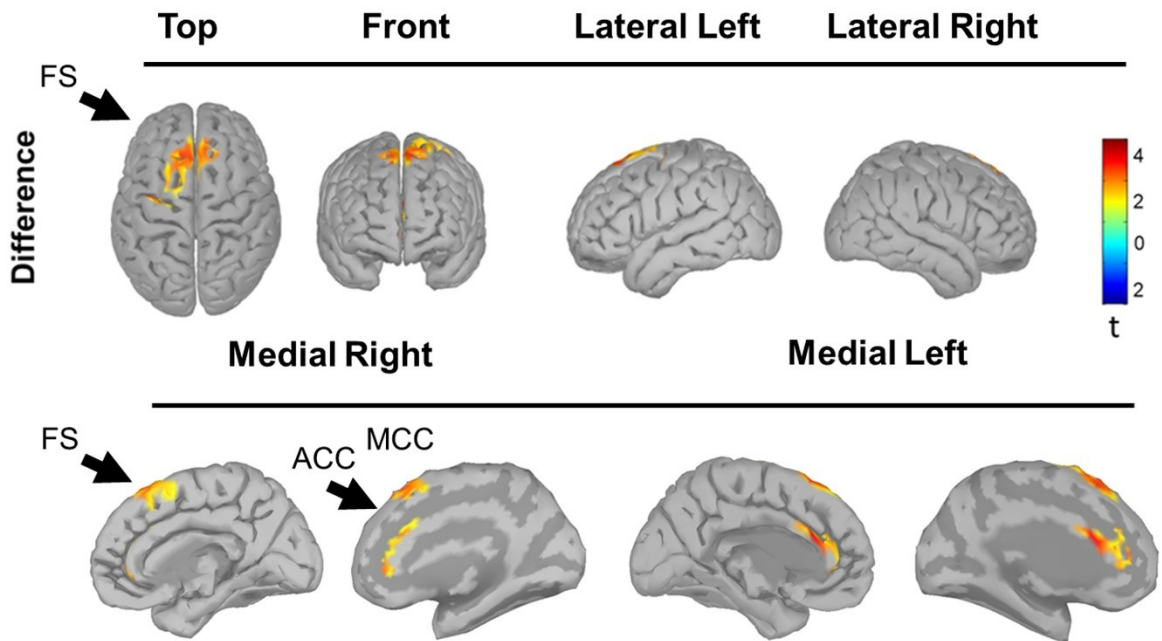
Figure 7. Source Reconstruction Comparison. sLORETA was applied to the task epoch (first four seconds of planning and control periods) for the preprocessed EEG signal (4-8 Hz bandpass filtered) for both conditions, normalized to z-score and averaged between 1 to 4 seconds, and then compared between conditions. A significant increase of theta activity was found in Prefrontal Cortex regions: the bilateral Frontal Superior area, the bilateral Anterior Cingulate Cortex, and the bilateral Mid-Cingulate Cortex. The plot shows significant t values of the permutation test (-2.1 to 4.5). Black arrows show FS, ACC, and MCC labels. FS: Frontal Superior; ACC: Anterior Cingulate Cortex; MCC: mid-Cingulate Cortex.
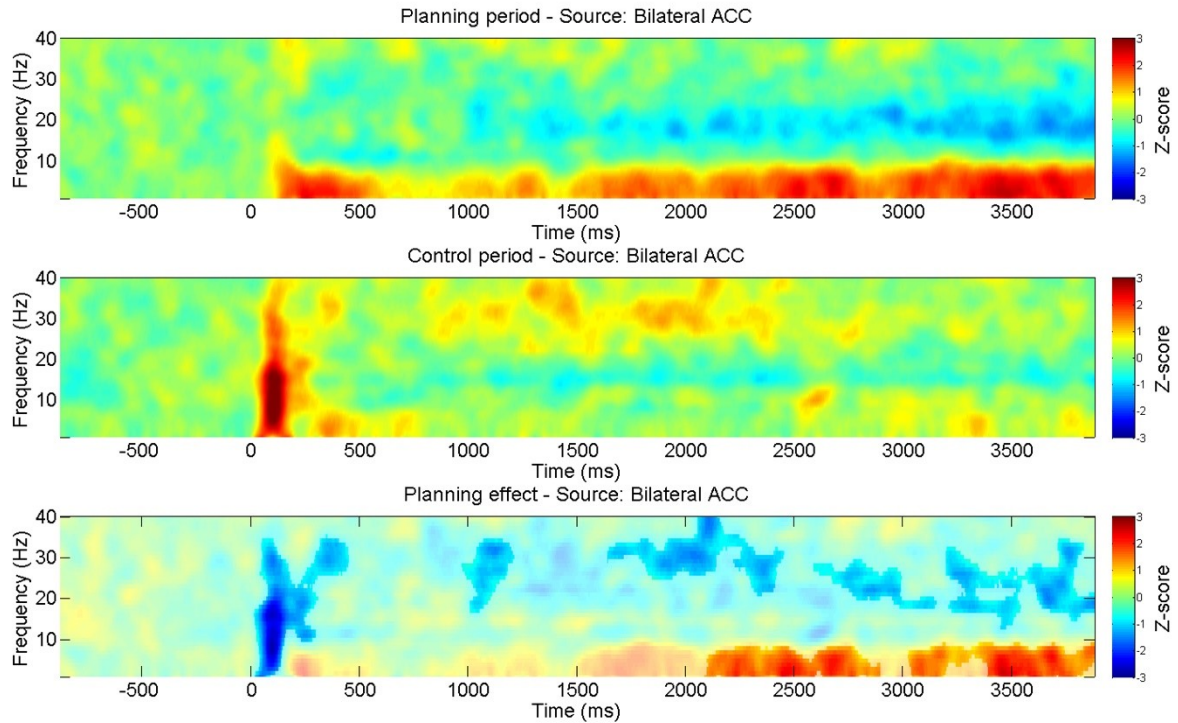
Figure 8. Time-Frequency charts for bilateral ACC Source. Top: Time-frequency plot for the planning period showing a marked increase in theta band power over time. Middle: Time-frequency plot for the control period. Bottom: Planning effect computed as the subtraction between planning and control period showing significant differences in theta activity after 2 seconds. Also, an early decrease in broadband frequencies is observed. Non-significant pixels are shown lighter in the plot. Color bar indicates units of z-score values between -3 to 3. ACC: Anterior Cingulate Cortex.

The left FP source (**Figure S14**) and the bilateral ACC (**Figure 8**) presented significant differences between planning and control period. The positive clusters suggested theta power increase during planning. Additional analysis on the bilateral dorsolateral PFC source was done and there were significant differences on the beta band which may reflect working memory engaging during planning (Lundqvist et al., 2011; Lundqvist et al., 2018) (Supplementary **Figure S16-S17**). Afterward, to confirm these results and evaluate theta changes over time, we performed a Hilbert Transform for each ROI time series separately (left and right) after which we compared the amplitude of theta frequency between conditions. We found that the left FP source presented significantly higher theta frequency band power between 2-4 seconds after the planning period onset. This was also exhibited by the bilateral ACC and the bilateral MCC in different time points of the planning period. The left ACC showed increase in theta amplitude since 1 second after the planning period onset. Similarly, the right ACC and the right MCC exhibited increase in theta amplitude after 2 seconds of the planning period onset. The left MCC presented a significant increase in theta power for the whole epoch

(**Figure 9**). Together, these results suggested that during cognitive planning the aforementioned PFC regions engaged in theta band.
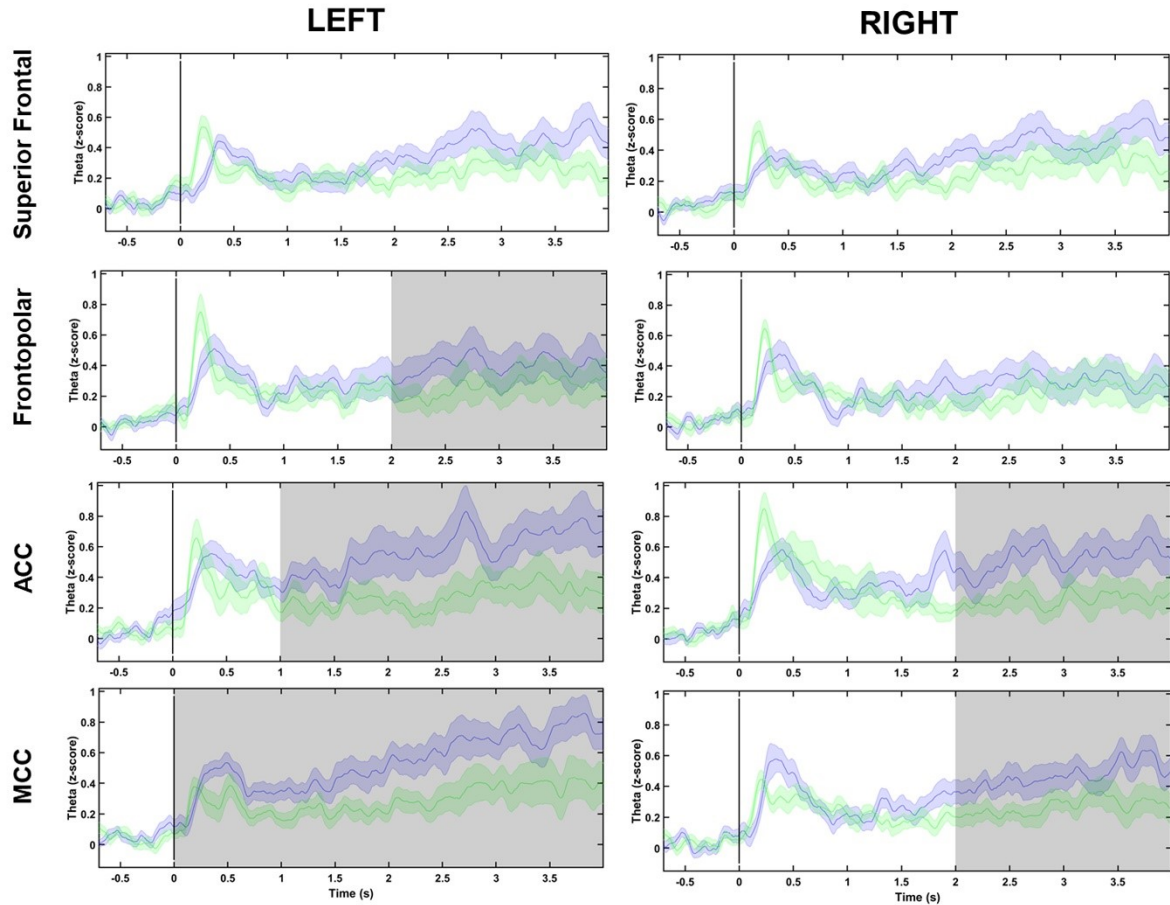
Figure 9. Source Theta Activity over Time. Hilbert transform was applied to first component of the PCA decomposition for each ROI (4-8 Hz bandpass filtered) and for both conditions (planning in purple, control in green), normalized to z-score, showing the instantaneous amplitude of source theta activity over time. Gray shaded areas show statistically significant differences according to a non-overlapping moving window with 1 s of steps of Wilcoxon signed-rank test comparison, FDR corrected. Shaded regions represent 95% confidence intervals. The left FP, the bilateral ACC, and the bilateral MCC showed increases in theta activity at different time points, mainly after 1 s after planning onset. ACC = Anterior Cingulate Cortex; MCC = mid-Cingulate Cortex.

Finally, we sought to evaluate whether the spectral features during planning can be different according to the level of complexity as shown in the behavioral results. Interestingly, we found that there was a significant difference in the left ACC in the alpha band. Hence, this contributed to the idea that the planning task assesses more intrinsic aspects of planning reflected in theta oscillation changes than other general cognitive demands typically present in cognitive control tasks (Supplementary **Figure S3**).

3.3.2.3. Correlations between Theta Activity and Planning Performance

To evaluate the relationship between the theta activity of cognitive planning and the planning performance, we performed Spearman's rho correlations using the theta relative increase from ROIs source and the Δ LISAS Planning or Δ Planning Execution as described in methods section. We found a negative correlation: higher the left FP Theta relative increase (its Δ theta activity as well) during the planning period, lesser the Δ LISAS Planning Execution (**Figure 10A-B**). There were no correlations between the dorsolateral PFC source and planning performance (Supplementary **Table S9-S10**). We found results in the same line using the RTs of correct responses of the planning execution period (Supplementary **Table S11**).
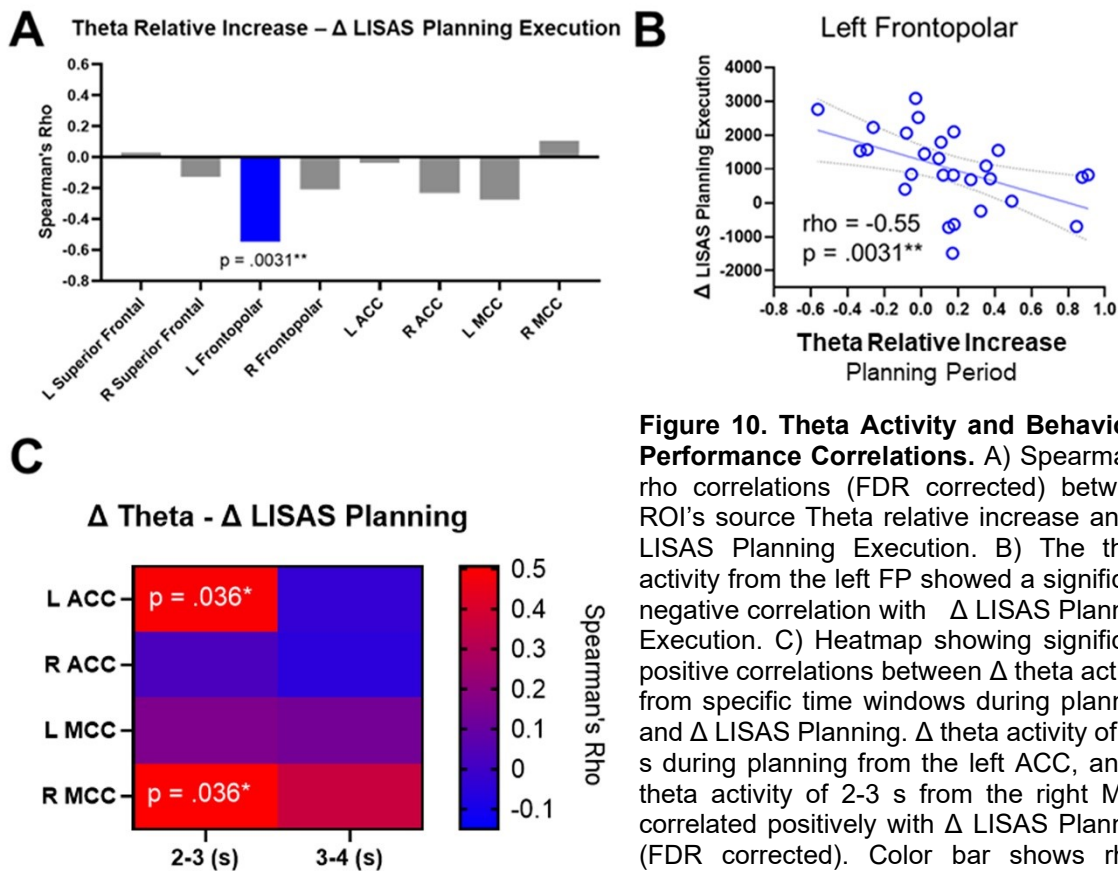
Figure 10. Theta Activity and Behavioral Performance Correlations. A) Spearman's rho correlations (FDR corrected) between ROI's source Theta relative increase and Δ LISAS Planning Execution. B) The theta activity from the left FP showed a significant negative correlation with Δ LISAS Planning Execution. C) Heatmap showing significant positive correlations between Δ theta activity from specific time windows during planning and Δ LISAS Planning. Δ theta activity of 2-3 s during planning from the left ACC, and Δ theta activity of 2-3 s from the right MCC correlated positively with Δ LISAS Planning (FDR corrected). Color bar shows rho's coefficients between -0.1 to 0.5.

Since, on the one hand different time points exhibited significant increases in theta activity in time-frequency charts and time profile slices of theta activity in late periods during planning. On the other hand, midfrontal theta increases have been related to slowing in RT, we evaluated

the Δ theta time dynamics correlations with the Δ LISAS Planning in two time-windows for the bilateral ACC and the bilateral MCC. We found the right MCC and the left ACC exhibited positive correlations: higher their Δ theta activity power, greater the Δ LISAS Planning during the planning period in the 2-3 s specific time interval (**Figure 10C**). Thus, the right MCC and the left ACC may play a pertinent role when the mental elaboration of a plan is being developed, while the left FP may become more involved to execute a plan successfully, which may suggest a differentiated role for theta activity and determined brain regions while cognitive planning processes are exerted compared to when the plan is executed.

3.3.2.4. Theta Phase Synchrony

To assess theta activity synchronization within PFC brain regions we analyzed time-resolved theta phase connectivity using the wPLI for each period and each pairwise ROI interactions. Results showed a significant theta phase synchrony increase between the right MCC and the right ACC in late segments after trial onset during planning. Furthermore, brief segments during the control period also exhibited theta phase synchrony increases but in earlier segments after trial onset for the left FP and the right FP cortex interactions. These results suggest that theta dynamics at the level of phase synchrony were present differentially between conditions in terms of PFC brain regions communication involved and their temporal computation for planning processes (Supplementary **Figure S18**).

3.3.2.5. Eye movements and Theta Activity.

The different goal and cognitive demands of each condition might prompt different types of eye movements in the planning versus the control condition which in turn could induce different patterns of oscillatory activity (Staudigl et al., 2017; Thaler et al., 2013). In order to address this issue, we first inspected the data at the level of single-subject and single-trial at different levels. Importantly, Fz row time series and the theta activity time dynamics seemed not related to the saccade rate over time (**Figure 11A**).
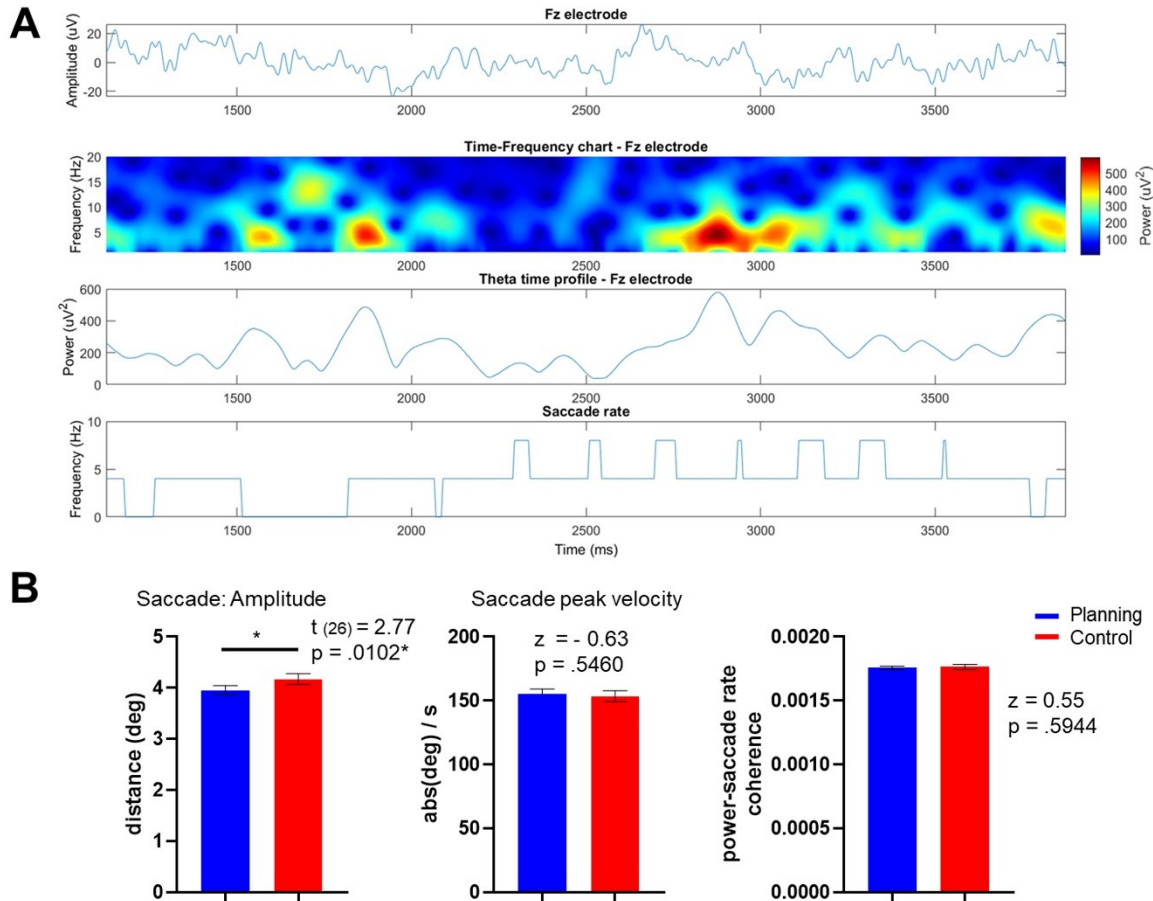
Figure 11. Results of EEG signals and eye movement recordings. A) Row EEG, time-frequency chart, and theta time profile from electrode Fz, and the saccade rate of the subject 8 and trial 9 for the planning condition are shown. B) The saccade amplitude, saccade peak velocity, and power-saccade rate coherence compared between conditions are shown. There were statistically significant differences in saccade amplitude between the planning and the control condition. Error bars represent SEM.

Second, we extracted the saccade amplitude and the saccade peak velocity from the whole trial (Supplementary **Figure S19**) and from 0 to 3.75 s being then compared (**Figure 11B**). For both periods we found that saccade amplitude was greater during the control condition. On the other hand, the coherence between Fourier theta power at electrode Fz and saccade rate was compared and there were no statistically significant differences between conditions (**Figure 11B**, Supplementary **Figure S19**) reflecting that any possible relation between saccades and theta activity is not different between conditions.

3.4. DISCUSSION

In this study, EEG activity was recorded during a novel and ecological planning task to evaluate whether cognitive planning implementation, as a higher-order cognitive control function, induces FMθ activity originating in PFC regions, and whether these sources are related to different aspects of planning performance. To address these questions, we designed a novel planning task with adequate psychometric properties in terms of reliability and variability.

There are studies that have assessed the reliability of planning tasks (Wilson et al., 1996; Porteus, 1959), however, there have not been any reports on psychometric properties needed for the adaptation of planning tasks for neuroimaging assessment (Kirsch et al., 2006; Tremblay et al.,1994) at least within the scope of our literature review. In this study, excellent reliability was found for the behavioral task outcomes in the two conditions: planning and control (Supplementary **Table S3**). Additionally, the task's behavioral parameters showed a normal distribution (Supplementary **Table S2**) and variance homogeneity (Supplementary **Table S4**).

Typically, behavioral paradigms used in cognitive neuroscience research are presented in lab-based sensory deprived settings using oversimplified stimuli, in order to avoid confounding factors that might interfere in the understanding of cognitive phenomena as much as possible (Miotto & Morris, 1998; Zaki & Ochsner, 2009; Shamay-Tsoory & Mendelsohn, 2019). For this reason, the brain mechanisms of several cognitive functions, including high-order cognitive functions such as planning, are lacking. There are two main limitations in studies using such tasks, *i)* the person-dependent factor, which establishes that artificial tasks may limit the active role of the participants in paradigms affecting their sense of agency and embodiment; *ii)* the situation-dependent factor, which states that the artificial context where participants perform on tasks might engage different mechanisms than what a real-life context would demand (Shamay-Tsoory & Mendelsohn, 2019). As a result, current trends in cognitive neuroscience encourage and promote experimental designs with greater ecological validity, since this might bring more extrapolatable findings to understand the brain mechanisms underlying human cognition (Caine, 2002; Kingstone, Smilek, Ristic, Friesen, & Eastwood, 2002; Zaki & Ochsner, 2009). Taking these factors into account, in this study we have designed a behavioral paradigm based on the Zoo Map and Porteus Maze Tasks that allowed the measurement of the planning function in a controlled setting. There are several trade-offs in our design. While our novel planning task sticks to a deprived lab-based setting, the task is enriched with meaningful stimuli and goals. The behavioral paradigm was composed of a planning task that demanded the

behavioral performance of a task analogous to a daily life situation, and which was divided into different periods that are present during cognitive planning. In our study, the bulk of the analyses were focused on the planning phase and the execution phase because they compound the main phases of planning function: In the first period, subjects have to plan a path while monitoring whether it follows a given set of rules, and then a second period where they store it in working memory. Subsequently, there is a third period in which subjects must carry out their former plan while monitoring the path's behavioral execution, making sure the path follows these rules. While planning and executing the plan, subjects must have enough cognitive flexibility to correct the trajectory adequately if planned or traced incorrectly. Thus, the task demands implementing cognitive control functions in a concerted manner as it may occur in real-life situations, where planning paths on maps are part of everyday life. For this reason, we decided to evaluate the planning function using this paradigm over other traditional and well-established planning tasks (such as the Tower of London or Tower of Hanoi-based tasks). Additionally, an ecological task design requires the paradigm to demand subjects to exert cognitive planning that an actual daily life situation would demand (Miotto & Morris, 1998; Burgess, Simons, Coates & Channon, 2005; Morris & Ward, 2005). However, the ecological validity of a task can range from artificial set-ups to real life situations, as shown in Shamay-Tsoory & Mendelsohn (2019). Accordingly, we argue that our task is a more ecologically valid task than the traditional neuropsychological tasks used to assess planning, where subjects meet an abstract and fictitious setting. Despite the fact that our task might not reflect a real-life scenario completely, we believe that planning trajectories is certainly more meaningful and similar to what people do in their daily routines. Moreover, designing an ecological-behavioral task not only has to be analogous to a real life situation but also requires predictive validity, i.e., that the task must be able to identify impaired planning function in patients with psychiatric or cognitive disorders who exhibit impaired planning performance in their daily life (Oosterman, Wijers, & Kessels, 2013). This was another reason of why our novel paradigm was based on the Zoo Map Task, which has been shown to have optimal predictive validity in previous studies (Oosterman, Wijers, & Kessels, 2013). Therefore, designing an adequate control task that effectively isolates the planning component was essential, and this is reflected in the results obtained in both behavioral and electrophysiological measures. Because the control condition required subjects to achieve a goal in a task that included the same stimuli but did not require planning, the planning component was successfully removed. Due to this removal, we observed FMθ activity induced by cognitive planning during the planning period, which was not observed in the control period.

The behavioral results for the planning condition were in line with our predictions. Since the planning task implies a high cognitive function (Lezak, 1995; Zwosta, Ruge & Wolfensteller, 2015), we predicted higher RTs and less accurate performances during the planning condition (complex task: plan a path in a complex map) than during the control condition (simple task: they only have to follow a marked path and decide whether it followed the rules). Moreover, in both periods of the planning condition (the planning period and the planning execution period) RTs were always higher than the control condition (the control period and the execution control period) reflecting how difficult and cognitively demanding the planning condition is (Owen, Doyon, Petrides & Evans, 1996; Voytek et al., 2015; Ossandón et al., 2012). Interestingly, the execution of the planned path (during the planning execution period) involved a considerably more cognitive effort during the planning task, as suggested by higher RTs during the planning execution period compared with the control condition periods (the control period and the control execution period, Supplementary **Table S5**). This can be explained by the requirement of high cognitive functions such as working memory and attentional control to perform the execution of the plan. All these observations are in line with the theoretical assumption of cognitive planning (Hayes-Roth & Hayes-Roth, 1979; Wilensky, 1983; Grafman & Hendler, 1991; Zwosta, Ruge & Wolfensteller, 2015).

Although the control condition was designed to measure less complex cognition as evidenced by better performances and faster processing times, and then to compare it against the planning condition, it was favorable to use planning tasks with different complexity levels and analyze planning function according to this. It was possible to identify behavioral differences between the 'easy' condition and the 'difficult' condition with any differences at the level of electrophysiological measures, suggesting that results account for intrinsic aspects of the planning function more than general features of cognitive control such as attention, cognitive effort, or high cognitive demand. However, this is unusual and further studies controlling different levels of complexity might be helpful to clarify this point.

Previous studies have reported that PFC has a critical role during cognitive planning (Kirsch et al., 2006; Newman, Carpenter, Varma, & Just, 2003; Owen, Doyon, Petrides & Evans, 1996; Nitschke et al., 2017) and the present results show that cognitive planning induces a FMθ activity (**Figures 4-6,** Supplementary **Figure S4**) originating in the PFC, specifically the ACC, the MCC, and the SF (**Figure 7**). These results are in line with previous studies on higher-order cognitive functions (Cavanagh & Frank, 2014; Hanslmayr et al., 2008; Cavanagh, Frank, Klein & Allen, 2010; Cohen & Cavanagh, 2011). Extensive evidence supports the role of FMθ

activity as a common top-down mechanism for realizing the need for cognitive control (Cavanagh & Frank, 2014; Cavanagh, Zambrano-Vazquez & Alen, 2012; Cooper et al., 2019). FMθ activity, as a marker of cognitive control, is thought to be exerted by recruiting and aiding communication between brain regions during tasks that require active cognitive engagement (Cavanagh, Cohen & Alen, 2009; Cavanagh & Frank, 2014; Sauseng, Tschentscher, & Biel, 2019).

Although few studies have attempted to deepen the understanding of the temporal dynamics of FMθ activity, most of them agree that its time profile could reflect different mechanisms of cognitive control and the different PFC areas involved for it (Cooper et al., 2019; Sauseng, Tschentscher, & Biel, 2019; Bartoli et al., 2018; van Driel, Swart, Egner, Ridderinkhof, & Cohen, 2015). Here, we characterized the FMθ activity time profile for the planning condition as more demanding and therefore requiring a higher extent of cognitive control. The control condition was characterized as demanding cognitive control to some extent but less than the planning condition. The FMθ temporal dynamic activity during the planning condition was characterized as an increase between the 4-8 Hz band that progressively grows over the first four seconds and then was kept increased over the last four seconds. On the other hand, the control condition showed just a transient stimulus-locked broadband increase showing no theta band increase over time (**Figures 4-6,** Supplementary **Figure S4**).

Here, we have shown that, for the first time, as other executive functions, FMθ also emerges during cognitive planning, and its temporal dynamics may be a marker of cognitive control. Additionally, source analysis confirmed that the primary sources of this FMθ activity are: SF, FP, ACC, and MCC (**Figures 7-9**, Supplementary **Figures S11-S15**).

The SF region is located in the superior part of the PFC and it has been described to be involved in a variety of functions associated to cognitive control functions, i.e., working memory (Boisgueheneuc et al., 2006, Owen, 2000; Owen et al., 1998, Petrides, 2000), attention (Corbetta, Patel & Shulman et al., 2008, Fox et al., 2006), and sensorimotor control-related tasks (Chouinard & Paus, 2010, Martino et al., 2011, Nachev, Kennard & Husain, 2008). Since planning requires working memory and attention, the FMθ activity observed in this region may reveal the participation of these higher-order cognitive functions to support the process of planning. Furthermore, the SF region is anatomically and functionally connected to the dorsolateral PFC and the cingulate cortex through the cingulum (Beckmann et al., 2009).

In the case of the FP region, it has been associated to higher cognitive functions, for instance, it becomes active during working memory, self-generated stimuli, planning, problem-solving and reasoning tasks (Braver & Bongiolatti, 2002; Baker et al., 1996; Christoff & Gabrieli, 2000). In this study, we observed discernable associations between these brain regions and different parameters of planning performance, for e.g., a higher theta relative increase from the left FP for elaborating a plan (the planning period), and a reduced Δ RT (corrected by incorrect responses) for executing a plan previously planned (the planning execution period) were correlated. Consistently, these results were replicated when RTs of the correct responses during the planning execution period were analyzed. This particular result is relevant, since most evidence in cognitive control study have shown that frontal theta predicts reaction time slowing in cognitive tasks (Cooper et al., 2019). In this case, theta activity from the left FP might be related to efficiency and accuracy, because quicker execution of plans was associated with accuracy (Supplementary **Figure S2**), this result is in line with studies that showed frontal theta predicts specific cognitive control-induced behavioral changes beyond general reaction time slowing (Cooper et al., 2019). There is extensive evidence showing that the FP cortex participates in monitoring and manipulating information internally generated such as in planning task, inductive reasoning, tasks that require a plan generation or monitoring of self-generated stimuli (Berman et al., 1995; Baker et al., 1996; Osherson et al., 1998; Goel et al, 1998; Christoff & Gabrieli, 2000), Additionally, it has been shown that the FP is involved in monitoring the relevance of alternative goals to replace the current one (Mansouri et al., 2017). Thus, we interpreted that during cognitive planning the left FP is recruited to elaborate a plan and to monitor different alternative paths while keeping the goal in working memory to successfully execute the plan which might be expressed in better reaction times. The ACC and the MCC have been associated with cognitive control (Cavanagh & Frank, 2014), i.e., conflict monitoring (Botvinick, Cohen, & Carter, 2004; Kerns et al., 2004; Sohn et al., 2007, Ursu et al., 2009), error detection (Carter et al., 1998; Gehring & Fencsik, 2001, Pourtois et al., 2010), response selection (Turken & Swick, 1999; Awh & Gehring, 1999; Paus, 2001), and attentional control (Aarts & Roelofs, 2011; Orr & Weissman, 2009; Crottaz-Herbette & Menon, 2006; Luo et al., 2007). Additionally, the MCC plays a role in regulating the autonomic nervous system, nocifensive and rewarded behaviors, multisensory orientation of the head and body in space (Amiez & Procyk, 2019; Vogt, 2016). Evidence have shown a differentiated role for the ACC and the MCC for minimizing distraction (Orr & Weissman, 2009). The MCC is involved in attentional control and the ACC in conflict detection. Consequently, in the context of cognitive planning, while the ACC might be recruited for conflict monitoring like verifying selected paths

to be used, the MCC could be contributing to exert attentional control which in turn ended up in RTs increases as seen in this study. Overall, the right MCC and the left ACC may play a pertinent role when the mental elaboration of a plan is being developed, while the left FP may become more involved to execute a plan successfully, and theta activity could be the biophysical mechanism to exert these cognitive control functions.

Interestingly, differences in other frequency bands such as alpha and beta were also observed at channel and source-level. We believe that these variations might express the enriched spectral nature of the brain functions in terms of coordination and communication within and between regions (Canolty & Knight, 2010; Fell & Axmacher, 2011). For instance, Sadaghiani and Kleinschmidt (2016) suggested three brain networks involved in cognitive control that modulate alpha oscillations influencing local signal processing, disparate information exchange, and behavior. Specifically, the alpha activity from the ACC and the MCC might reflect the cingulo-opercular network engagement proposedly provide an updating mechanism for incoming signals supporting and maintaining tonic alertness or vigilance through cortical alpha oscillations to exert attentional control (Sadaghiani et al., 2010; Sadaghiani et al., 2015). On the other hand, decreased prefrontal beta oscillations were observed in time-frequency charts during planning. Recent studies have suggested that beta oscillations have a role in executive functions such as working memory (Lundqvist et al., 2011; Lundqvist et al., 2018). Specifically, it has been shown that beta drops during encoding and before response, when the stored information is needed (Lundqvist et al., 2018). We interpreted that during planning, beta suppression might be acting as an inhibitory filter, controlling working memory components and expressing similarities with motor preparation beta (Schmidt et al., 2019; Fairhall, Kirk & Hamm, 2007; Doyle, Yarrow & Brown, 2005) to execute the plan in the next period. Further analyses need to be done to clarify the role of these oscillations during cognitive planning and the possible interaction between theta and alpha/beta oscillations at the level of cross-frequency synchrony phase-amplitude coupling.

One major limitation of the present study are the differences in saccade amplitude during the planning period compared to the control period (**Figure 11B**, Supplementary **Figure S17**), which could lead to introduce artifacts in the EEG signal (Thaler et al., 2013). However, several studies proposed a direct relationship between different eye-movements parameters and specific cognitive phenomena. For instances, Bodala et al. (2016) showed that, along with a decrease in frontal midline theta, saccade amplitude and velocity also decrease with sustained attention and, Velasques et al. (2013) found that the saccade amplitude produces oscillatory

changes in the frontal gamma band in a prosaccadic attention task. It has also been shown that the amplitude of occipital alpha band activity predicts the impact of eye-movements (blinks and saccades) in a perceptual task (Nakatani et al., 2013). Thus, saccade amplitude (along with other eye-movement parameters) might reflect different cognitive mechanisms instead of solely adding confounding noise to the EEG signal. In the present study, we improved the detection of eye-movement related artifacts by ICA method using the saccade-to-fixation variance ratio criterion between 10 ms pre- and post-saccade (Plöchl, Ossandón, & König, 2012). This criterion optimizes the artifact removal process for free viewing tasks (see Dimigen, 2020). Additionally, there were no differences in saccade peak velocity and no differences in theta power-saccade rate coherence between conditions. However, further studies to address these questions are strongly recommended.

Altogether, we postulate that the FMθ activity from the PFC, and the implementation of working memory, attention, and monitoring function, might be aiding cognitive planning by contributing to the dynamic internal elaboration of a plan and its motor execution. These results are in agreement with the consensus of the existence of cognitive control core functions (Lehto, Juujärvi, Kooistra & Pulkkinen, 2003; Miyake et al., 2000) like working memory, inhibitory control, attention, upon which higher-order cognitive control functions such as reasoning, problem-solving and cognitive planning are built (Collins & Koechlin, 2012; Lunt et al., 2012).

3.5. CONCLUSIONS

The present study evaluated a novel cognitive planning task with behavioral and electrophysiological measurements. Results suggest that the proposed planning task is optimal to evaluate planning, and that it induced FMθ activity originating in the PFC. We characterized for the first time both the spatial and temporal dynamics of this activity during planning. A specific association between theta activity from the left FP and planning performance was found, which may reflect the participation of this brain region in a successfully self-generated plan. Furthermore, the associations between theta activity from the right MCC and the left ACC with reaction times of the planning period may reflect high cognitive demand of the task, engaging in attentional control and conflict monitoring implementation. The findings in this work are in accordance with the broad body of evidence supporting the role of local FMθ activity in cognitive control.

3.6. ACKNOWLEDGMENTS

3.7. SIDENOTE

Additionally, single-subject inspection was done in order to visualize variability at behavioral and electrophysiological level in the planning condition. We found that subjects consistently exhibited maximum values in the theta band power but with different time onset (Supplementary Figure **S18**). However, in the alpha and beta band subjects showed more variability. This might reflect individual differences in cognitive processes such as working memory that the averaging process could have hidden, but further analyses should be conducted to clarify this phenomenon. At the level of behavioral performance, reaction times and accuracy data were consistent.

4. <u>STUDY 2: Frontal Theta Phase Connectivity during Cognitive Planning</u>.

Frontal Theta Phase Connectivity during Planning

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In preparation

ABSTRACT

Cognitive planning, the ability to develop a sequenced plan to achieve a goal, plays a crucial role in human goal-directed behavior. It has been suggested that cognitive control might result from frequency-specific interactions of specialized and widely distributed cortical regions due to the enriched rhythmic structure nature of the brain. In a previous study, using a novel and ecological planning task, a strong increase of frontal midline theta (FMθ) was induced by planning, and the prefrontal cortex theta activity sources were correlated with behavioral performance. However, the connectivity dynamics between frontal and distal sites and their relationship with planning behavior remain elusive. Using Weighted Phase Lag Index, we found a robust increase in theta phase connectivity during planning. These results support the idea of cognitive control implementation is performed via theta phase connectivity which may be coordinating information, such as visuospatial analysis and motor control preparation, through the prefrontal cortex and disparate brain regions.

Keywords: planning; prefrontal cortex; cognitive control; theta phase connectivity.

4.1. INTRODUCTION

The executive control that guides our thoughts and behavior seems to be one of the most remarkable human behavior characteristics. In general terms, cognitive control alludes to the ability to perform goal-directed behavior (Cohen, 2017). This includes mentally elaborating possible plans, among other abilities such as taking the time to decide before acting, solving unanticipated challenges, postponing rewards, and staying focused (Diamond, 2013). On the apex of executive functions is cognitive planning (Collins & Koechlin, 2012; Sira & Mateer, 2014; Lunt et al. 2012), which consists on the ability to develop a sequenced plan to achieve a goal in an organized, strategic and efficient manner (Hayes-Roth & Hayes-Roth, 1979). Planning allows imagining what the future might be, and how our behavior could affect and change the current state, leading us to this imagined future (Benson, 1993). However, as essential is the capacity of cognitive planning, its underlying neural mechanisms are poorly understood.

Extensive neuroimaging findings have shown valuable evidence about the critical role of the Prefrontal Cortex (PFC) in cognitive control, including planning. For instance, the implication of the dorsolateral PFC (Nitschke et al., 2017), the Frontopolar Cortex (FPC) (Braver & Bongiolatti, 2002; Baker et al., 1996; Christoff & Gabrieli, 2000), the mid-Cingulate Cortex (MCC), and the superior parietal lobe, among other brain regions (Kirsch et al., 2006; Newman, Carpenter, Varma, & Just, 2003; Owen, Doyon, Petrides & Evans, 1996) using behavioral paradigms such as Tower of London (Shallice, 1982; Unterrainer et al., 2004) or Porteus Maze (Porteus, 1959; Gallhofer, Bauer, Lis, Krieger, & Gruppe, 1996; Krieger, Lis, & Gallhofer, 2001; Lee et al., 2007; Lezak, 1995; Peters & Jones, 1951; Tremblay et al., 1994).

While the precise brain regions involved during planning are amenable to imaging studies that use fMRI or PET, its fine temporal and oscillatory neural properties remain elusive. To address this issue, in a previous study, Domic-Siede et al. (2020) showed that planning induced a progressive and sustained increase of frontal-midline theta activity (FMθ) over time. Source analyses indicated that this activity was generated within the prefrontal cortex. Furthermore, theta activity in core executive regions correlated with behavioral performances. Cavanagh and Frank (2014) proposed that FMθ activity is a common marker of cognitive control that may indicate how the need for control is biophysically realized and communicated to other brain regions via theta phase connectivity (for instance, Hanslmayr et al., 2008, Cavanagh et al., 2009; Cohen et al., 2009; Cohen & Cavanagh, 2011; Cohen & van Gaal, 2013; Nigbur et al., 2012; Van de Vijver et al., 2011; Van Driel et al., 2012; Narayanan et al., 2013; Anguera et al.,

2013). Extensive electrophysiological evidence has suggested that different spectral signatures are functionally coupled through phase - amplitude or phase to phase synchrony (Canolty & Knight, 2010; Fell & Axmacher, 2011), and this constitutes a key mechanism to coordinate the spatio-temporal organization of neural networks. However, whether cognitive planning is exerted via theta phase connectivity between PFC and sensory-motor regions remains unknown. Under this context, the present study attempts to evaluate the connectivity dynamics during planning function using a novel and experimental ecological paradigm.

4.2.   MATERIALS AND METHODS

We applied analysis methods described below to datasets from a previous study using a novel planning task based on the Zoo Map Task (Wilson et al., 1996) and Porteus Maze (Porteus, 1959). Here we briefly describe this task's key features; further details can be found in Domic-Siede et al. (2020).

4.2.1. Participants

Twenty-seven healthy adults (13 females) between 19 to 38 years old with normal or corrected-to-normal vision participated in this study (Domic-Siede et al., 2020). No participant reported neurological or psychiatric disorders according to the International Neuropsychiatric Interview, Spanish version adapted (Ferrando, Bobes, Gibert, & Soto, 2000). The bioethics committee of the Faculty of Medicine of Pontificia Universidad Católica de Chile approved procedures. Written informed consent was obtained from all participants before the experiments (research project number: 16-251).

4.2.2. Experimental Design and Procedure

The behavioral paradigm was programmed in the Presentation Software® by Neurobehavioral Systems (Version 18.0, www.neurobs.com, Neurobehavioral Systems, Inc., Albany, CA). First, it comprises a planning task that consists of solving different mazes (representing zoo maps) containing several paths, some of them leading to four animals dispersed along the map. To solve the task, participants must go through four stages. First of these is the **planning period** where the zoo map is presented, with a range of time to mentally elaborate a route that allows visiting all the animals inside the map following some rules (e.g., to not cross a dead end). Second is the **maintenance period**. Here, the map disappears, and the previously generated plan is expected to be retained in the participant's working memory. Next is the **execution**

period. In this period, the map reappears. Here, the idea is to draw the path that was planned (using the gaze and online feedback given by an Eye-Tracker System: EyeLink 1000 Plus, www.sr-research.com, SR Research, Mississauga, Ontario, CA) and retained in working memory in the previous period. Finally, in the fourth stage i.e. **response period**, the order of animals visited is reported, and the trial culminates with the delivery of feedback indicating whether the participant's performance was correct or incorrect (for more details, see the methods section). This paradigm allows measuring different parameters that account for the planning capacity using different stages, including the display of its different components involved (working memory, attentional control, visuospatial analysis, among others) in a more analogous to real-life situations way, since planning paths on maps is a common daily activity. Furthermore, to control confounding factors, the paradigm considers a control task with the same structure as the planning task, but a different goal. In the first period of the control task, i.e. the **evaluation period** (that serves as the counter part to the **planning period** mentioned above), the goal is to look at the different maps, which are the same as the planning task, except that they contain already drawn routes (stimuli were controlled by illuminance), and participants have to evaluate whether these routes follow the previously stated rules or not, as a result which the cognitive planning component was removed. Then, participants retain in their working memory for the **maintenance period**, whether the road drawn complied the rules. In the third period, i.e. the **execution period**, participants overwrite the drawn route, and finally in the **response period** they report whether the road complied with the rules, at which stage, the trial ended in the delivery of a feedback of whether the performance was correct/incorrect (more details are also available in the methods section). To sum up, having a control task that contains the same or similar psychophysical stimuli, and demands the implementation of cognitive components that also emerge during cognitive planning (working memory, attentional control, and visuospatial analysis), except the elaboration of a plan per se, allows an adequate or acceptable isolation of the cognitive planning factor by contrasting the parameters of both behavioral performance and electrophysiological signals (**Figure 1**; for further details see Domic-Siede et al., 2020).

A Planning Condition
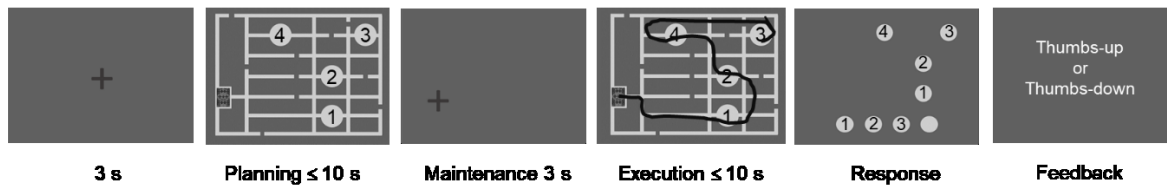
B Control Condition
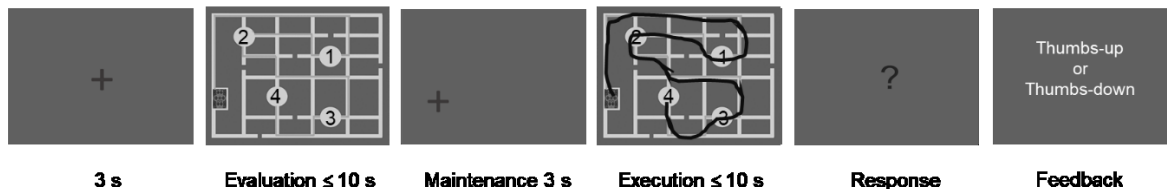
Sample trial

Figure 1. Experimental Design. A) Representative planning condition trial. Planning trial started with a fixation cross presented for 3 seconds. Subjects were then instructed to plan a path visiting all the four animal locations with a maximum time of 10 seconds, following a set of rules (previously explained). Afterward, a shifted fixation cross was shown. Once the maze appeared again, subjects had to execute the trace planned in the previous planning period using their gaze with a visual feedback (given by an eye-tracker system) that delineated their gaze movement in real-time (dark line) with a maximum time of 10 seconds. Then occurred the response period where the subjects had to indicate the sequence made during execution by arranging the animals in the chosen order with a joystick. Based on their response, subjects received feedback (thumbs-up when correct and thumbs-down when incorrect). B) Representative control condition trial. A fixation cross appeared for 3 seconds. Next, subjects were instructed to look at an existing traced path (dark line) and evaluate whether it followed the rules or not. Next, a shifted fixation cross appeared again after which the maze reappeared. This time subjects had to replicate the already traced route having the same visual feedback as the execution planning period. Next came the response period where they had to answer if the traced sequence followed the previously stated rules or not by pressing a joystick button. Based on their response, subjects received feedback. Numbers inside of circles represent animal locations. Numbers at the bottom in the response represent the order of animals visited reported by the participant.

4.2.3. EEG Data Acquisition and Preprocessing

Electroencephalography brain activity was recorded at 2048 Hz from sixty-four scalp electrodes placed following the international 10/20 system. Four additional electrodes measured electro-oculography (EOG) activity. Data were referenced offline to average mastoids, downsampled to 1024 Hz, high-pass filtered at 1 Hz, and low-pass filtered at 40 Hz using EEGLAB toolbox codes (Delorme & Makeig, 2004). Eye movement activity recorded from eye-tracker was synchronized with EEG recordings using EYE_EEG extension (Dimigen, Sommer, Hohlfeld, Jacobs, & Kliegl, 2011). Afterward, Logistic Infomax Independent Components Analysis (ICA) algorithm (Bell & Sejnowski, 1995) was used to identify and

remove artefactual components from EEG data following the same procedure as Domic-Siede et al. (2020). The EEG signal was epoched from −1 s to 4 s locked on planning/control stimulus onset; -4 s to 0 s locked on planning/control period end; and 0 s to 1 s locked on maintenance period onset. Incorrect trials were deleted.

4.2.4. Data Analyses

4.2.4.1. Analysis of Theta Phase Synchrony

To identify theta phase synchrony communication, we first computed individual electrode-electrode interaction matrices for each condition (planning and control) and their periods (baseline, first 4 seconds; last 4 seconds; and maintenance) in the theta frequency band (4-8 Hz) using the weighed Phase Lag Index (wPLI) (Vinck et al., 2011). The wPLI was chosen because of its lack of sensitivity to zero phase-lag interactions. Afterward, we subtracted the wPLI values of the baseline from each period per condition respectively. Then, we compared zeros using t-test corrected by FDR. Next, Fz electrode was selected as a seed to construct topographic maps of connectivity. This selection was made due to: *i)* There is extensive evidence supporting FMθ as a biophysical mechanism of cognitive control implementation (Cavanagh & Frank, 2014); *ii)* the Fz electrode is widely used in frontal midline theta/cognitive control studies (Onton, Delorme & Scott Makeig, 2005; Gartner, Grimm & Bajbouj, 2015; Wang, Viswanathan, Lee & Grafton, 2016); *iii)* the theta band power increase in frontal midline electrodes during planning found in Domic-Siede et al. (2020); *iv)* Several significant connectivities observed between frontal electrodes and posterior electrodes in the connectivity matrices.

4.2.4.2. Correlations between Connectivity measures and Planning Behavior

The behavioral parameters used to perform correlations with connectivity measures were the Linear Integrated Speed-Accuracy Score (LISAS) (Vandierendonck, 2017; Vandierendonck, 2018) of the planning/control period, and the planning/control execution period, which are a performance index based on a linear combination of reaction time (RT) and proportion of errors (PE). These behavioral data were used in Domic-Siede et al. (2020). To test whether there is a relationship between connectivity measures and planning performance, we performed Spearman's rho correlations between sixty-three wPLI values of Fz-electrode electrode pairs, and the control electrode pairs. The behavioral parameters used were the Planning Execution RT and LISAS of this parameter.

4.2.4.3.   Analysis of Theta Phase Synchrony Dynamics

Using Fieldtrip toolbox, we calculated theta phase wPLI synchrony dynamics using Fz as seed for the first and the last four seconds of the planning and the control period using time windows of 400 ms with 10 ms steps for each time period. Finally, each time period Theta wPLI was compared between conditions using Wilcoxon signed-rank test (matched-pairs, 35 ms of non-overlapping windows) and corrected by FDR.

4.3.   RESULTS

4.3.1. Theta Phase Synchrony Results

Theta phase synchrony matrices for each period suggested a strong increase for the first and the last four seconds in the planning condition (**Figure 2**). To evaluate midfrontal theta phase connectivity, we used Fz electrode as a seed which, exhibited a broad inter-regional brain communication in this planning period, where 49 out of 63 pair of electrodes were significantly greater while only 25 out of 63 pair of electrodes were significantly greater in the control condition. However, neither the matrices nor topographic maps showed significant differences between conditions.
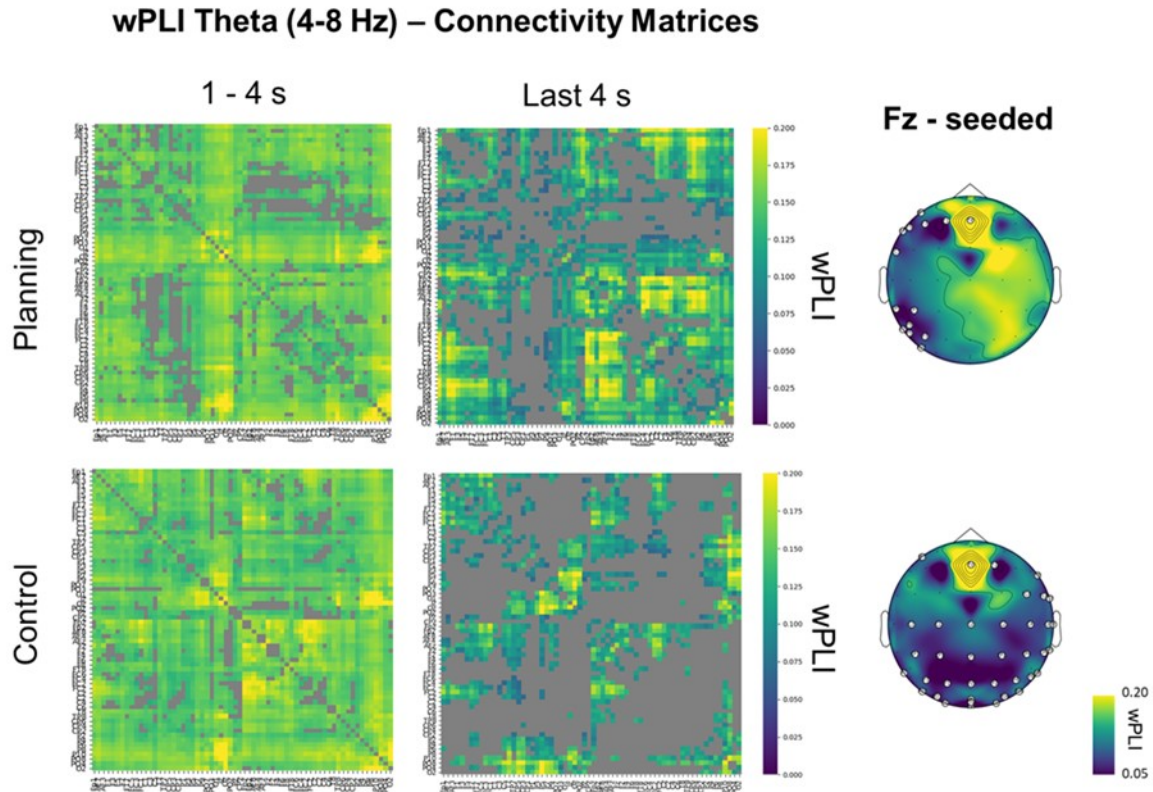
wPLI Theta (4-8 Hz) – Connectivity Matrices

Figure 2. Theta Phase Synchrony. Theta phase connectivity matrices (left) for the planning and the control period during the 1 to 4 seconds and the last four seconds of each task in each electrode pair. Color bar represents units of wPLI values (0 to 0.2). Non-significant areas are masked in grey color. Topographic maps (right) showing theta phase connectivity Fz-seeded for the last 4 seconds of each condition showing 49 out of 63 significant increase in theta phase synchrony for the planning condition and 25 out of 63 significant increase for the control period. wPLI color bar units between 0.05 to 0.20. Non-significant Fz-electrode pair are marked in white circles.

4.3.2. Correlations between Theta Phase Connectivity and Behavior

Theta phase connectivity between electrodes Fz-seeded correlated mainly negatively with planning execution reaction time (**Figure 3**). It is possible to identify a local pattern of frontal connectivity negative correlations with planning performance and a long-range fronto-posterior negative correlation which means an increase in connectivity is associated with lesser reaction time during the planning execution period. On the other hand, control condition exhibited frontal positive correlations lateralized to the right hemisphere. However, these correlations were no significant once corrected by FDR.
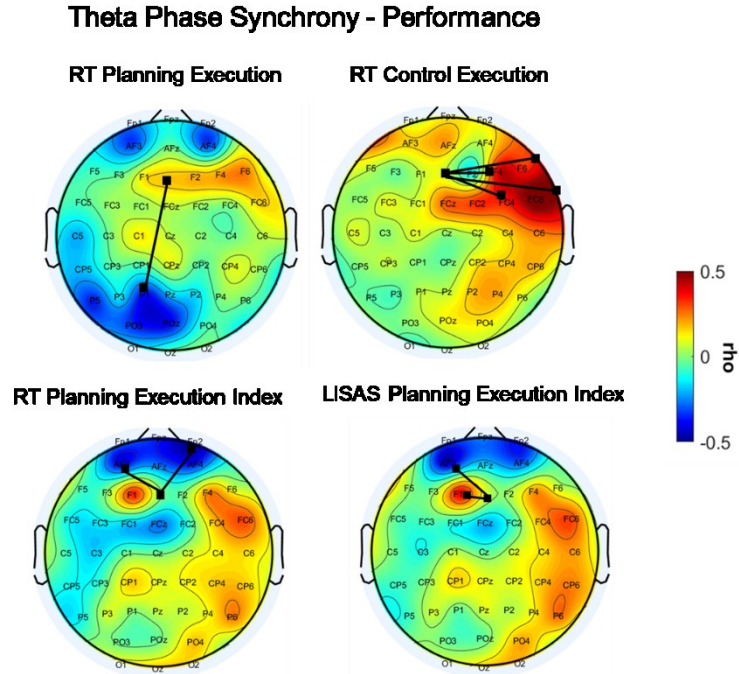
Figure 3. Theta Phase Synchrony correlations with behavior. Topographic maps showing Fz-seeded theta phase connectivity correlations with different parameters of planning execution reaction times. Above Fz-P1 electrode pair correlated negatively with planning execution RT period (left). In control condition, theta phase connectivity between Fz and F4, F8, FC4, and FT8 electrode pairs correlated positively with control execution RT period (right). At bottom, there are two parameters of performance Planning Execution Index and LISAS Planning Execution Index showing negative correlations between seed Fz and AF3, and Fp2 electrodes pairs (left); and negative correlations as well between Fz-AF3 electrode pair, and a positive correlation for the electrode pair Fz-F1 for LISAS Planning Execution Index (right). Color bar represents units of Spearman's rho correlation coefficient values (-0.5 to 0.5). Uncorrected significant electrode pairs are shown with black squares and lines.

4.3.3. Theta Phase Synchrony Dynamics

In order to characterize the temporal dynamic of the increase in theta phase synchrony, we averaged the wPLI between 4-8 Hz for both conditions, obtaining the average of theta phase wPLI over time. We found that the increase in theta phase activity was significantly greater for the planning period for Fz electrode interactions with other frontal electrodes: AF8 and F2, and a long distant electrode: POz for the first four seconds of planning (**Figure 4**).
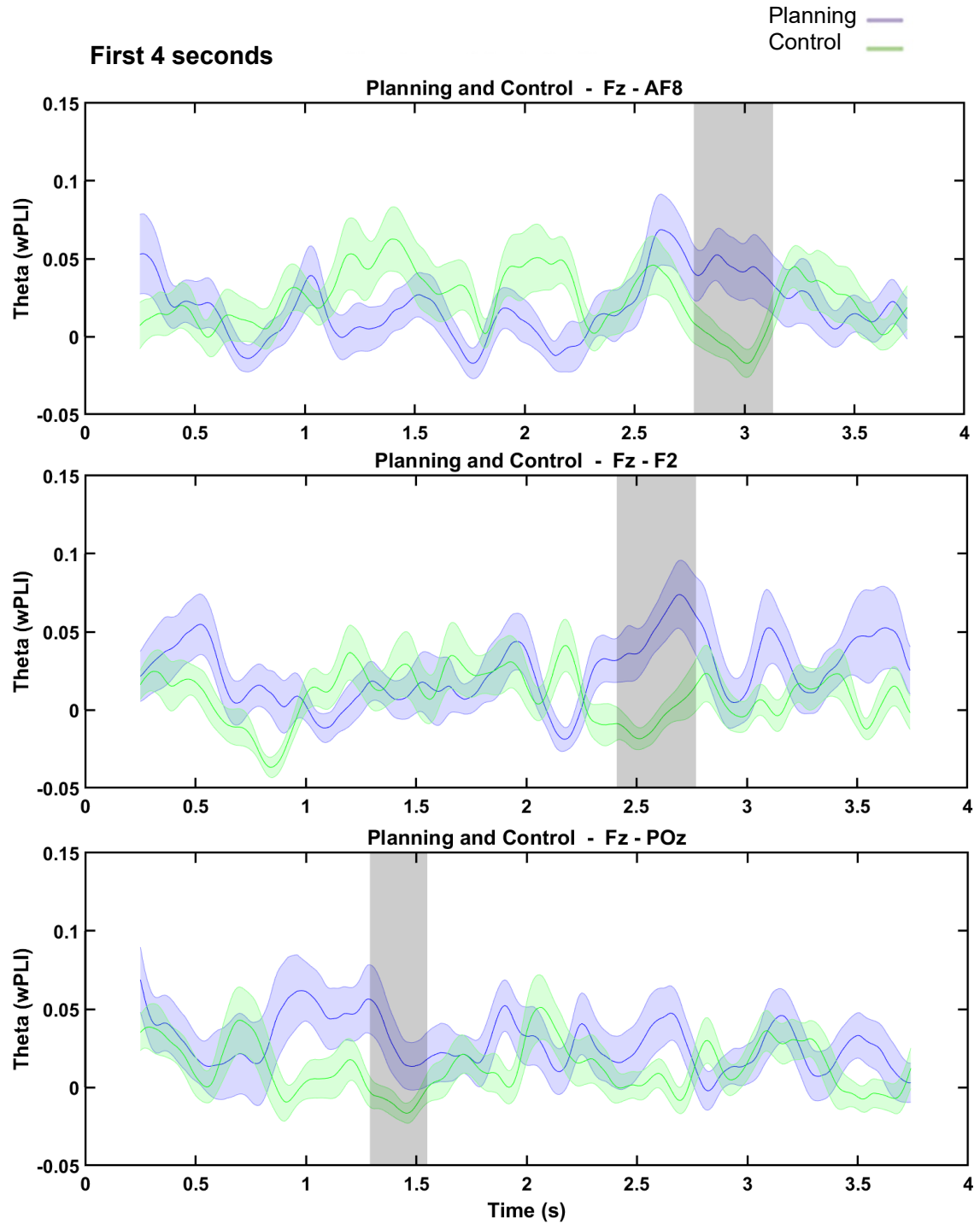
Figure 4. Theta Phase Synchrony Dynamics of the first period. Fz electrode interactions with AFz (top), F2 (middle), and POz (bottom) electrodes during the first four seconds of the planning period (purple) and the control period (green) showing significant theta phase synchrony increase during planning at different time points compared to the control period. Gray shaded areas show statistically significant differences according to a non-overlapping moving window with steps of 35 ms of Wilcoxon signed-rank test comparison, FDR corrected. Shaded regions represent 95% confidence intervals.

4.4. DISCUSSION

In the present study we explored long-range phase connectivity during cognitive planning using EEG scalp recording using a novel behavioral paradigm. Our results highlight the theta-phase connectivity increase between midfrontal site and posterior sites in the planning condition. This result was observed in both planning periods of interest including the first four seconds and the last four seconds of planning implementation. When Fz-seeded topographic maps were observed, a wide synchronization in theta band was found for the last four seconds of planning. However, there were no significant differences between conditions. We believe that the increases in theta range wPLI during the control period were strong enough to cancel the effects observed before the comparison. For this reason, observing the temporal dynamics of midfrontal theta phase synchrony was useful and exhibited a significant increase at specific time points in frontal electrodes as well as a parietooccipital central electrode.

Our results are in line with the proposition of the crucial role of the frontal theta activity in exerting control over disparate brain regions to transfer and coordinate behavioral relevant information via theta phase connectivity as a biophysical mechanism to implement cognitive control (Cavanagh & Frank, 2014; Hanslmayr et al., 2008, Cavanagh et al., 2009; Cohen et al., 2009; Cohen & Cavanagh, 2011; Cohen & van Gaal, 2013; Nigbur et al., 2012; Van de Vijver et al., 2011; Van Driel et al., 2012; Narayanan et al., 2013; Anguera et al., 2013). Here, we have shown that, for the first time, as other cognitive control functions, theta-phase synchronization also emerges during cognitive planning, and its dynamics may be a marker of cognitive control.

In our previous study, we showed that theta activity in core PFC executive regions correlated with behavioral performance (Domic et al., 2020). Specifically, frontopolar theta activity was associated with quicker RT during plan execution, and theta activity from the MCC and the ACC were associated with longer RT during planning. Similarly, in this study, Fz-seeded theta phase connectivity between Fz-P1 electrode pair correlated negatively with RT of the planning execution period: greater the theta-phase connectivity during the planning period, lesser RT of the planning execution period (**Figure 3**). This result might be relevant, since in our previous study we found that theta activity may be related to efficiency and accuracy, because quicker execution of plans was associated with accuracy (Domic et al., 2020) which is in line with studies that showed frontal theta predicts specific cognitive control-induced behavioural

changes beyond general reaction time slowing (Cooper et al., 2019). Interestingly, Fz-AF3 and Fz-Fp2 were also negatively correlated with RT Planning Execution Index and LISAS Planning Execution Index respectively. This result showing a more local relationship between theta phase connectivity and performance may reflect the participation of frontopolar theta activity, as shown in Domic et al. (2020). However, these correlations should be considered with caution since they did not survive the multiple comparison correction.

4.5.   CONCLUSIONS

We explored long-range phase connectivity during cognitive planning using EEG scalp recording using a novel behavioral paradigm. Results suggest that theta phase connectivity may be coordinating information, such as visuospatial analysis, motor control preparation, and plan execution from prefrontal cortex to disparate brain regions via theta phase connectivity during planning performance.

5.   GENERAL DISCUSSION

In the executive functions' apex, cognitive planning allows us to organize and coordinate goal-directed behavior in sequenced steps. This doctoral thesis's main objective was to study how planning implementation induces frontal theta oscillations exerting control via theta phase connectivity in disparate brain regions. To do this, a novel and ecological planning task was designed based on traditional neuropsychological tests: The Zoo Map Task (Wilson et al., 1996) and the Porteus Maze (Porteus, 1959).

EEG activity was recorded while participants performed the planning task in two conditions: The planning condition, where participants were instructed to elaborate a plan to visit four locations in a zoo map and the to execute the planned path. The control condition consisted of evaluating a path already drawn on the zoo map. This condition was intended to remove the cognitive planning component under the context of a similar setting.

This experimental design allowed to evaluate whether cognitive planning, as a cognitive control function, induces FMθ activity originating in PFC regions, and whether different PFC theta oscillation sources were related to different aspects of planning performance, as well as theta phase connectivity using a frontocentral electrode as seed.

In the first place, the reliability as a psychometric property was evaluated since is relevant to use tasks with excellent or adequate reliability which is not usually reported in studies using planning tasks adapted for neuroimaging assessment (Kirsch et al., 2006; Tremblay et al.,1994) at least within the scope of our literature review. In this thesis, excellent reliability was found for the behavioral task outcomes in the two conditions. However, it is necessary to confirm this by a psychometrical properties study using a greater sample and then compare the results with these obtained in our study (Merino-Soto & Lautenschlager, 2011; Merino-Soto, 2016).

Secondly, to design an ecological-behavioral task, different levels were considered as suggested by current trends in cognitive neuroscience (Dudai, 2002; Kingstone, Smilek, Ristic, Friesen, & Eastwood, 2002; Zaki & Ochsner, 2009; Shamay-Tsoory & Mendelsohn, 2019). Even though the planning task was performed under a traditional lab-based setting (inside of a room, stimuli presented on a screen, etc.), the task was enriched with meaningful stimuli and goal where subjects could interact with the stimuli presented on the screen. Moreover, the task demands subjects to engage in a widespread daily life situation-like such as planning paths to

visit different places. An ecological task design requires the paradigm to demand subjects to exert a specific behavior or cognitive function just as an actual daily life situation would demand (Miotto & Morris, 1998; Burgess, Simons, Coates & Channon, 2005; Morris & Ward, 2005). To achieve this, the planning task considered: the planning of paths to visit different places involving different stages or periods. In the first period, subjects planned a path while monitoring whether the plan follows a given set of rules. Then, a second period where they kept the plan in their working memory. Afterward, in a third period, subjects carried out their former plan while monitoring the path's behavioral execution, making sure the path follows these rules. All these periods resemble the different planning stages (Grafman & Hendler, 1991) including the orchestration of other executive functions including cognitive flexibility and attentional control in a concerted manner. There are additional perspectives that consider relevant predictive validity when designing an ecological-cognitive task. This means that the task must be able to identify impaired the specific cognitive function to evaluate in patients with psychiatric or cognitive disorders who exhibit deficits in that specific cognitive function performance in their daily life (Oosterman, Wijers, & Kessels, 2013). Despite detecting planning impairment was not part of the aim of this thesis's aim, the novel paradigm was based on the Zoo Map Task, which has shown optimal predictive validity in previous studies (Oosterman, Wijers, & Kessels, 2013).

The behavioral results were in line with the experimental predictions: the planning condition was more cognitive demanding than the control condition which was shown in parameters such as reaction times and accuracy which may reflect the recruitment of high cognitive functions to implement planning (Hayes-Roth & Hayes-Roth, 1979; Wilensky, 1983; Grafman & Hendler, 1991; Zwosta, Ruge & Wolfensteller, 2015; Owen et al., 1996; Voytek et al, 2015; Ossandón et al, 2012; Lezak, 1995). These results were relevant because they express a remarkable behavioral difference once the planning component was removed from the task and transformed into a control condition allowing further comparisons.

Although the control condition was designed to measure less complex cognition as evidenced by better performances and faster processing times, and then to compare it against the planning condition, it was favorable to use planning tasks with different complexity levels and analyze planning function according to this. It was possible to identify behavioral differences between the 'easy' condition and the 'difficult' condition with any differences at the level of electrophysiological measures, suggesting that results account for intrinsic aspects of the

planning function more than general features of cognitive control such as attention, cognitive effort, or high cognitive demand.

In this doctoral thesis, FMθ temporal dynamic activity was characterized as an increase between the 4-8 Hz band that progressively increase over the first four seconds and then was held up increased over the last four seconds. Similarly, FMθ cognitive control emerges in a variety of cognitive control tasks. Hence it has been proposed as a common mechanism for realizing the need for cognitive control (Cavanagh & Frank, 2014; Cavanagh, Zambrano-Vazquez & Alen, 2012; Cooper et al., 2019). However, considering FMθ temporal dynamics, its brain sources, and connectivity dynamics, it was possible to reveal specific aspects that linked electrophysiological characteristics with behavior. Specifically, theta activity dynamics at the level of power/amplitude with planning behavior in terms of efficiency for plan execution and RT slowing plan generation.

Different bilateral PFC sources exhibited increases in theta activity: SF, FP, ACC, and MCC. These PFC sources have been widely described as involved in a variety of cognitive control functions. However, the temporal dynamic of their theta activity was significantly prominent only for the left FP, the bilateral ACC, and the bilateral MCC sources.

Interestingly, a particular association was found between increases in the left FP theta activity and faster RTs. Typically, behavioral performance relationships with cognitive control frontal theta marker have been described in terms of slower performance indicating cognitive control implementation (Cooper et al, 2019; Gratton et al., 1992; Rabbitt & Rodger, 1977). However, several processes might be operating during a determined cognitive control task that might be hidden specific particularities of a cognitive phenomenon.

For example, Wessel (2018) proposed that errors during a cognitive control task cause a cascade of processing that commonly inhibit ongoing behavior and cognition, orienting attention to the error source, followed by engagement of strategic control processes to adapt ongoing behavior. Thus, solely comparing the theta power averaged of correct condition and error condition might lead to an incomplete description of the neural dynamics involved and their link with behavior. Thus, it was essential to consider the division of different phases of the planning process and the relationship between theta activity dynamic during the planning period and how this impact in performance of the next phase, the execution of the plan previously planned. This allowed observing that higher theta relative increase from the left FP for elaborating a plan (the planning period) was associated with a reduced Δ RT (corrected by

incorrect responses) for executing a plan (the planning execution period). On the other hand, considering that RTs of the planning execution period were positively correlated with accuracy (Supplementary **Figure S2**), the result mentioned above suggests that theta activity from the left FP might be related to efficiency and accuracy extent.

These results agree with the model proposed by Mansouri et al. (2015) that account for human sequential choices in uncertain, changing, recurrent or open-ended environments (Koechlin, 2011; Koechlin et al., 1999; Donoso, Collins & Koechlin; 2014; Koechlin, 2014; Wan, Cheng & Tanaka, 2016). This model considers a basic system mediated by the medial FP that monitors the importance of the ongoing behavior, in the context of planning could be when subjects were building a specific step of their plan to achieve a goal. Whenever the ongoing behavior is deemed irrelevant, for instance, the plan's current step does not lead to achieve the goal, the medial FP triggers undirected exploration to evaluate other options (Mansouri et al., 2015; Masouri et al., 2017). Several studies have shown the lateral FP cortex's implication when monitoring alternative behaviors to replace the ongoing behavior (Koechlin, 2011; Koechlin et al., 1999; Donoso, Collins & Koechlin; 2014). Additionally, the FP cortex is involved in cognitive branching, the ability to perform tasks related to one goal, while keeping in working memory information related to a secondary goal, which is expected to occur during planning tasks (Koechlin et al.1999, Koechlin et al. 2000, Braver & Bongiolatti, 2002; Ramnani & Owen, 2004).

Furthermore, Christoff and Gabrieli (2000) proposed a hierarchical model of the PFC functioning where dorsolateral PFC and FP cortex are serially recruited as reasoning requires evaluation of internally generated information. In this model, the dorsolateral PFC participates when externally generated information needs to be evaluated (working memory demanding), whereas the FP cortex is recruited when internally generated information needs to be evaluated. This is in line with the results in this doctoral thesis, that might be interpreted as the FP cortex participates in monitoring and manipulating information internally generated such as plans generation during tasks in which self-generated stimuli need to be elaborated and monitored (Berman et al., 1995; Baker et al., 1996; Osherson et al., 1998; Goel et al, 1998; Christoff & Gabrieli, 2000).

Considering these models, we interpreted that during cognitive planning, the left FP is recruited to elaborate a plan and monitor different alternative paths while keeping the goal in working memory to successfully execute the plan and perform branching expressed in better reaction times in the planning execution period.

In this doctoral thesis, the ACC and the MCC showed interesting results. Both areas have also been associated with a variety of cognitive control functions (Cavanagh & Frank, 2014), i.e., conflict monitoring (Botvinick, Cohen, & Carter, 2004; Kerns et al., 2004; Sohn et al., 2007, Ursu et al., 2009), error detection (Carter et al., 1998; Gehring & Fencsik, 2001, Pourtois et al., 2010), response selection (Turken & Swick, 1999; Awh & Gehring, 1999; Paus, 2001), and attentional control (Aarts & Roelofs, 2011; Orr & Weissman, 2009; Crottaz-Herbette & Menon, 2006; Luo et al., 2007). Particularly, it was found increases in theta activity in late periods of planning and during specific segments there were positive correlations with RTs of the planning period. These results may reflect the ACC's recruitment for conflict monitoring, for instance, monitoring the plan that is being elaborated to detect any conflict, rule violation, or errors. In contrast, the MCC may be participating in attentional control. Typically, these cognitive control functions have been associated with RT slowing as seen in our results. In summary, the right MCC and the left ACC may assume a relevant subserving the mental elaboration of a plan, while the left FP may become required to monitor and manipulate self-generated plans in order to execute the plan successfully. Theta activity could be the biophysical mechanism to exert these cognitive control functions.

Additionally, theta phase synchrony was explored at the channel and at ROI source-level. Interestingly, it was found that a global theta-phase synchrony increases during planning at the channel-level. Between ROI source, a theta phase synchrony increases between the right MCC and the right ACC was found at late periods of planning consistent with the time dynamic theta power-level results. To our knowledge, these results are the first to support that theta phase synchrony is involved in human planning. However, since it was found the involvement of other frequency modulation as changes in alpha/beta oscillations, further analyses need to be done in order to address the complex spectral architecture of the brain that transfer and communicate information through disparate brain regions. It might be interesting to analyze the cross-frequency dynamics such as theta phase-alpha/beta amplitude communication which we believe might be a candidate mechanism that accounts for long-distance connectivity required to exert cognitive control during planning.

6. CONCLUSIONS

The present doctoral thesis contributed new evidence to understanding the neural mechanism that underlies an elusive control function, such as cognitive planning. Our results provide insights about the neurobiology of cognitive control and planning function from an electrophysiological and behavioral perspective using a novel and ecological planning task that assesses more intrinsic aspects of planning reflected in theta oscillation changes than other general cognitive demands typically present in cognitive control tasks.

Our results highlight that cognitive planning induces FMθ activity whose source is the PFC. We characterized for the first time both the spatial and temporal dynamics of this activity during planning at the power and phase level. Interesting associations with planning performance was found. Theta activity from the left FP and was related to efficiency to successfully execute the previous elaborated plan, which may reflect the participation of this brain region in a successfully self-generated plan. Furthermore, theta activity from the right MCC and the left ACC was related to reaction time slowing of the planning period, which may reflect the task's high cognitive demand, engaging in attentional control and conflict monitoring implementation. Additionally, theta phase connectivity may be coordinating information, such as visuospatial analysis, motor control preparation, and plan execution from the prefrontal cortex to disparate brain regions via theta phase connectivity during planning to exert control over disparate brain regions to successfully perform planning.

7.   REFERENCES

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8. SUPPLEMENTARY MATERIAL

8.1. Supplementary Tables

Table S1. ROIs Brain Activity Sources

ROIs	MNI* [x y z]	Area (cm^2)	Vertex (amount)
Left Superior Frontal gyrus	[-8 32 62.5]	0.3	1
Right Superior Frontal gyrus	[8.2 34.8 61.7]	1.01	3
Left Transverse Frontopolar gyrus and sulcus	[-8.3 72.2 9.7]	0.16	1
Right Transverse Frontopolar gyrus and sulcus	[5.1 71.1 9.1]	0.5	3
Left Anterior Cingulate Cortex gyrus and sulcus	[-10.9 43.9 8.2]	0.17	1
Right Anterior Cingulate Cortex gyrus and sulcus	[13 40.4 19.7]	0.2	3
Left Middle Cingulate Cortex gyrus and sulcus	[-3 24.1 30]	0.12	1
Right Middle Cingulate Cortex gyrus and sulcus	[1.1 13.1 29.4]	0.75	3

* The standard Montreal Neurological Institute (MNI) brain based on the localization of each ROI.

Table S2. Normality Distribution of Behavioral Parameters

Parameters*	D'Agostino & Pearson omnibus	
	K2	p-value
RT Planning	4.18	.12
RT Planning Execution	1.60	.45
Accuracy Planning	6.20	.05
RT Control	1.55	.46
RT Control Execution	1.80	.41
Accuracy Control	20.50	< .0001****
LISAS Planning	4.57	.10
LISAS Planning Execution	1.93	.38
LISAS Control	0.35	.84
LISAS Control Execution	1.12	.57
Planning RT 'easy'	5.80	.06
Planning RT 'difficult'	3.79	.15
Planning Execution RT 'easy'	2.02	0.36
Planning Execution RT 'difficult'	1.89	0.39
Accuracy Planning 'easy'	2.92	0.23

Accuracy Planning 'difficult'	5.67	.06

RT: Reaction Time; LISAS: Linear Integrated Speed-Accuracy Score; *Values of RT used were in seconds and values of accuracy were percentage of correct responses. Values of LISAS were calculated in milliseconds.

Table S3. Internal Consistency of tasks according to Alpha of Cronbach coefficient

Parameters	Alpha
RT Planning	0.95
RT Planning Execution	0.95
RT Control	0.97
RT Control Execution	0.97

RT: Reaction Time; *Values of RT used were in seconds and values of accuracy were percentage of correct responses.

Table S4. Homoscedasticity Analysis

Parameters		Levene's test	
		F	p-value
RT Planning	RT Control	0.81	.37
RT Planning Execution	RT Control Execution	1.04	.31
Accuracy Planning	Accuracy Control	6.31	.02

RT: Reaction Time; *Values of RT used were in seconds and values of accuracy were percentage of correct responses.

Table S5. Behavioral Performance Statistical Comparison

Parameters*		Statistical hypothesis	
		t-test / Wilcoxon	p-value
RT Planning	RT Control	t (26) = 6.23	<.0001****
RT Planning Execution	RT Control Execution	t (26) = 3.41	.0021**
RT Planning	RT Planning Execution	t (26) = 7.65	<.0001****
RT Control	RT Control Execution	t (26) = 4.02	.0004***
Accuracy Planning	Accuracy Control	Z = 375	< .0001****
LISAS Planning	LISAS Control	t (26) = 6.98	<.0001****
LISAS Planning Execution	LISAS Control Execution	t (26) = 4.61	<.0001****
LISAS Planning	LISAS Planning Execution	t (26) = 7.19	<.0001****
LISAS Control	LISAS Control Execution	t (26) = 4.43	.0002***

Planning RT 'difficult'	Planning RT 'easy'	$t(26) = 4.23$	.0003***
Planning Execution RT 'difficult'	Planning Execution RT 'easy'	$t(26) = 4.53$	.0001***
Accuracy Planning 'difficult'	Accuracy Planning 'easy'	$t(26) = 4.37$	.0002***

RT: Reaction Time; LISAS: Linear Integrated Speed-Accuracy Score; *Values of RT used were in seconds and values of accuracy were percentage of correct responses. Values of LISAS were calculated in milliseconds. ** All statistical analyses were corrected by FDR.

Table S6. Behavioral Correlations

Parameters*		Statistical hypothesis	
		Spearman's rho	p-value**
RT Planning	Accuracy Planning	.05	.80
RT Planning Execution	Accuracy Planning	-.49	.009**
RT Control	Accuracy Control	.17	.39
RT Control Execution	Accuracy Control	-.09	.65
LISAS Planning	Accuracy Planning	-.18	.36
LISAS Planning Execution	Accuracy Planning	-.52	.005**
LISAS Control	Accuracy Control	.03	.88
LISAS Control Execution	Accuracy Control	-.19	.33

RT: Reaction Time; LISAS: Linear Integrated Speed-Accuracy Score; *Values of RT used were in seconds and values of accuracy were percentage of correct responses. Values of LISAS were calculated in milliseconds. ** Corrected by FDR.

Table S7. Descriptive Statistics of Averaged Theta Activity

Electrode and Period	Descriptive Statistics*		Normality Distribution	
			D'Agostino & Pearson omnibus	
	mean	SD	K2	P value
Fz Planning (first 4 s)	1.28	1.54	0.67	0.7200
Fz Control (first 4 s)	0.06	1.05	5.94	0.0500
Pz Planning (first 4 s)	0.42	1.23	0.68	0.7107
Pz Control (first 4 s)	0.05	0.66	2.07	0.3558
Oz Planning (first 4 s)	0.96	1.30	0.77	0.6795
Oz Control (first 4 s)	0.63	0.67	0.68	0.7130
Fz Planning (last 4 s)	0.96	1.64	27.51	<0.0001****
Fz Control (last 4 s)	-0.47	0.72	1.39	0.4993
Pz Planning (last 4 s)	0.01	1.41	20.73	<0.0001****
Pz Control (last 4 s)	-0.24	0.67	1.80	0.4057
Oz Planning (last 4 s)	0.24	1.26	4.50	0.1051
Oz Control (last 4 s)	0.11	0.89	1.42	0.4911

*Values are z-score units; SD = Standard deviation; SEM = Standard error of the mean.

Table S8. Averaged Global Theta Power Statistical Comparison

Parameters*		Statistical hypothesis	
		t-test / Wilcoxon	p-value**
Fz Planning (first 4 s)	Fz Control (first 4 s)	t (26) = 3.79	.0008***
Pz Planning (first 4 s)	Pz Control (first 4 s)	t (26) = 1.50	.1459
Oz Planning (first 4 s)	Oz Control (first 4 s)	t (26) = 1.43	.1653
Fz Planning (last 4 s)	Fz Control (last 4 s)	Z = -3.59	.0001***
Pz Planning (last 4 s)	Pz Control (last 4 s)	Z = -0.72	.4846
Oz Planning (last 4 s)	Oz Control (last 4 s)	t (26) = 0.44	.6632

RT: Reaction Time; LISAS: Linear Integrated Speed-Accuracy Score; *Values of RT used were in seconds and values of accuracy were percentage of correct responses. Values of LISAS were calculated in milliseconds. ** Corrected by FDR.

Table S9. Correlations between left dorsolateral PFC Theta activity and planning performance's parameters

Behavioral parameters*	Statistical hypothesis	
	Spearman's rho	p-value
RT correct Planning	.08	.6745
RT correct Planning Execution	.06	.7808
LISAS Planning	.24	.2267
LISAS Planning Execution	.13	.5140
Δ LISAS Planning	-.04	.8442
Δ LISAS Planning Execution	.22	.2693

RT: Reaction Time; LISAS: Linear Integrated Speed-Accuracy Score; *Values of RT used were in seconds and values of accuracy were percentage of correct responses. Values of LISAS were calculated in milliseconds.

Table S10. Correlations between right dorsolateral PFC Theta activity and planning performance's parameters

Behavioral parameters*	Statistical hypothesis	
	Spearman's rho	p-value**
RT correct Planning	-.14	.4832
RT correct Planning Execution	.25	.2079
LISAS Planning	-.06	.7654
LISAS Planning Execution	.29	.1450
Δ LISAS Planning	-.16	.4363
Δ LISAS Planning Execution	.09	.6562

RT: Reaction Time; LISAS: Linear Integrated Speed-Accuracy Score; *Values of RT used were in seconds and values of accuracy were percentage of correct responses. Values of LISAS were calculated in milliseconds.

Table S11. Correlations between bilateral sources theta relative increase and planning execution RTs of correct responses

ROIs theta relative increase	Statistical hypothesis	
	Spearman's rho	p-value
Left Superior Frontal	-.02	.9038
Right Superior Frontal	.07	.7416
Left Frontopolar	-.56	.0023**
Right Frontopolar	-.18	.3573
Left ACC	-.33	.0950
Right ACC	-.23	.2573
Left MCC	-.32	.1073
Right MCC	.08	.7052

RT: Reaction Time; LISAS: Linear Integrated Speed-Accuracy Score; *Values of RT used were in seconds and values of accuracy were percentage of correct responses. Values of LISAS were calculated in milliseconds. ** Corrected by FDR.

Table S12. Descriptive Statistics of the planning and the planning execution RTs of correct responses

Parameters	Descriptive Statistics*			
	Mean	Median	SD	SEM
Planning RTs correct	8.74	9.11	1.23	0.24
Planning RTs correct	6.14	6.10	1.04	0.20

SD = Standard deviation; SEM = Standard error of the mean; RT = Reaction Time in seconds.

8.2. Supplementary figures
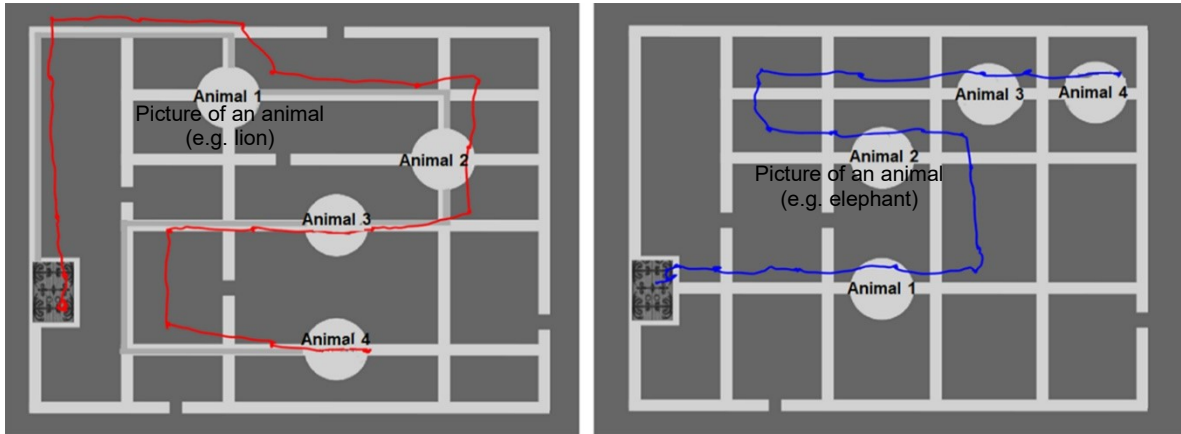
Figure S1. Path reconstruction for evaluating accuracy. Two illustrative examples of a path reconstruction of following an already marked path and drawing over it (line in red, control execution period) and the motor execution of a plan (in blue, planning execution period) from two different subjects using eye-tracker data. Using the path reconstructed for the planning condition, we evaluated the accuracy of planning per trial. Animals inside of circles were picture of animals.
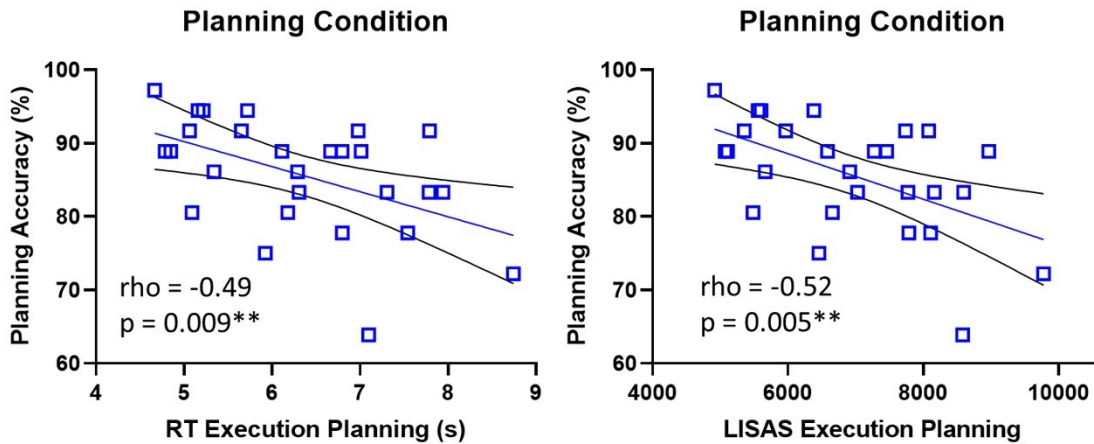
Figure S2. Behavioral Correlations. Spearman's rho correlations were performed to analyze the relationships between reaction times (RT) and accuracy. RT and LISAS (Linear Integrated Speed-Accuracy Score) of the planning execution period showed significant negative correlations with the accuracy of the planning condition. Each square is the value of a subject. All analyses were corrected by FDR.
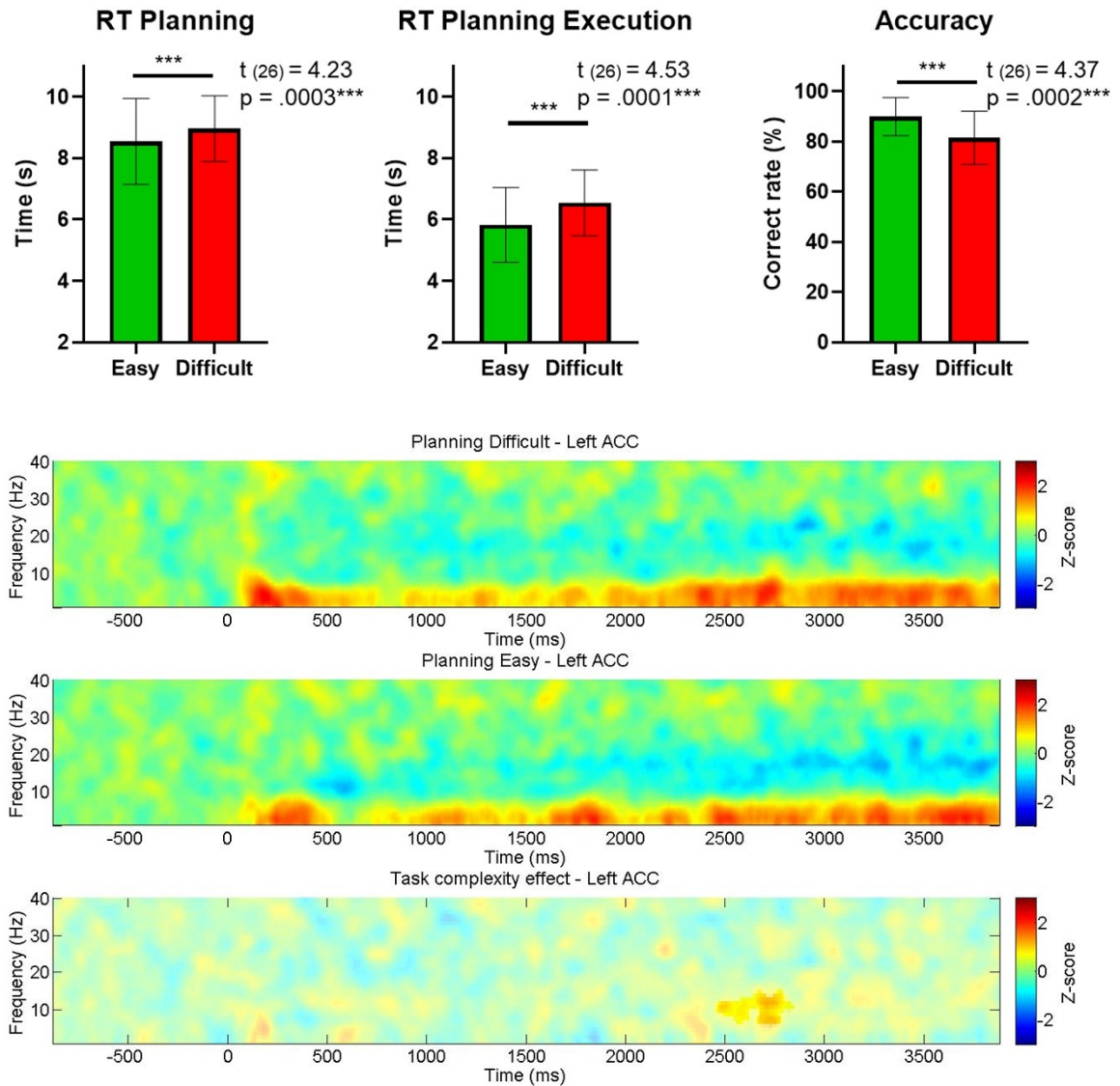
Figure S3. Complexity levels of planning. Comparisons between 'easy' and 'difficult' levels of complexity at the behavioral level (top), and at time-frequency level (bottom). There were significant differences between levels of complexity showing lower RT during the planning (left) and the planning execution period (middle) for the 'easy' level in comparison to the 'difficult' level, whereas the accuracy was higher for the 'easy' level. Time-frequency charts of ROIs exhibited a significant positive cluster in alpha band only in the left Anterior Cingulate Cortex for the 'difficult' level. Non-significant pixels are shown lighter in the plot. Color bar indicates z-score units between -3 to 3.
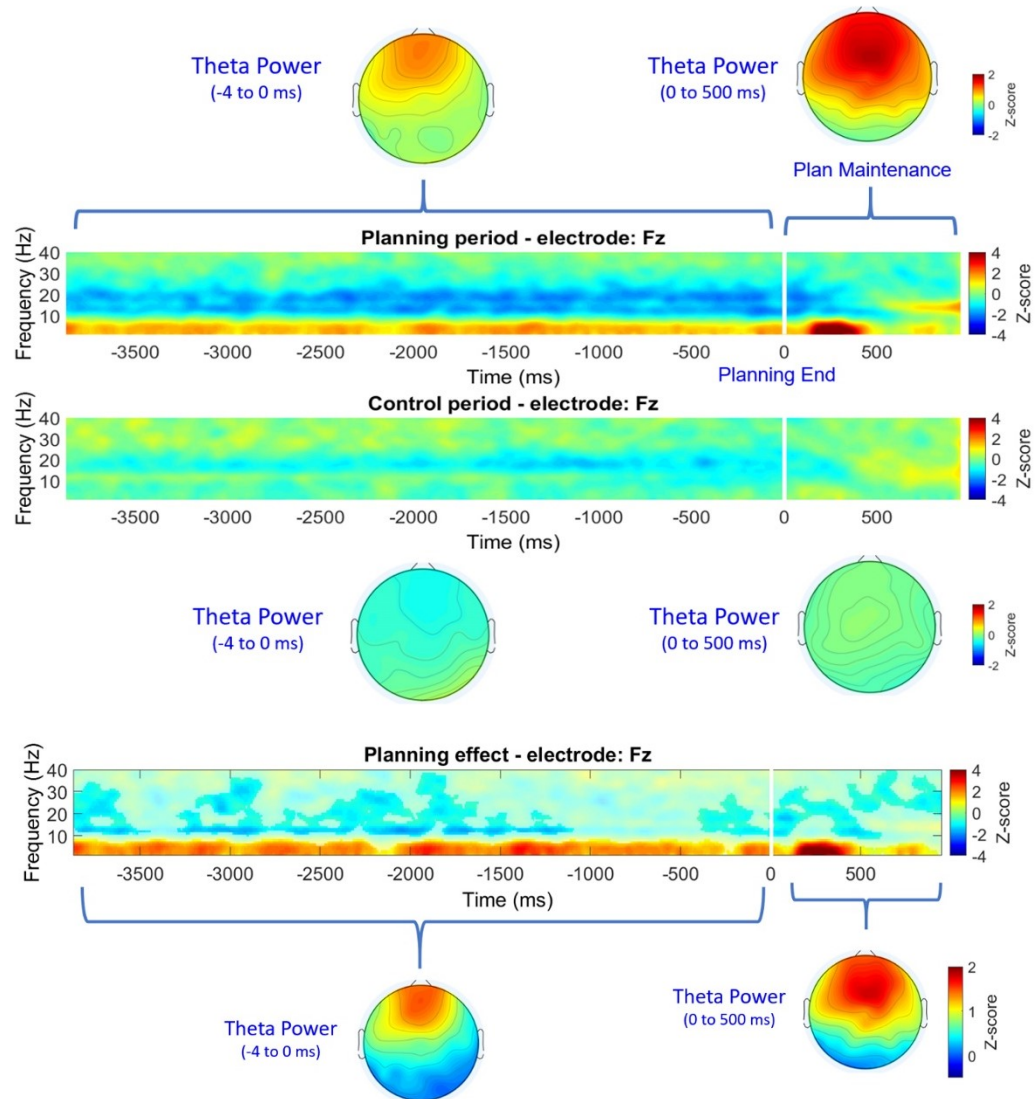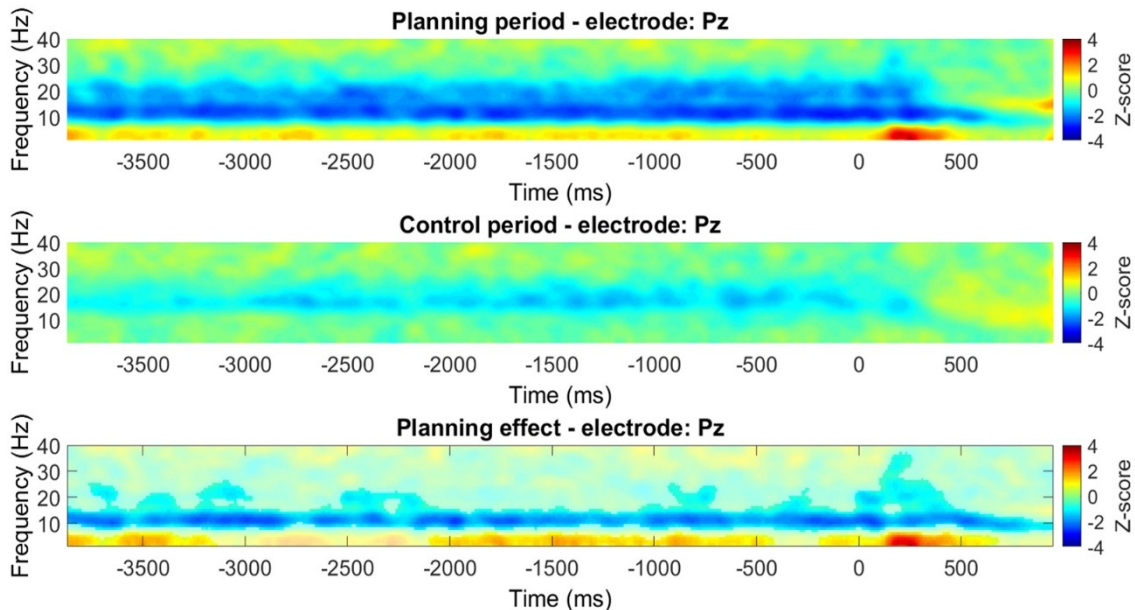
Figure S4. Time-Frequency charts for last 4 seconds of Fz electrode and maintenance period. Top: Time-frequency plot for the planning period, time-locked to the end of planning, showing a marked increase in theta band power with time. During the maintenance period there was a greater increase of theta activity. Middle: Time-frequency plot for the control period. Bottom: Planning effect computed as the subtraction between planning and control period showing increase in theta activity. Non-significant pixels are shown lighter in the plot. Color bar indicates z-score units between -4 to 4. Topographic maps show averaged theta activity of the last four seconds of planning and control, and their respective maintenance period (color bar between -2 to 2 units of z-score). Color bar of planning effect topoplots between -0.5 to 2.
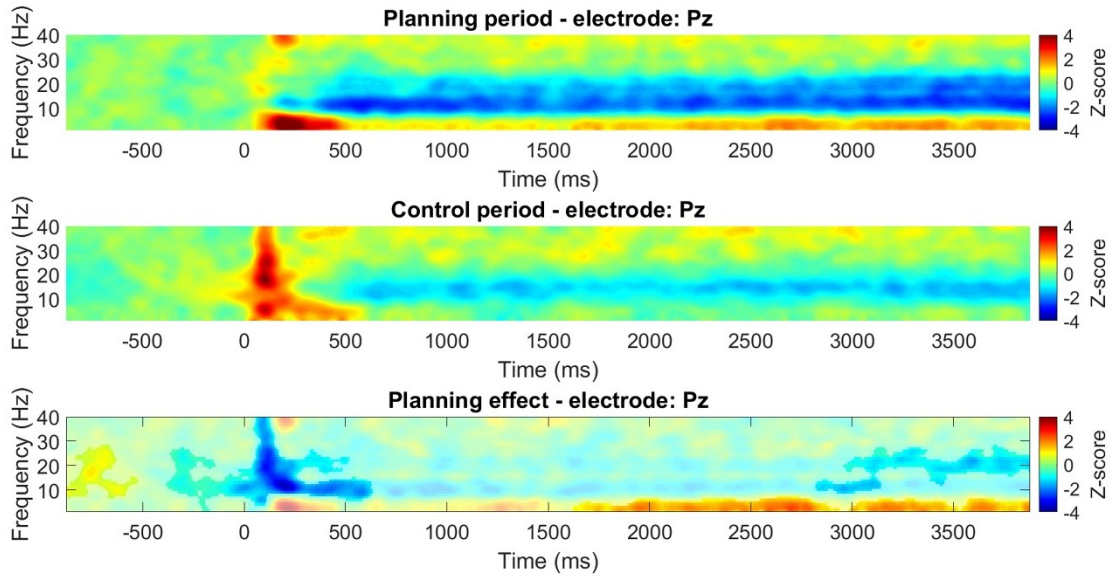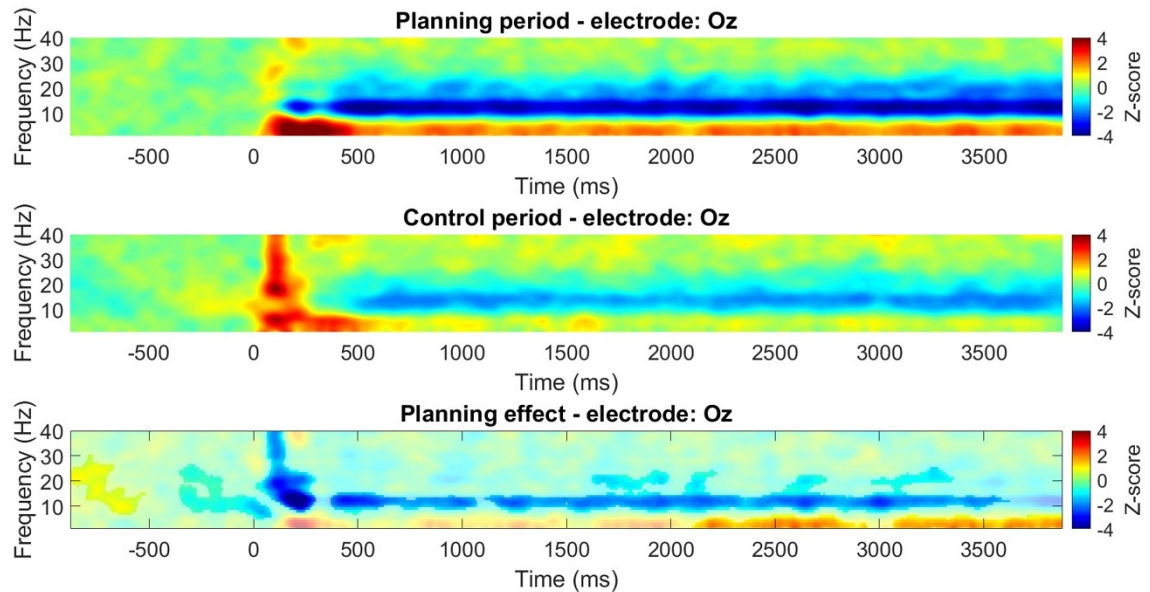
Figure S5. Time-Frequency charts for first 4 seconds of Pz electrode. Top: Time-frequency plot for the planning period showing an increase in theta band power with time. Middle: Time-frequency plot for the control period. Bottom: Planning effect computed as the subtraction between planning and control period. Non-significant pixels are shown lighter in the plot. Color bar indicates z-score units between -4 to 4.
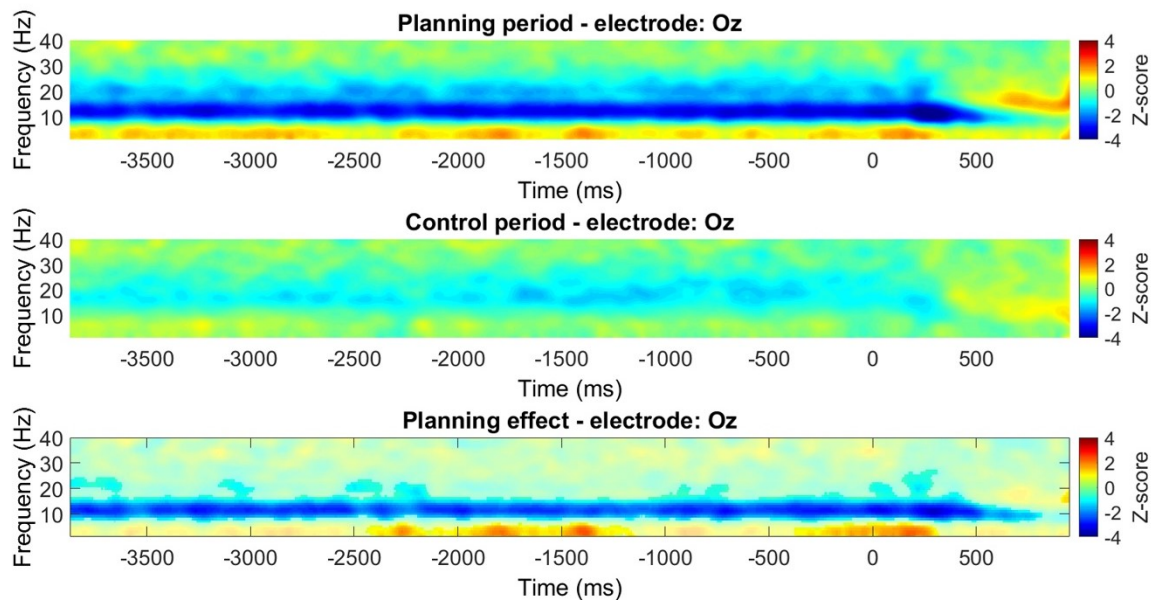

Figure S6. Time-Frequency charts for last 4 seconds of Pz and maintenance period. Top: Time-frequency plot for the planning period, time-locked to the end of planning, showing an increase in theta band power with time. During the maintenance period there was a greater increase of theta activity. Middle: Time-frequency plot for the control period. Bottom: Planning effect computed as the subtraction between planning and control period showing some clusters with increases in theta activity, and a sustained negative cluster in alpha band. Non-significant pixels are shown lighter in the plot. Color bar indicates z-score units between -4 to 4.

Figure S7. Time-Frequency charts for Oz electrode. Top: Time-frequency plot for the planning period showing an increase in theta band power and a marked decrease in alpha band power with time. Middle: Time-frequency plot for the control period. Bottom: Planning effect computed as the subtraction between planning and control period showing some positive clusters in theta activity, and a negative cluster in alpha band. Non-significant pixels are shown lighter in the plot. Color bar indicates z-score units between -4 to 4.

Figure S8. Time-Frequency charts for last 4 seconds of Oz and maintenance period. Top: Time-frequency plot for the planning period, time-locked to the end of planning, showing an increase in theta band power with time. During the maintenance period there was a greater increase of theta activity. Middle: Time-frequency plot for the control period. Bottom: Planning effect computed as the subtraction between planning and control period showing some clusters with increase in theta activity, and a sustained negative cluster in alpha band. Non-significant pixels are shown lighter in the plot. Color bar indicates z-score units between -4 to 4.
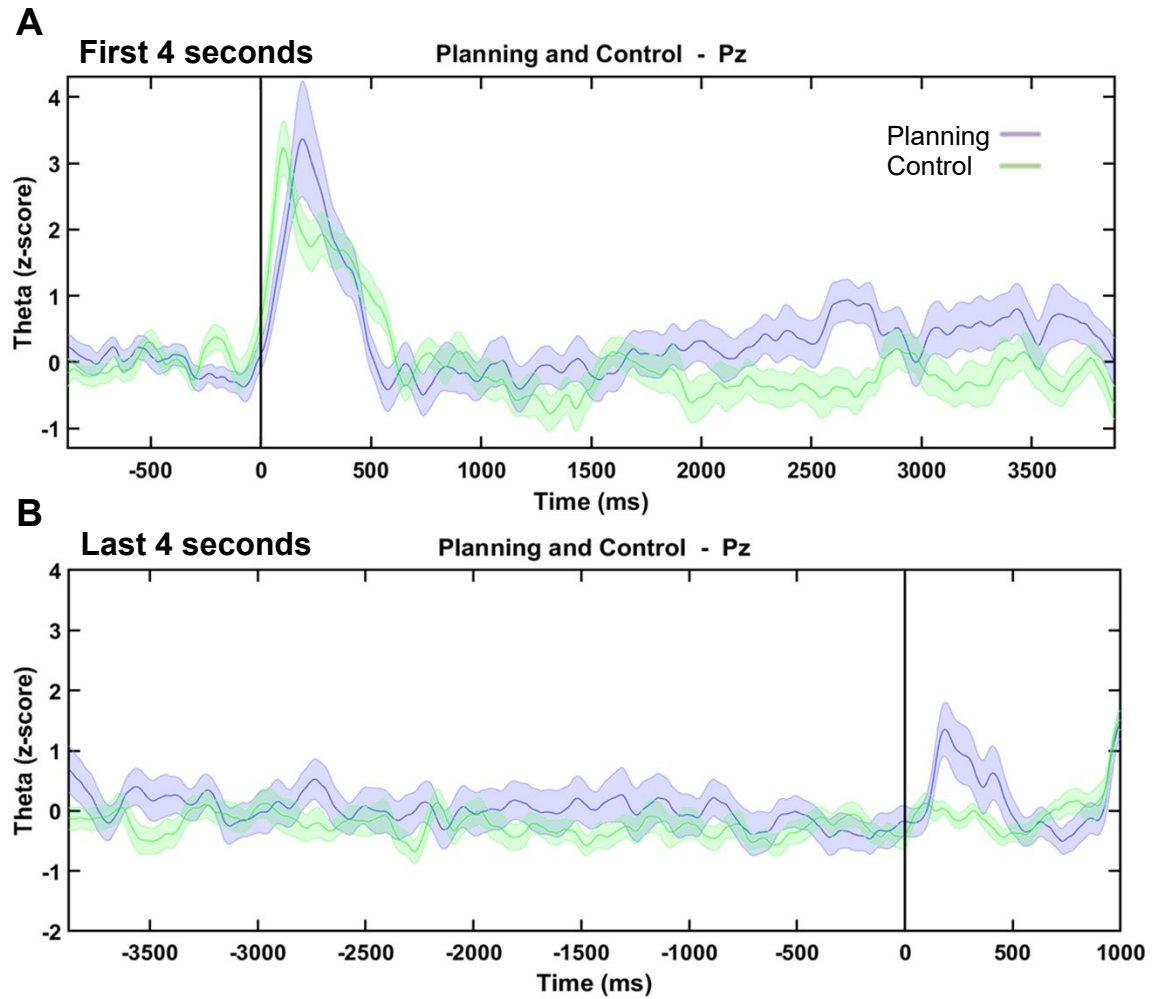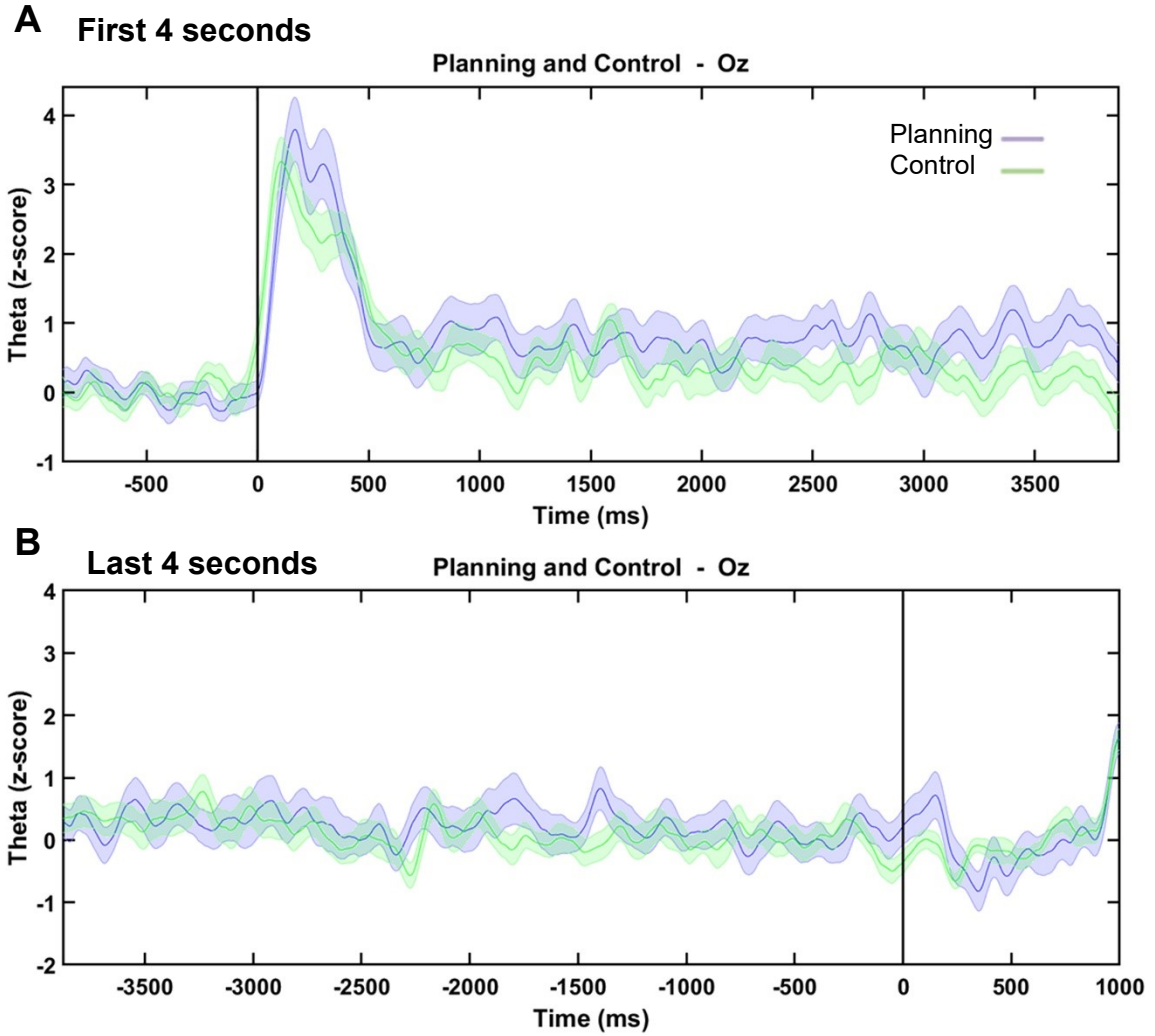
Figure S9. Time Theta Frequency Slices for Pz electrode. A) Pz first 4 seconds of planning (purple) and control (green) period showing there was no significant increase in theta activity compared to the control period. B) Pz last 4 seconds of planning showing there was no significant increase in theta activity during planning nor during the maintenance period. Statistical test: non-overlapping moving window with steps of 88 ms of Wilcoxon signed-rank test comparison, FDR corrected. Shaded purple and green color around theta power mean of each condition corresponds to 95% interval confidence.

A **First 4 seconds**

B **Last 4 seconds**

Figure S10. Time Theta Frequency Slices for Oz electrode. A) Oz first 4 seconds of planning (purple) and control (green) period showing there was no significant increase in theta activity compared to the control period. B) Oz last 4 seconds of planning showing there was no significant increase in theta activity during planning nor during the maintenance period. Statistical test: non-overlapping moving window with steps of 88 ms of Wilcoxon signed-rank test comparison, FDR corrected. Shaded purple and green color around theta power mean of each condition corresponds to 95% interval confidence.
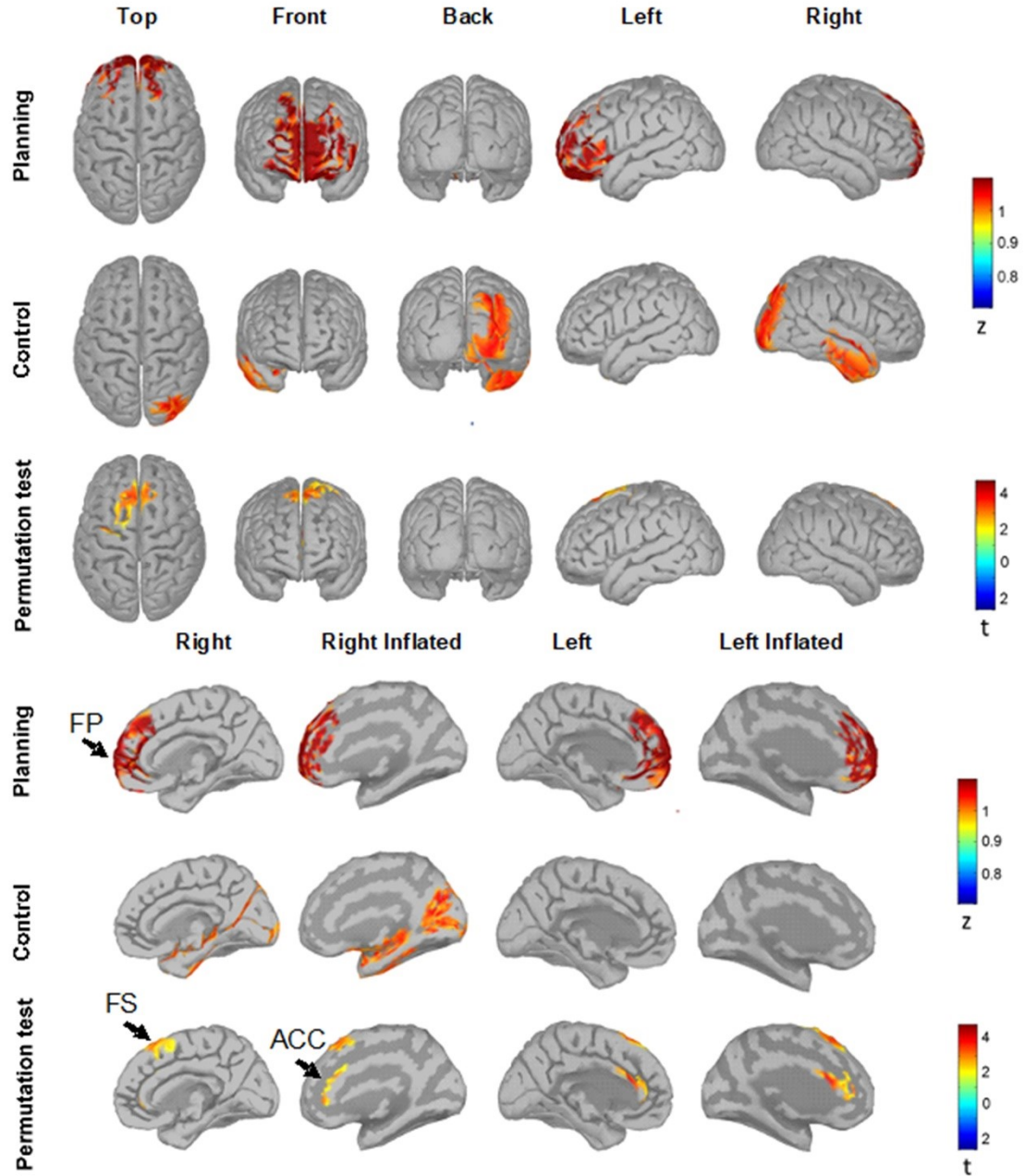
Figure S11. Source Reconstruction. sLORETA was applied to the task epoch (first four seconds of planning and control periods) for the preprocessed EEG signal (4-8 Hz bandpass filtered) for both conditions, normalized to z-score and averaged between 1 to 4 s. Sources were projected to a template brain model. (top) A whole brain model is shown. (bottom) a sagittal plane of the brain is shown. Sources showed increase in theta activity in lateralized right-occipital and right-temporal regions for the control condition. The increase in theta activity in prefrontal regions is noticeable for the planning period. The plot shows absolute values of z-score between 0.77 and 1.08 units, and significant t values of the permutation test (-2.2 to 4.5). Black arrows show FP, FS and ACC labels. FP: Frontopolar; FS: Frontal Superior; ACC: Anterior Cingulate Cortex.
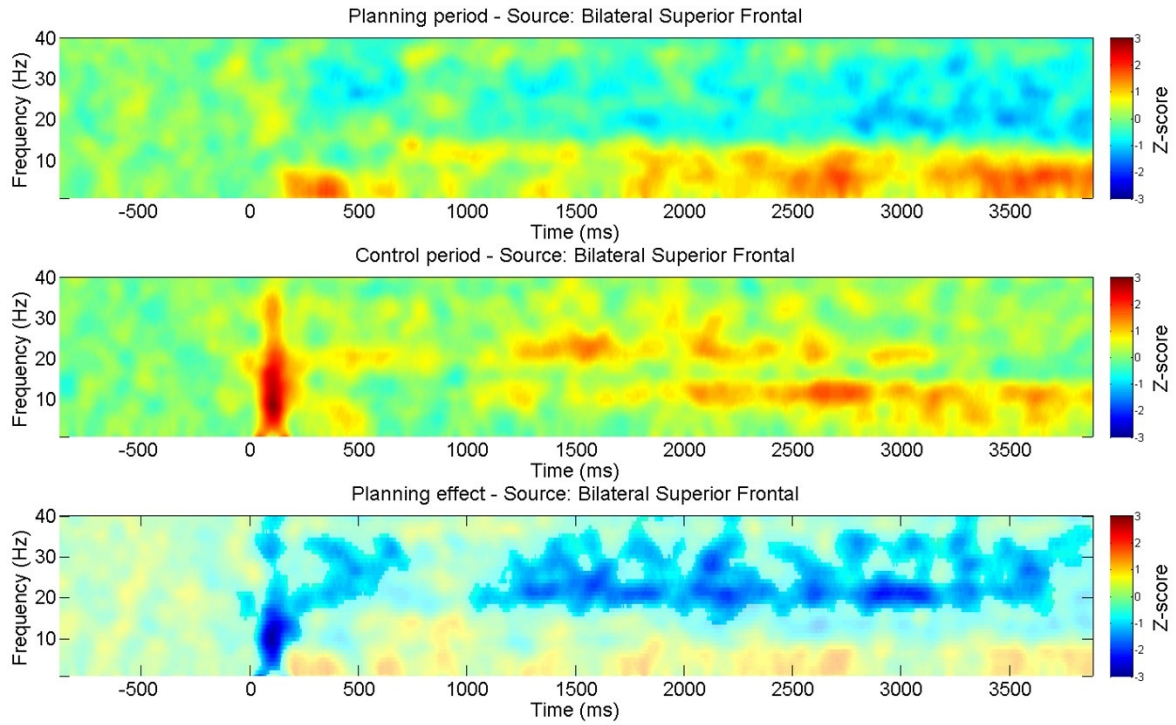
Figure S12. Time-Frequency charts for bilateral Superior Frontal Source. Top: Time-frequency plot for the planning period showing an increase in theta band power over time. Middle: Time-frequency plot for the control period. Bottom: Planning effect computed as the subtraction between planning and control period. An early decrease in broadband frequencies is observed and then, a negative cluster was found in beta band. Non-significant pixels are shown lighter in the plot. Color bar indicates units of z-score values between -3 to 3.
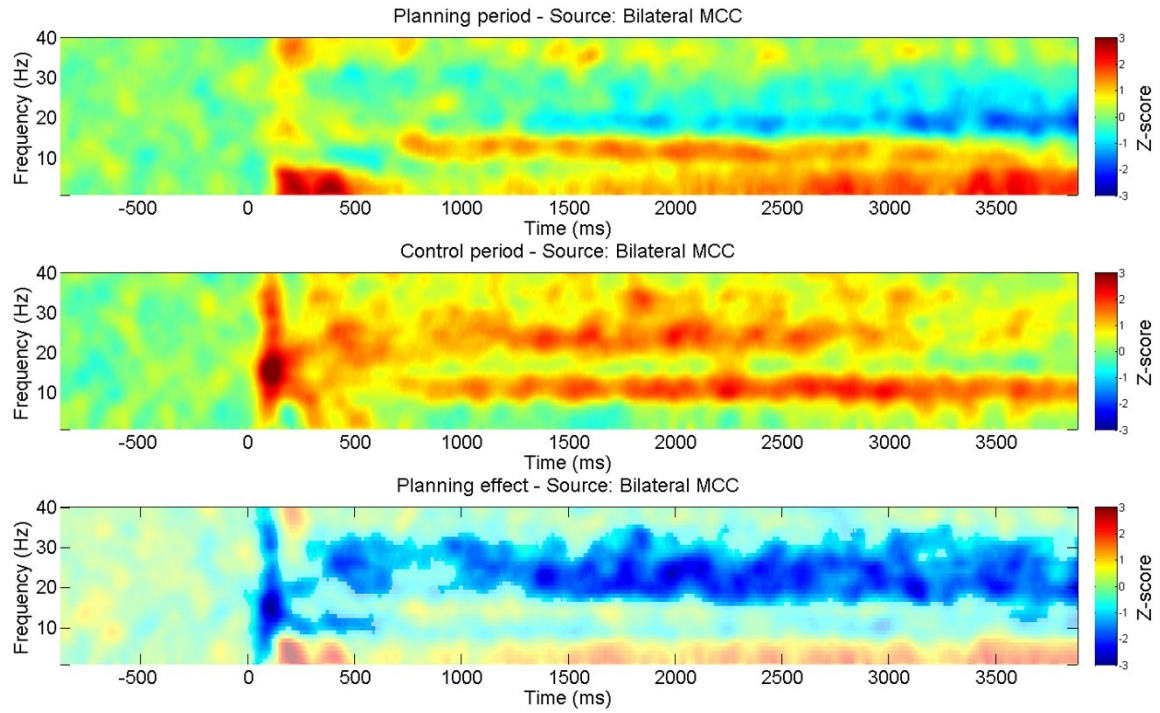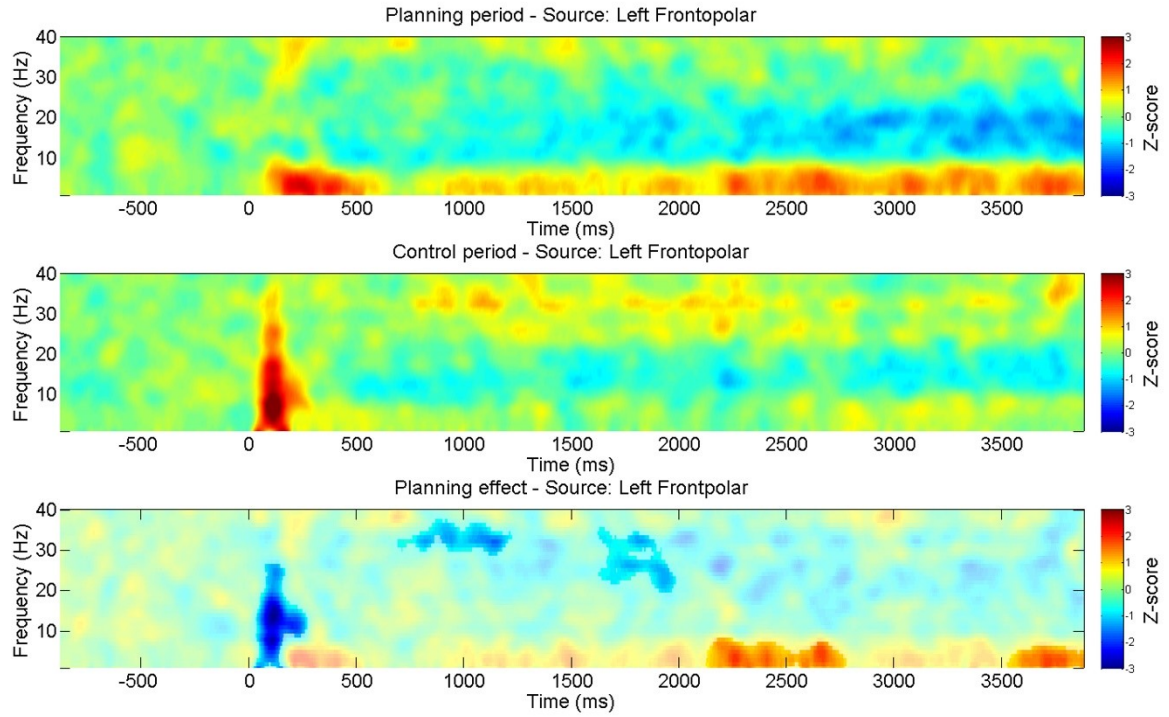
Figure S13. Time-Frequency charts for bilateral MCC Source. Top: Time-frequency plot for the planning period. Middle: Time-frequency plot for the control period. Bottom: Planning effect computed as the subtraction between the planning and the control period showing an early decrease in broadband frequencies and a sustained decrease in beta band. Non-significant pixels are shown lighter in the plot. Color bar indicates units of z-score values between -3 to 3. MCC: Mid-cingulate Cortex.

Figure S14. Time-Frequency charts for Left Frontopolar Source. Top: Time-frequency plot for the planning period showing a marked increase in theta band power over the time. Middle: Time-frequency plot for the control period. Bottom: Planning effect computed as the subtraction between planning and control period. Non-significant pixels are shown lighter in the plot. Color bar indicates units of z-score values between -3 to 3.
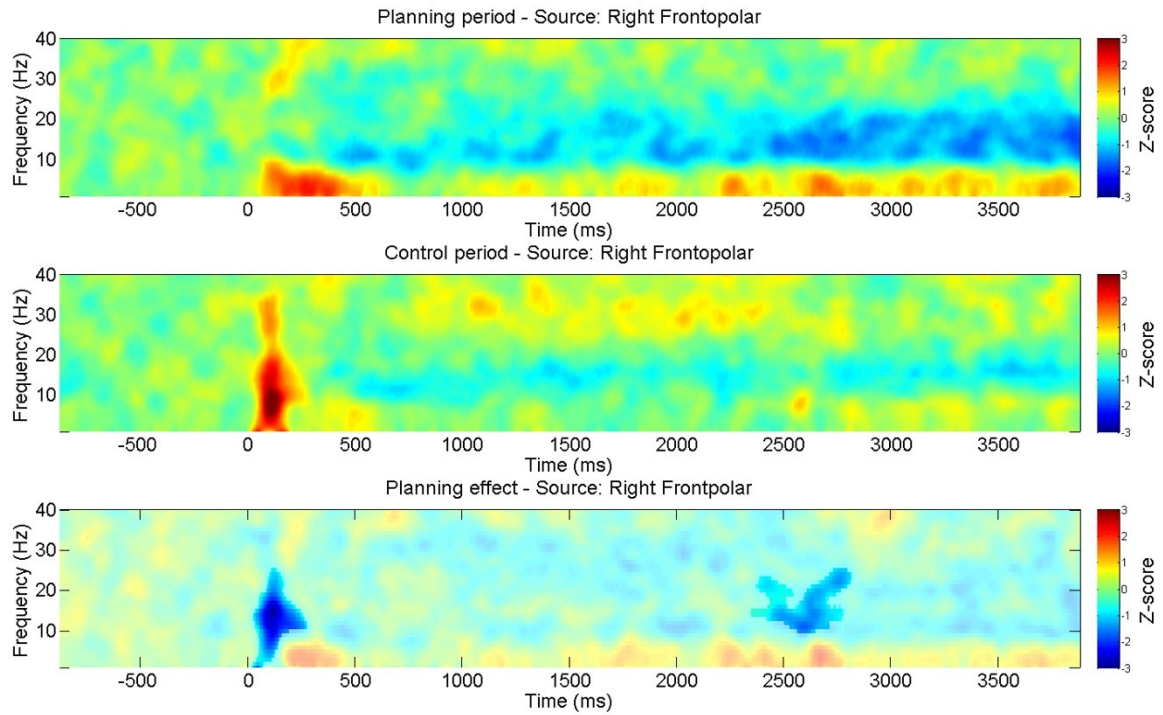
Figure S15. Time-Frequency charts for Right Frontopolar Cortex Source. Top: Time-frequency plot for the planning period showing a slightly increase in theta band power over the time. Middle: Time-frequency plot for the control period. Bottom: Planning effect computed as the subtraction between planning and control. Non-significant pixels are shown lighter in the plot. Color bar indicates units of z-score values between -3 to 3.
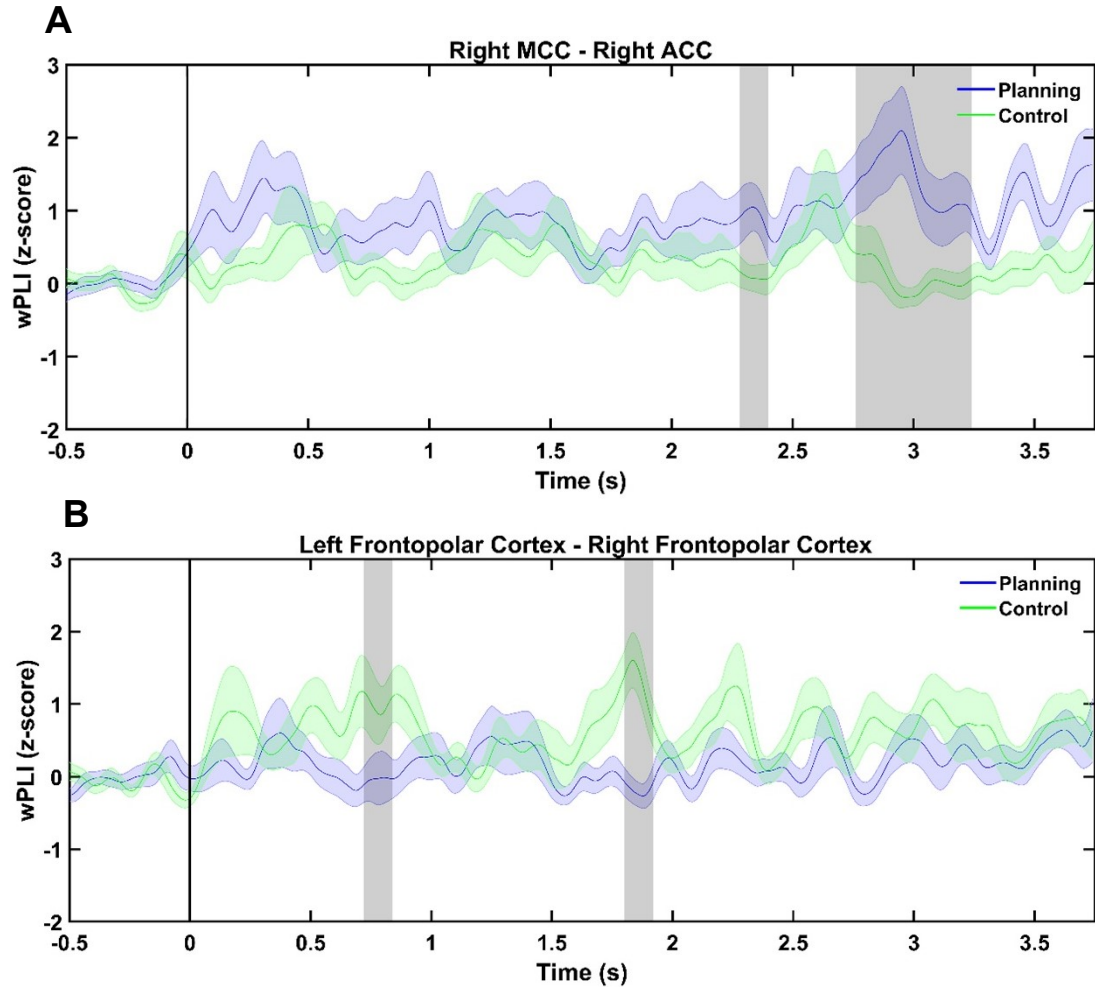
Figure S16. Theta Phase Synchrony. Weighted Phase Lag Index between PFC regions. A) Theta phase synchrony between the right MCC and the right ACC showing significant increases in theta connectivity for the planning period around 3 s after planning onset compared to the control condition. B) Theta phase synchrony between the left frontopolar and the right frontopolar cortex showing significant increases in theta connectivity for the control period around 0.8 s and 1.7 s. Statistical test: non-overlapping moving window with steps of 250 ms of Wilcoxon signed-rank test comparison, FDR corrected. Shaded purple and green color around theta wPLI mean of each condition corresponds to 95% interval confidence.
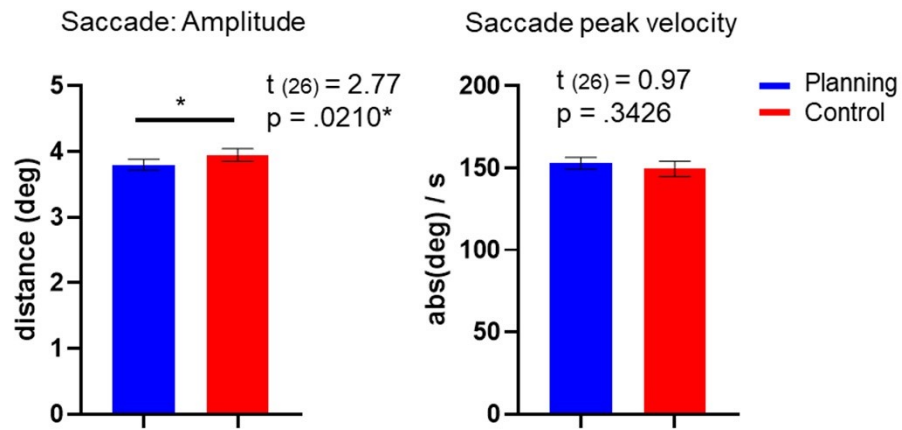
Whole trial

Figure S17. Eye Movements comparisons. Left: Saccade amplitude; right: Saccade peak velocity for the whole trial. There were statistically significant differences between the planning condition and the control condition in saccade amplitude.
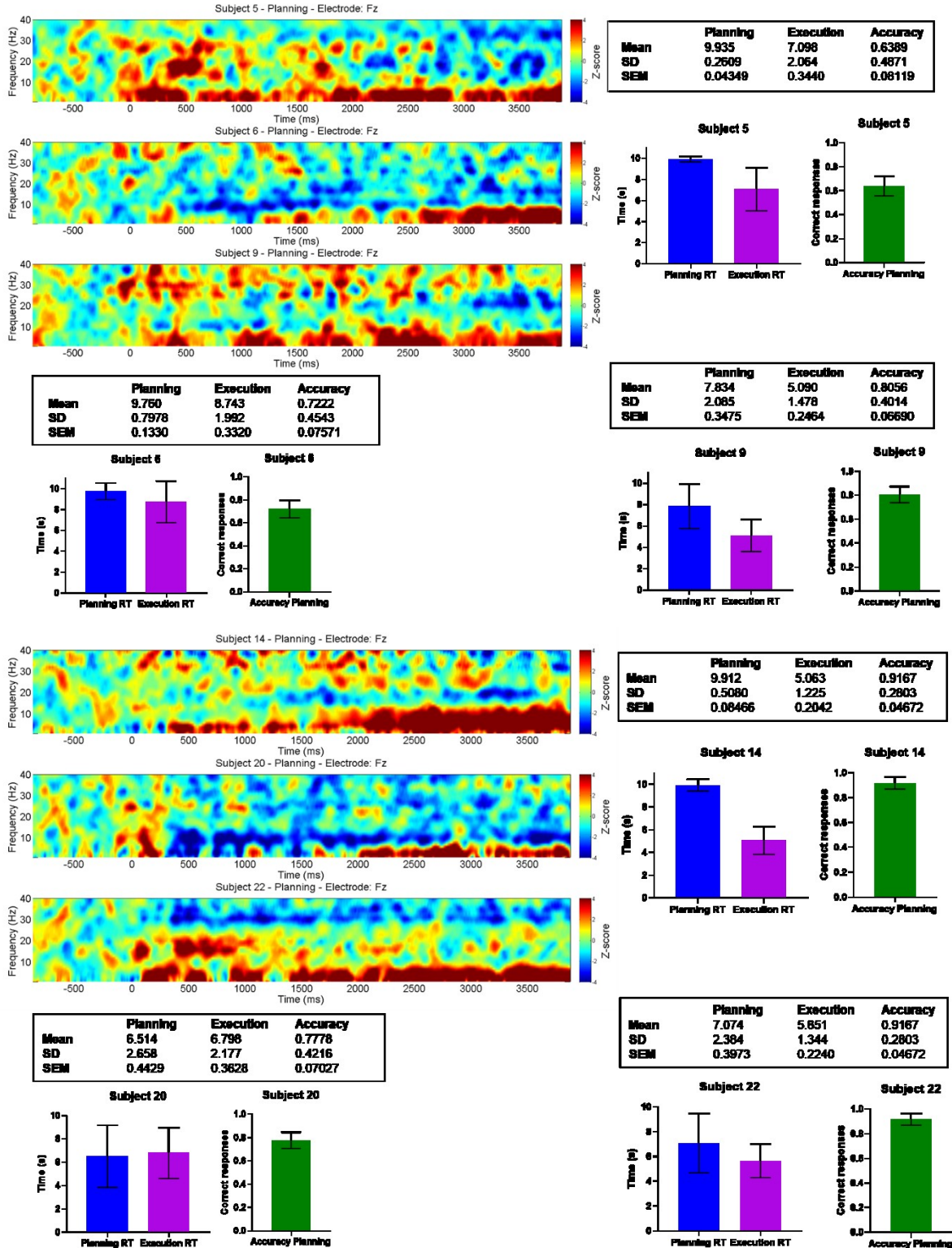
Figure S18. Single-subject data at electrophysiological and behavioral level. Illustrative data from subjects 5, 6, 9, 14, 20, and 22 to depict variability in the time-frequency domain, and at behavioral level: reaction times (blue: planning period; lilac: planning execution) in seconds and accuracy in number of correct responses (green: the planning condition).