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Final dissertation

Functional connectivity patterns associated with time-based and event-based prospective memory

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ABSTRACT

The ability to remember to perform intentions at a specific time (time-based) or after the appearance of a cue (event-based) is defined as Prospective Memory (PM). It allows to flexibly manage everyday tasks by executing them at the most appropriate moment, making PM a crucial part of our daily life. The PM field has grown considerably in recent years, but despite the scientific community recognizing its importance, different aspects of PM research need further investigation. Many studies have been focusing on the processes underlying event-based tasks, while only a few investigated the underpinnings of time-based PM. The experimental design of studies has sometimes lacked ecological validity, creating situations that are far off real-life PM. Finally, many studies have employed Electroencephalography (EEG) to study PM because of the centrality of temporal dimension in PM and the excellent temporal resolution of EEG, but none of them used this technique to investigate functional connectivity during PM processes. To fill these gaps, the present study aims to explore the functional connectivity of time-based and event-based PM tasks by implementing a pseudo-naturalistic design while recording EEG. Capturing the functional connectivity patterns intrinsic to the EEG signal requires a method sensible to the dynamic states encompassed by neural activity. A promising novel method called Hidden Markov Modelling (HMM) was adopted, because of its ability to identify stable patterns of whole-brain activity without any prior knowledge over the data. HMM was employed to obtain six recurrent brain states, with significant differences in the time spent in those states between conditions. Results confirmed the key role of Dorsal Attention Network in time-based PM as proposed by the AtoDI model of Cona and colleagues (2015), as well as the allocation of attentional resources towards internal processes in PM conditions. Additionally, a configuration resembling posterior Default Mode Network supported the retrieval of intention in PM tasks.

1. Chapter 1

Prospective Memory

1.1 Introduction

Time can be defined as the continuous sequence of events that occurs from the past, through the present, and into the future. The distinction between these three concepts appears relatively consistent, but our daily perception has past and future intertwined in the present, making it hard to draw a clear line between them. The main reason for that is our ability to remember. Memory allows events that have occurred and will occur to have an important role in the present, constantly influencing our current activities. While the concept of memory is usually associated with the past, we make use of it more than we realize to fulfill our future behaviors. In fact, there are things we remember without a clear purpose (e.g. remembering the first time we drove a bike), and things we are supposed to remember (e.g. remembering to return a borrowed object when we meet its owner). The former situation refers specifically to the past and can be categorized as Retrospective Memory (RM), whereas the latter is referred to as Prospective Memory (PM). PM can be defined as the ability to remember to carry out future intentions when we are supposed to or when a specific event occurs (McDaniel and Einstein, 2007).

Many examples of PM can be taken from everyday life, such as remembering to take laundry out of the washing machine or take the prescribed medications every Tuesday morning. While forgetting about the first one would not create a problem, not taking medicine at the right time could have harmful consequences. In fact, PM effectiveness has a meaningful impact over different domains of our life, ranging from work, through social life to personal health. Therefore, the crucial role that PM plays in everyday life makes this field fundamental to study and research. By characterizing the neural and behavioral underpinnings of PM, we can gain a deeper understanding of a key ability unique to the human mind, while also developing tools to treat and support individuals who have lost their capacity for prospective remembering. The mundane nature of PM intentions obliges researchers to pay much attention to the experimental design and laboratory setting in which PM is studied. Ecological validity plays a pivotal role in studying PM, as the generalizability of studies greatly rely on it (Kvavilashvili & Ellis, 2004). Following the experimental paradigm proposed by McDaniel & Einstein in 1990 (which later became the standard procedure), most studies proposed lab-based settings to allow control over experimental factors and to manipulate different PM processes. Nevertheless, lab-settings were not always able to correctly represent real-life PM, resulting in controversial phenomena such as the Age PM paradox (Rendell & Thomson, 1999), for which older adults perform worse than young adults in labs, but the opposite happens in real-life. Recently, a growing number of studies designed their PM paradigms to increase the ecological validity of their lab settings, using artificial settings that mimic daily environments (Altgassen et al., 2015), virtual reality (Trawley et al., 2017), and more life-like tasks (Mioni et al., 2014). "Naturalness" has indeed emerged as a key topic to address in PM research.

According to the Phase Model (Kliegel et al., 2011; Kvavilashvili & Ellis, 1996), PM can be divided into three stages: first, an intention must be created by encoding information about future actions to be performed later (Intention-formation phase); then, after a memory trace and a motor plan have been developed, there is a delay between encoding and the actual execution of the intention, in which the environment is scanned for salient stimuli and the intention rehearsed (Intention-retention phase); finally, PM intention has to be triggered, either voluntarily or spontaneously, and executed (Intention-retrieval phase). The standard experimental paradigm used to study these processes usually involves two different tasks, the ongoing and the PM task (McDaniel & Einstein, 1990). The ongoing task is usually a binary-choice reaction task, e.g., a lexical decision task (Rummel & McDaniel, 2019). Ongoing tasks must be simple (so that the cognitive demands do not deplenish participant's resources from PM processes) but also engaging enough to distract participants from the intention they are maintaining. After instructions about the ongoing tasks are given, participants receive information about a PM intention to encode and later perform on top of the ongoing task. PM tasks differ mostly on the stimulus associated with intention retrieval (called "PM cue"). In fact, depending on the PM cue, PM tasks can be distinguished in event-based or time-based. In event-based tasks, the PM intention must be performed whenever a particular stimulus is found in the environment, such as a target appearing on the monitor. For instance, an event-based experiment would have the participant distinguishing words from non-words as the ongoing task, pressing a key each time a word written in all caps appears. PM cues in event-based tasks can vary depending on how easily these events can be distinguished from ongoing task targets. PM targets are defined as "salient" if they are very distinguishable independently from the PM intention (e.g. spotting a face among squares and triangles), while they are defined "focal" if they are associated with the encoded intention (e.g. pressing the spacebar three times when the number 3 appears). In time-based tasks, the PM cue is associated to a specific time or to the expiration of a certain amount of time. For example, participants may be asked to perform the ongoing task while monitoring the passing of time, pressing a key every two minutes. A clock is usually present in these instances, being available either in the periphery of the monitor or as a hidden clock made available by pressing a key.

1.2 Multiprocess Framework

The Multiprocess Framework View (MPV) is a model proposed by McDaniel & Einstein in the first international conference on PM, which later resulted in the special issue of Applied Cognitive Psychology (2000). Introducing their model, the authors focused on what was different in the modalities by which RM and PM were studied in research. Specifically, they pointed out that investigations over RM involve an explicit request to retrieve the memory trace, while this happens rarely in PM studies. Therefore, the aim of the model was to address how the retrieval mode in PM is activated without any specific external demand, to better understand which processes mediate the attentional switch from the ongoing task to the PM retrieval and execution.

According to the MPV model, PM retrieval can be mediated by multiple processes. This assumption is supported by the fact that PM is ubiquitous in our daily activities and is intimately connected to planning and future-oriented behaviors. Thus, to support the flexibility necessary for the wide variety of contexts in which PM occurs, multiple cognitive functions may be employed. Different situations may require different strategies, depending on the context in which the intention is remembered and on its characteristics. Specifically, the authors state that prospective remembering can depend on either strategic, top-down processes or spontaneous, bottom-up processes. Top-down processes are internally induced phenomena in which the environment is actively explored for information depending on chosen factors (Katsuki et al., 2014). Main top-down processes used in PM are rehearsal (the intention is repeated in one's memory until fulfillment) and monitoring (each new situation/task's trial is analysed in search of PM cues). While providing a strategy to maintain and retrieve the PM intention, top-down processes take a toll on working memory resources, slowing down or costing the performance of the ongoing task (Shelton et al., 2017). Bottom-up mechanisms, on the other hand, operate by involuntarily shifting attention to objects that may carry important information for us (Connor et al., 2004). In the context of PM, a typical bottom-up process is spontaneous intention retrieval modulated by stimuli's saliency, or by the association between environmental cues and intention (focality).

A significant role in modulating the two processes is attributed to target characteristics, which can trigger the PM intention. Particularly, target's distinctiveness and associativity are reported as crucial in re-orienting attention to the intention (Shelton et al., 2019).

In summary, the MPV assumes that PM strategic/top-down processes are engaged whenever spontaneous retrieval is not possible, due to the ongoing and PM task characteristics and due to individual differences. In a recent work by Rummel and Kvavilashvili (2023), the main theoretical models of PM were reviewed to put different approaches into a common framework. This review will be used as the main reference to point out advantages and limits in the MPV and other models that will be introduced next. The authors highlighted how the MPV can account for most of the benchmark PM effects. Specifically, bottom processes involved in PM can explain intention importance, target list length, encoding strength, target focality, target saliency and lure interference effects on performance. By ensuring that the connection between the PM and the target is efficiently established in the encoding phase and correctly elicited in the retrieval phase, spontaneous processes can occur more automatically, requiring less resources and contributing to a better performance. On the other hand, the involvement of high-order, strategic processes is confirmed by other effects: the prospective memory costs effect, for which the same ongoing task is performed worse if there is a PM task, due to the allocation of cognitive resources to the maintenance of the intention; the intention context, for which a target is looked for only in a context where one may find some. Nevertheless, the MPV has been criticised because it cannot account for the ongoing task load effect in the presence of focal targets. According to the model, if targets are salient/focal to the tasks, the PM should be elicited spontaneously and not require strategic processes. Still, it has been reported that increasing the difficulty of the ongoing task hampers PM task performance and results in a frontoparietal activation, which is typical of top-down processes (Shelton et al., 2019). While the model can explain most benchmark effects, it is difficult to reconcile the MPV framework with the notion of ongoing task impacting spontaneous retrieval. An effort in this direction was made by revising the MPV into the Dynamic Multi-Process framework View (DMPV) (Scullin et al., 2013; Shelton & Scullin, 2017).

The rationale behind this change was to account for the dynamicity that characterizes human behaviour, including prospective remembering. Posing as a dual process theory (McDaniels et al., 2015), it assumes the process A is active in task A and process B is active in task B. However, the interval between the encoding and the execution of an intention is realistically too long and filled with many different situations to require just one of the two processes. Therefore, the main change in DMPV is that bottom-up and top-down processes dynamically interact depending on the context of the PM intention. For example, one individual could go out to work, creating the intention of buying milk after work because it was finished at breakfast. Then, there would be a retention-phase without spontaneous or strategic processes involved, in which the individual apparently forgot about the milk. Going back home from work, he/she notices a billboard on the road with a milk's company advertisement. After the spontaneous retrieval, strategic monitoring for supermarkets would be employed, leading to the fulfillment of the intention. A bi-directional talk between the two processes would allow for flexibility and for the most suited process to be engaged during the life of an intention. Another change proposed in the DMPV was the involvement of bottom-up and top-down processes in each phase of PM. The MPV focus was on how spontaneous and strategic processes played a pivotal role in the retention phase, while in the DMPV it is pointed out how a range of processes, from top-down to bottom-up ones, can deeply impact intention formation, retention, retrieval and deactivation.

1.3 Preparatory attentional and memory processes theory

The preparatory attentional and memory processes (PAM) theory (Smith et al., 2003) is an alternative model of PM that originated after MPV theory. As the model of McDaniel and Einstein, PAM focuses on event-based PM, and there is a considerable degree of similarity in how the two models describe a top-down/non-automatic process supporting PM. Nevertheless, the main difference relies on the fact that PAM assumes that we enter a preparatory attentional mode each time we create an intention, allowing the retrieval of the intention once a target is detected. Compared to MPV, automatic processes are not considered plausible in eliciting the retrieval of the PM, stating that a conscious, non-automatic process is always engaged. The rationale behind PAM theory is that this preparatory attentional process draws cognitive resources from a common, limited capacity, which is Working Memory. Working Memory (WM), sometimes also acknowledged as Short-Term memory, can be defined as a system for the temporary storage and manipulation of information (Baddeley 1998; 2012). This system serves as a relé for information that will be encoded in Long-Term memory, but also supports the maintenance (and potential manipulation) of the information for the current task. Considering the limited capacity of this system, a preparatory attentional process would ask for its share of WM, not granting the entirety of available resources to the ongoing task. Consequently, the PM retention-phase will hamper the ongoing task performance (admitting that the two tasks combined are exceeding the WM capacity). Additionally, PAM highlights the importance of RM for PM success, as RM processes are considered necessary for the discrimination of PM targets from non-targets, resulting in further usage of cognitive resources.

According to Rummel and colleagues' review (2023), both Prospective memory costs and ongoing task load are direct evidence in support of PAM's theory. Critically, it is important to point out that the presence of ongoing task load with focal/salient targets fits perfectly in the theoretical framework of PAM, while also being the principal limit found in MPV framework.

However, the review shed light on some benchmark effects that were difficult to conciliate with the model. Particularly, the prospective memory lure effects appear troublesome to explain within the PAM. The lure interference is a post-retrieval effect in which the performance of the ongoing task is affected whenever stimuli that resemble PM targets appear after the PM retrieval. The behavioural cost triggered by stimuli like PM cues cannot be explained by PAM theory because a preparatory mode would not be compatible in a post-retrieval phase, but it is found empirically (Scullin et al. 2012). More generally, the main criticism towards the PAM model is that preparatory attentional processes that are engaged for each new intention are hard to fit with the several PM intentions we create and maintain every day, which can often span from hours to days. The PM toll on WM would be constant, and the cognitive system would be slowed down every time we are maintaining PM intentions (which is almost always).

In a similar fashion to MPV's answer to criticism, PAM addressed the plausibility issue in the 2017 paper of Smith and colleagues, where it was stated that withdrawing capacity from the ongoing task would have no benefit if the possibility to satisfy the delayed intention is not imminent (Smith et al., 2017). This acknowledgement was furtherly supported by reports of studies in which there were no PM cost to ongoing task performance in blocks of trial which explicitly did not contain PM cues (Cook et al., 2005; Marsh et al., 2006). Therefore, even though PM intention was formed, PM cues were not expected resulting in no capacity withdrawal. Altogether, these results point to a critical role for context in the allocation of attentional resources (Smith et al., 2017). While the studies reporting differences on PM cost depending on the instructions had significant results, they were limited to different blocks within the same task. In the study of Smith et al. (2017), three different experiments were carried out to test the hypothesis that familiar context could be used to decide whether to engage preparatory attentional processes. They found that spatial contextual information could be effectively used to dynamically allocate attentional resources, with different impacts on the ongoing task and stable high levels of PM performance. These results were integrated into an evolved version of PAM theory, in which decisions about the need for preparatory attentional processes is made at point of transitions. Within these transition points, information from the environment captures attention and trigger the preparatory mode, almost spontaneously. Arguably, context-dependent PAM theory included a reactive, automatic component in their framework, assuming a dual-process status (Rummel et al., 2023) and moving closer to DMPV's formulation.

1.4 Prospective Memory Decision Control Theory

The Prospective Memory Decision Control theory (PMCD) (Strickland et al., 2018) represents a third model which focuses on different aspects to explain PM compared to previous models, while also explicitly accounting for the theoretical assumptions made in MPV and PAM. The goal behind this theory was to quantitively model PM and ongoing tasks, as this has been attempted previously, but either the data could not fit the theoretical models (Arnal, 2008; Gilbert et al., 2013) or models were applied only on non-PM tasks

(Ratcliff et al., 2004; Brown et al., 2008). The model was therefore based on a Linear Ballistic Accumulator (LBA; Brown & Heathcote, 2008), which was applied to PM data so that three decisions (two binary choices of the ongoing task, and the "PM choice") corresponded to three accumulators, that gather evidence until a threshold is reached and a decision is made. Specific stimuli could be excitatory for one accumulator while also inhibiting the other two. Consequently, PM is here conceptualized as a parallel independent race with feedforward excitation and inhibition and linear updating, having three main parameters modulating the model: start-point variability, thresholds, and evidence accumulation rates. Since start-point variability is assumed not to vary between conditions, the last two classes of parameters play the most important role in determining the decision within a task. Specifically, thresholds can vary the amount of evidence necessary for the accumulator to reach the decision-status, while accumulation rates depend on the provided stimuli. Using these measures, the authors criticized the notion of capacity sharing in PM, which was fundamental in PAM framework, as they deemed it not responsible for PM cost. In fact, they argued that withdrawing capacity from the ongoing task in favour of PM task would result in slower speed processing, and therefore in differences in evidence accumulation rates. Nevertheless, they revealed through two different experiments that PM costs was largely due to changes in response threshold rather than changes in accumulation rates, excluding a role for capacity sharing in PM cost (Strickland et al., 2018).

To account for PM cost and other PM phenomena, PMCD postulates two forms of cognitive control, which is high-level ability that allows one to act in a goal-directed and flexible way (Miller, 2000; Botvinick et al., 2001). Namely, proactive and reactive control are hypothesised as the two main mechanisms regulating PM within the standard PM experiment (Einstein and McDaniels, 1990). Proactive control is described as a process which is initiated before the cognitively demanding effect, resembling preparatory processes in PAM (but still taking distances from capacity sharing notion for reasons reported above). This form of control should work by either lowering the decision threshold of the PM, or by increasing the threshold of the ongoing task. Both would result in a facilitated PM decision. The other form is defined as Reactive Control, which would increase the evidence accumulation rates rather than thresholds, in a "just-in-time" manner. A specific stimulus could reactively trigger this mechanism, which both increase the accumulation rate for the PM and actively inhibits the ongoing task accumulators. The fact that focal tasks are more likely to elicit such a reactive response posits this process close to spontaneous retrieval conceptualized in MPV theory.

According to Rummel and Kvavilashvili (2023), PM cost, PM-importance and target-list-length effect can all be explained within PMCD by proactive control: the fact that a block of trials will contain PM cues will increase the threshold of the ongoing task in favour of the PM task; therefore, the ongoing task will be hampered, especially with long target lists, and especially of the importance of the PM was stressed. Additionally, the fact that proactive control is initiated only in situations where it makes sense to prepare for PM cues can explain Intention Context effect. On the other hand, reactive control can explain the changes in performance elicited by target-focality and target-saliency. What is difficult to reconcile with PMCD is lure interference effect, since the authors did not postulate bottom-up processes, but rather a reactive top-down process which is cognitive control.

1.5 Neural Basis of Prospective Memory

Over the last 25 years, many efforts were spent to determine how the behavioural phenomena concerning prospective remembering can be understood at the neural level. A different number of studies have used positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) to explore which regions are active during different PM processes and phases. Both neuroimaging techniques detect regions whose blood level has risen significantly during a task compared to a resting condition or between two different tasks, indicating their involvement in the processes underlying the task. To measure how cognitive processes are differently supported in the brain, PET monitors the accumulation of a radiolabelled isotope during a task (Buckner et al., 1995). Then, the degree of accumulation is interpreted as an increase of the metabolic demand from a specific region and is computed as regional cerebral blood flow (rCBF), indicating the region's involvement in the task. FMRI is a technique focused on brain's blood fluctuations, relying on changes in blood-oxygen-level-dependent (BOLD) during the execution of specific tasks (Heeger et al., 2002). Representing a less invasive and more accurate alternative to PET, it has been largely used to investigate PM's neural substrates, returning significant data to the literature. The combination of different PET and fMRI studies altogether revealed a broad set of neural regions involved in PM, including the anterior prefrontal cortex (aPFC), frontoparietal networks, cingulate and insular regions, temporal regions, thalamus, putamen, caudate nucleus, and cerebellar regions (Burgess, et al., 2001; McDaniel et al., 2013; Cona et al., 2015).

In the first studies investigating the neural underpinnings of PM, PET was used to explore which regions support event-based PM tasks (Okuda et al., 1998; Burgess et al., 2001). Initial investigations pointed to a key role for the anterior Prefrontal Cortex (aPFC), as both studies reported a change in rCBF during event-based PM task. Particularly, Okuda et al. (1998) found a significant activation of aPFC in the left hemisphere. The aPFC (Brodmann's area 10) is involved in a wide variety of tasks and high-level processes, coordinating information processing and transfer to permit selection between multiple cognitive operations (Ramnani & Owen, 2004; Gilbert et al., 2005). In fact, the contribution of this region has been reported in many subsequent studies using different PM tasks (time-based and event-based), materials, responses, and using PET and fMRI (Burgess et al., 2001, 2003; den Ouden et al., 2005; Gilbert et al., 2009; Oksanen et al., 2014; Okuda et al., 2007).

Subsequent studies have delineated two distinct roles for the medial and the lateral sections of the aPFC (Burgess et al., 2005; 2007; Gilbert et al., 2005; 2006). The medial aPFC is specifically involved in stimulus-oriented situations, where participants had to attend to external stimuli, compared to stimulus-independent situations, where no sensory input was given. On the other hand, the lateral aPFC seems significantly involved during situations where the focus of attention is internally generated (i.e. stimulus-independent). A theoretical account of the role of these sub-regions of aPFC was given within the Gateway Hypothesis (Burgess et al., 2007). According to the Gateway Hypothesis, the medial and lateral aPFC comprise a mechanism underlying the balance between externally and internally oriented attention. In the context of PM, the maintenance of PM intention would be coupled with an increase in the activation of lateral aPFC and a decrease in the medial aPFC. The contribution of different sections of aPFC to PM, as suggested by the Gateway Hypothesis, found further support from a meta-analysis conducted by Cona and collaborators (2015). The study suggested that these regions allow individuals both to maintain intentions actively in mind by activating lateral aPFC, while also monitoring for the presence of the PM cue in the environment by dynamically increasing and decreasing the activation of medial PFC. Moreover, the authors proposed a role for aPFC beyond the maintenance of the PM intention, suggesting that aPFC could play an important part in the encoding and the retrieval of the intentions. APFC would then be, more broadly, responsible for the representation of the intention and, as other authors reported, for the association between the PM cue and action (McDaniel and Einstein, 2000; Moscovitch, 1994; Cona et al., 2015). The contribution of aPFC and other brain regions across the different phases of PM will be discussed below, as part of the model proposed by Cona et al. (2015), the Attention to Delayed Intention model (AtoDI).

Finally, other studies investigated if the activation of aPFC during the maintenance phase of PM could contribute to the representation of the content of intentions (Haynes et al., 2007; Momennejad and Haynes, 2013; Gilbert, 2011). Particularly, Gilbert et al. (2011) found that the anterior medial PFC seems to be more specifically involved with the representations of the content of delayed intentions compared to lateral aPFC, which may play a “content-free” role in PM. In the study of Momennejad and Haynes (2013), the results indicated that medial aPFC could serve a role for representing the “what” component of the intention, while the lateral section would be more specialized for the “when” component.

Following the MPV framework, many studies focused on exploring how the theoretical pillars of this theory, which are strategic monitoring and spontaneous retrieval, can be supported differently in the brain. Particularly, a key role for frontoparietal networks was suggested (Reynolds et al., 2008; Beck et al., 2014; McDaniel et al., 2013). Frontoparietal networks comprise two different networks: the Dorsal Frontoparietal/Dorsal Attention Network (DAN), which is responsible for top-down control and goal-directed attention, and is composed by Dorsolateral Prefrontal Cortex (DLPFC), frontal eye fields (FEF), premotor regions, precuneus and superior parietal lobule; and the Ventral Frontoparietal/Ventral Attention Network, which is specifically involved in bottom-up attentional phenomena, composed by Temporal Parietal Junction (TPJ) and the ventral Prefrontal Cortex (vPFC) (Corbetta and Shulman, 2002; Vossel et al., 2014). A dissociation between the functional role of these two networks has been reported (Beck et al., 2014; Kalpouzos et al., 2010; McDaniel et al., 2013), as the DAN seems to be more involved in maintenance and the VAN in the retrieval of the PM intention. It is important to mention that while not explicitly declared as part of the DAN in the original model, lateral aPFC is sometimes considered a part of the network or at least a strong connection from it. Converging evidence from the functional role of DAN and VAN in the human brain and their implications in prospective remembering led to the Dual Pathways hypothesis (McDaniel et al., 2015), which suggests that DAN might be responsible for top-down attentive allocation necessary to maintain the PM intention and to monitor for cues in the environment (i.e. strategic monitoring), while VAN would support the automatic allocation of attention to the detected PM cue, allowing the retrieval of the intention (i.e. spontaneous retrieval).

An attempt to put together the pieces of the PM puzzle, which is putting into a common framework the role of regions and networks within different PM phases and processes, was offered by Cona et al. (2015) with the Attention to Delayed Intention model (AtoDI). This model explores different brain regions' role in prospective remembering, from the encoding to the retrieval phases. According to the AtoDI model, once the to-be-encoded PM cue reaches sensory areas in Occipital Cortex, attention allocation to the external cue and representation in a memory is mediated by the ventral Parietal Cortex (vPC). Afterwards, attention is shifted to the internal representation via the Posterior Cingulate Cortex (PCC), and content is represented in the left anterior Prefrontal Cortex (aPFC) while actions for later executions are coded in the Somatosensory Areas (S1).

After the encoding phase, the intention is maintained through the mediation of the aPFC, by deactivation of its medial section and activation of its lateral section. The balance between the fulfilment of the ongoing task and intention maintenance is obtained thanks to aPFC's connections to the DAN, actively maintaining the intention while monitoring for cues.

Finally, either the intention is maintained until fulfilment, or a salient cue evokes the intention: when the PM cue occurs, the Insula detects the relevant stimulus and transfers the information to the anterior (ACC) and posterior Cingulate Cortex. The ACC might detect the conflict between the ongoing task and the necessity for intention execution, signalling to the aPFC the necessity to switch from the ongoing to the PM task. The PCC would instead activate the VAN, which is responsible for bottom-up mechanisms. Together, these regions support both the attentional allocation to the external cue and the shift to the internal representation of the intention, which ultimately results in the activation of the Supplementary Motor Area and S1, translating the intention on an action-level.

Critically, most studies on the neural bases of PM focused on event-based PM tasks, while only a few studies explored the substrates of time-based PM. This was accomplished by two studies that explicitly addressed the difference in the modalities using PET (Okuda et al., 2007) and fMRI (Gonneaud et al., 2014). In the study of Okuda et al. (2007), time-based tasks showed activation in a larger set of frontal regions compared to event-based tasks. This result has pointed to the presence of a "future-mentalizing" component necessary to time-based tasks, since insights into one's own future behaviour are required in the absence of external cues (Okuda et al., 2007). In the study of Gonneaud et al. (2014), event-based PM tasks were specifically linked to the activity of occipital lobes, related to the constant target-checking which requires visual attention to correctly spot PM cues amid ongoing task's stimuli. On the other hand, time-based PM tasks showed activations in the middle and superior frontal gyri, the precuneus, the dorsolateral frontal cortex and in the DAN. Nevertheless, there was a large overlap between the two conditions across different PM phases. The authors proposed that this pattern resulted from the fact that the conditions may differ in the maintaining phase (target-checking versus time-estimation) but are not so distant in the retrieval and encoding phase, as other studies have suggested (Gonneaud et al., 2014; Cona et al., 2012; Guynn et al., 2003). Therefore, event-based PM would primarily employ visual areas, in addition to frontal and prefrontal areas, to check for the visual cues associated with PM intention, while the network linked to time-based PM tasks would serve mentalizing and time-estimation.

Before discussing the neurophysiological correlates of PM in the next chapter, it is worth mentioning how non-invasive brain stimulation has contributed to the PM literature, particularly through Transcranial Magnetic Stimulation (TMS). The exclusive advantage of TMS is to enhance or inhibit brain regions' activity directly, so that it is possible to make hypotheses about the causal role of those regions in influencing cognition (Miniussi et al., 2010). The technique comprises a powerful and rapidly changing current passing through a wire positioned over the scalp; the electric field creates a magnetic field, which penetrates the cranium and induce a new electrical field that depolarizes neurons of the interested area (Terao et al., 2002). Only a handful of studies investigated the neural underpinnings of PM using TMS. Nevertheless, this technique posits as a powerful tool to study causal relations between brain and cognitive processes, adding informative data to a literature composed mainly by study of correlational nature. For instance, the study of Basso et al. (2010) inspected whether stimulation over bilateral DLPFC affected PM and/or WM. They found that PM performance was hampered by stimulation on both experimental sites, while the effect was only marginal for WM performance. Consequently, the authors suggested that PM and WM might not be supported by the same memory system, not excluding the possibility PM may draw on WM resources at high demand (Basso et al., 2010). To further explore the role of this prefrontal area in PM, Bisiacchi et al. (2011) applied 10 Hz repetitive TMS (rTMS) over DLPFC and inferior parietal lobule to gather evidence over their differential function. A significant association with PM performance was found for right DLPFC stimulation at 150-300 ms after the stimulus onset, and for inferior parietal lobule at 400-600 ms. These results suggest that right DLPFC might be involved in the early phases of PM, such as target-checking, while parietal areas may be employed primarily in later stages, such as intention retrieval (Bisiacchi et al., 2011). The contribution of parietal lobes to PM was also the focus of the study by Cona et al. (2017), where they applied 1 Hz rTMS to bilateral superior parietal cortex. An improvement in PM performance was found for stimulation over the left superior parietal cortex, while stimulation over both sites resulted in worse ongoing task performance in the condition where participants had to allocate attention internally. This suggested that superior parietal cortex might play a causal role in the attentive allocation towards external environment versus internal environments (Cona et al., 2017). Other studies focused on the asymmetrical pattern shown by aPFC, which was already reported by the neuroimaging literature (Cona et al., 2016; Okuda et al., 2007). Specifically, a causal role for left aPFC in prospective remembering was confirmed, as an inhibitory TMS protocol resulted in worse performance, while an excitatory protocol returned an improvement (Costa et al., 2011; Debarnot et al., 2015)

2. Chapter 2

Neurophysiological correlates of prospective memory

2.1 Introduction

Investigating the neural correlates of human cognition has benefitted largely from the implementation of fMRI and PET neuroimaging techniques, since their spatial resolution (in the order of millimetres) is extremely accurate and has no equivalents between non-invasive techniques. Nevertheless, such techniques present a low temporal resolution. Neural activity tends to occur at very fast rate, in the order of milliseconds and even microseconds, whereas the metabolic and hemodynamic modulations collected by neuroimaging techniques happen at the level of seconds, hampering PET and fMRI ability to correctly address the temporal dynamics of brain communication. Electroencephalography (EEG) and Magnetoencephalography (MEG) represent an alternative solution to overcome this issue. Relying on electrical and electro-magnetic phenomena rather than hemodynamic processes, they present a temporal resolution in the order of milliseconds, which can be efficiently employed to capture neural oscillations and transient phenomena. Additionally, even if the spatial resolution of M/EEG techniques is not always excellent *per se*, a great number of sensors and the possibility to co-registrate M/EEG data with structural MRI has provided the possibility to perform accurate source localization (Hedrich et al., 2017). Considering that only two studies used MEG to investigate PM (see Martin et al., 2007; Cona et al., 2020), we will focus on the contribution that EEG has made in the PM literature, after briefly describing its principles and characteristics.

EEG measures neuronal oscillations that are generated by the postsynaptic potentials in cortical pyramidal neurons (Speckmann et al., 1993). These neurons are assumed to be responsible for the scalp-recorded signal because their dendritic trunks are positioned parallel to each other and perpendicular to the scalp, so the excitatory and inhibitory potential are summated to create a measurable signal (Pizzagalli, 2007). To capture this activity, EEG employs a cap which can usually comprise from 32 to 256 electrodes, and the EEG signal always represents the difference between an active electrode and a reference.

Different analyses can be carried out starting from the same EEG signal. In this context, two types of analyses will be considered: Event-related potentials (ERPs), which are voltage deflection time-locked to a relevant event; and Time-frequency analyses, which divide the EEG signal into different band of frequency. Furthermore, the last section will focus on the source-imaging approach to EEG analyses.

2.2 Event-related potential

Event related Potentials (ERP) are small variations in the EEG signal time-locked to a specific event, which have been largely used to study the psychophysiological correlates of cognition (Sur & Sinha, 2009; Blackwood and Muir, 1990). Considering the difference between ERP and EEG amplitude (a few microvolts vs 50 microvolts), this method requires increasing the so-called “Signal-to-Noise ratio” (SNR). SNR compares the amount of data we are interested in, to noise we do not want to consider. In this context, ERP is the signal and the remaining EEG data is noise. To increase SNR, the most common approach is averaging a sample of the EEG signal that is time-locked to the repeated occurrence of an event. Assuming that signal should be constant because it is time-locked to the stimulus/event and that noise is randomly distributed, averaging cancels out noises and returns a set of negative and positive signal deflections, which underlie cognitive processes elicited by the event and its processing. ERPs waveforms are usually referred to as *components,* and they typically start with either P or N, indicating the polarity (Positive versus Negative), and a number indicating the latency (e.g P300 is an ERP component with a positive polarity, which occurs approximately around 300 ms). ERPs have been abundantly employed to investigate the neural dynamics underlying PM processes. Specifically, ERPs paradigms in PM studies can be categorized into three main classes: ERPs underlying the encoding of PM delayed intentions; ERPs focusing on the maintenance phase of PM; ERPs elicited by the appearance of the PM cue (Cona & Rothen, 2019; West, 2011).

The standard paradigm used to study PM encoding through ERPs has PM encoding trials sorted into "hits" or "misses" depending on the accuracy of the later retrieval, following RM literature (West et al., 2011). Then, ERPs are used to distinguish PM trials from ongoing trials, while also assessing how the components are correlated to the proportion of hits and misses. In the study of West and Ross-Munroe (2002), three components were significant in telling PM encoding trials apart from ongoing task trials, namely the N200, the P300 and frontal slow wave potential. However, the only component that had a significant memory effect in the study was the latter, frontal slow wave, emerging as a correlate of elaborative encoding strategies and recollection at retrieval. Interestingly, the pattern for the two types of retrospective and prospective memory was opposite, as better performance was associated with a positive frontal increase in episodic memory but with a negative frontal increase in PM.

Further support to the crucial role of frontal activity for PM fulfilment was found in studies exploring the neural correlates of PM maintenance and of strategic monitoring, a concept from the PM Multi Process View (MPV) (Cona and Rothen, 2019). In fact, in the study of Cona et al. (2012), ERPs were analysed for two subcategories of strategic monitoring: retrieval mode (in which the intention is actively maintained until execution) and target-checking mode. Their results confirmed the importance of slow wave frontal activity, which was prominent in retrieval mode, suggesting that the component probably reflects the intentions iteratively represented into one's memory.

Some studies investigated how different factors could affect PM peculiar modulations. For example, in the study of Cona et al. (2014), they showed how the focality of the PM cue over strategic monitoring was mirrored by frontal and parietal modulations: focal tasks showed a smaller amplitude in ERP modulations, while non-focal tasks, requiring more effortful top-down strategies, returned a greater amplitude. A similar result was obtained in the study of Hering and colleagues (2018), in which different extent of emotional valence of the PM cue modulated ERPs so that the amplitude was smallest with negative cues, intermediate with neutral and largest with pleasant cues.

Finally, many studies focused on ERPs that were time-locked to the appearance of the PM cue in PM trials, with the aim of unveiling the neurocognitive processes of PM's intention fulfilment. Three components/modulations emerged as significant in differentiating PM cues from ongoing task stimuli: N300, frontal positivity (FN400) and parietal positivity. (West et al., 2001; West & Krompinger, 2006; West & Ross-Munroe, 2002). Furthermore, the increase in the amplitude of parietal sites is expressed three further components, which are P3b, parietal old-new effect and prospective positivity (see *Fig 2.1* for a showcase of PM-related ERP components).

The N300 component is elicited over the occipital and parietal lobes, starting at 200ms, and peaking between 300ms and 500ms. FN400 is a positive component which originates in the frontal midline; it starts around the same moment as the N300, but its duration can exceed the N300. The coupling between these two components appears to be consistently elicited by PM cues (West et al.,2003; West and Wymbs, 2004). While an important role for N300 and FN400 in PM was established, their functional meaning still had to be accounted for. A solution was proposed by the study of West et al. (2007), in which N300 and FN400 were hypothesized to represent the neural correlate of the detection of the PM cue. To support this, they investigated how the components related to correct retrieval ("PM hits") compared to "PM misses" and ongoing tasks.

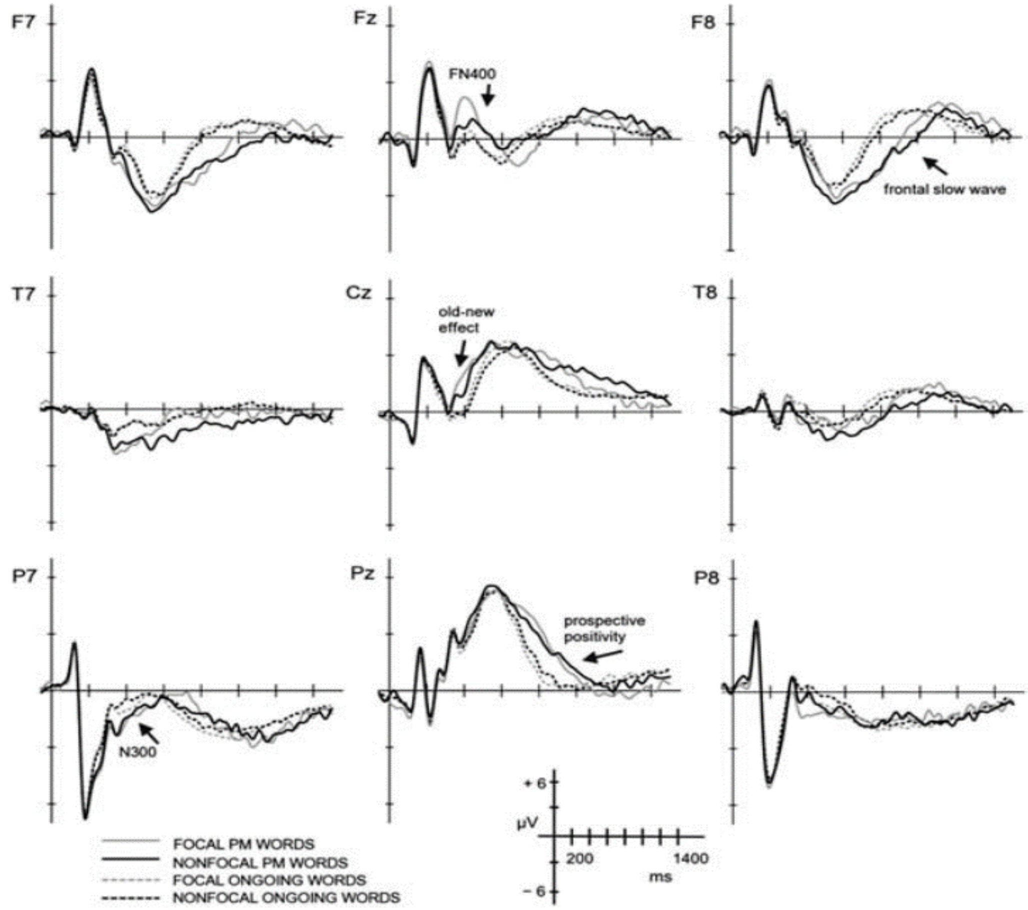


Figure 2.1 In this figure it can be observed how ERPs components are differently expressed over time and space upon the presentation of a PM word compared to the presentation of an ongoing task word. At the top of the figure, three electrodes from frontal regions (F7, Fz, F8) show a positive signal variation corresponding to P3b. It is also possible to notice how PM words (solid lines) contribute to FN400 in FZ and a gradual increase in the signal (frontal slow wave) in F7 and F8. Similarly, at the bottom of the figure, PM words elicit a negative variation corresponding to N300 at 300-400 ms in P7 and the prospective positivity component in PZ. Finally, in the medial part of the figure, the old-new effect can be appreciated in Cz (Cona et al., 2014).

As shown in *Fig 2.2*, both components' amplitude was greater when the PM elicited a response (hits), relative to other conditions. Furthermore, a specific role for FN400 within the process of detection has been suggested: the component may underlie RM processes necessary to retrieve the memory trace of the PM cue, so that the intention can be fulfilled (West et al. 2006). Such a role for FN400 would be consistent with the functional meaning proposed by episodic memory literature (West & Krompinger 2005).

As mentioned above, another ERP modulation that is distinctive of PM processes is parietal positivity, which has been further divided into P3b, prospective positivity and the parietal old-new effect (West et al., 2011). This distinction is supported by temporal and functional differences between these components, as P3b is associated with the detection of low probability targets (peaking at 400-600ms), the parietal old-new effect with

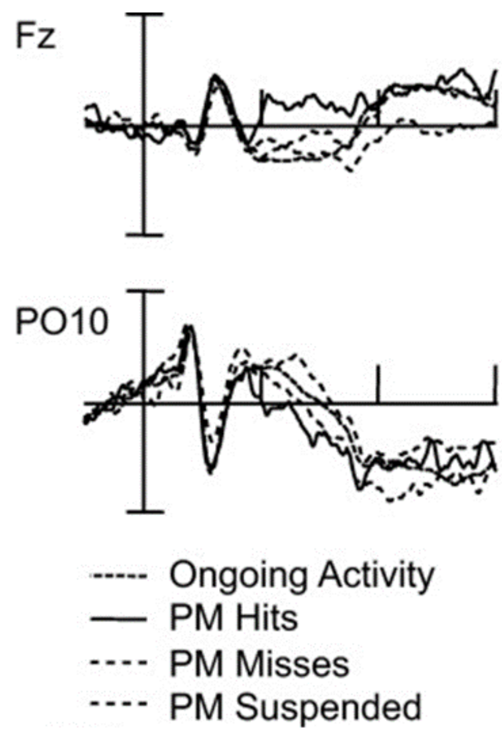


Figure 2.2 In the figure, PM hits (solid lines) can be differentiated from other conditions by the presence of FN400 over FZ (top of the figure) and N300 (bottom of the figure) at PO10 (West et al., 2007).

recognizing PM cues (peaking at 600ms), and the prospective positivity with the configuration of the PM task set (peaking at 700ms) (McNerney, 2006). It is not straightforward to assume that differences between these components are caused by differences in paradigms, as they share the same polarity, and they are all generated within the parietal lobes. In the review of West et al. (2011), the authors suggested that prospective positivity may be separable from P3b and old-new effect, being peculiarly associated to PM. Two studies (West & Bowry, 2005; West et al., 2003) tried to explore the functional distinction between the P3b and prospective positivity by manipulating the working memory load and focality associated with PM cues, as these features are reported to influence the expression of P3b (Donchin & Fabiani, 1991). They found that increasing the number of items to encode decreased significantly the P3b but did not affect prospective positivity, and changes in focality of PM cue only influenced the amplitude of P3b and not the other component. Furthermore, a distinction between prospective positivity and parietal old-new effect was established through a study that compared PM retrieval through recognition and cued-recall paradigms (West and Krompinger, 2005). The results indicated that while old-new effect was elicited in both PM and recognition/cued recall conditions, prospective positivity was only evoked in the presence of PM cues.

2.3 Time-frequency analyses

The abundant literature focusing on ERP and PM allowed the exploration of the temporal dynamics of prospective remembering. However, ERPs represent only one way to approach EEG data. A popular alternative adopted for EEG data analysis is the time-frequency method, which employs the whole EEG signal to provide information over magnitude, phase and frequency (Roach & Mathalon, 2008; Laera et al., 2021). The most common approach is to divide the EEG frequency spectrum into five bands, which traditionally are delta (0.5–2 Hz), theta (3–7 Hz), alpha (8–12 Hz), beta (13–30 Hz), gamma (30–100 Hz) (Pletzer et al., 2010). The amount of power for each band is then confronted between different conditions, as these bands have been correlated to different cognitive states and degrees of alertness (Sugumar & Vanathi, 2017). In particular, the theta and alpha bands have been reportedly linked to memory and attentional processes (Kilimesch, 1999; Herweg et al., 2020). Therefore, time-frequency studies on prospective remembering have focused over these two bands (Martin et al., 2007; Cona et al., 2020; Cruz et al., 2017; Vicentin et al., 2024).

The first study to implement the time-frequency approach in PM was carried by Martin and colleagues (2007), in which theta, lower and upper alpha (8-10 Hz and 10.5-12 Hz respectively) were analysed to assess parietal, hippocampal and frontal contributions in PM, RM and oddball tasks. A prominent upper alpha activity emerged over posterior parietal areas during oddball tasks and PM tasks compared to RM tasks, while an increase in the theta band was observed specifically in RM compared to PM and oddball tasks. Altogether, these results were interpreted as a sign of the distinctive role of posterior parietal areas in PM compared to RM. While being the first study to apply time-frequency analyses for the investigation of PM, the work of Martin and colleagues presented some limitations, such as the sample size (only five participants). Furthermore, the study included only a focal event-based PM condition, not exploring patterns of alpha and theta power associated with time-based PM or strategic monitoring.

To partially overcome these issues, further evidence was given by the study of Cona et al. (2020), which focused on how theta and alpha oscillations could characterize strategic monitoring. In fact, the authors investigated the functional role of the two frequency bands over distinct conditions, namely a retrospective-load condition, in which cues were highly salient and there were multiple intentions to maintain, versus a monitoring-load condition, where there was only one intention to maintain, associated with a covert PM cue. The first condition required an internally oriented focus of attention to maintain and retrieve multiple intentions from memory, while the second condition required external attentional allocation to spot lowly-salient cues. An increase in theta band power was observed over medial temporal and frontal regions in the retrospective-load condition, pointing towards a role for theta band in the RM processes involved in PM. Conversely, the monitoring-load condition resulted in a decrease in the alpha band over occipital, occipito-parietal and fronto-temporal regions. Importantly, these results fit with both the Dual Hypothesis and the AtoDi Model, as theta increases resulting from cues-evoked retrieval were mostly elicited over the regions within the Ventral Attention Network (VAN) network, whereas alpha decreases in the monitoring-load condition over Dorsal Attention Network (DAN) regions. The AtoDI model is also compatible with the results obtained by the study of Cruz and colleagues (2017), in which the time-frequency method was used to investigate time-based PM. Participants had to reset a clock every 4 minutes, with the possibility to check clocks in that time span. Alpha band was strongly suppressed within the ACC after clock-checks, and this is coherent with the AtoDi's role for ACC, whose activity should be associated with retrieval of the PM intention.

Finally, in a recent study by Vicentin and colleagues (2024), the contributions of alpha and theta bands were also observed in different sensory modalities, employing and comparing auditory and visual PM tasks. The authors found that, while alpha and theta oscillations played pivotal roles in PM processing in both conditions, alpha decrease showed a similar pattern across modalities, posing as a supra-modal/ stimulus-independent mechanism (strategic monitoring), whereas theta activity was more significantly affected by sensory modality, as the onset and latency of the neurophysiological oscillation differentiated between the two modalities.

In summary, alpha and theta oscillations seem to play a pivotal role in PM, mediating the dynamic balance between internal and external focuses of attention. Particularly, theta increases seem to support internal monitoring and maintenance, while alpha suppression seems associated with the external allocation of attention for the detection of PM cues.

2.4 Source localization and brain network analysis

As it was mentioned in the previous paragraphs, M/EEG techniques provide excellent temporal resolution that brought exclusive knowledge to the literature, but PET and fMRI techniques have often been preferred due to their spatial resolution. Since postsynaptic potentials measured by EEG flow through the head volume, a "natural" spatial filter is applied over the EEG signal, distributing it over the scalp. While the dipolar activation of a single area would be relatively easy to localize even considering the head volume, the simultaneous activation of several brain regions creates a complex pattern of potentials that is not straightforward to address, originating the "EEG source localization problem" (Michel & He, 2019). Furthermore, the problem has been divided into two distinct challenges: the "forward" problem, which refers to modelling the signal distribution over the scalp given a set of neural generators, and the "inverse" problem, which consists in the localization of the underlying sources given a signal collected over the scalp.

Different solutions to the forward problem correspond to different models used to calculate head conductivity. Two popular solutions are the spherical model (Michel and Murray, 2012) and the Boundary Elements Method (BEM) (He et al., 1987). A spherical model conceptualizes the head model as a set of distinct, homogenous shells with different conductivity, usually using three different layers: scalp, skull, and brain. While posing a relatively simple solution, considering shells as homogenous ignores tissue's peculiar properties such as thickness, shape and convolutions, which are fundamental to properly model the propagations of potentials. Conversely, the BEM implements information from magnetic resonance imaging (MRI) to incorporate anatomical properties into a forward model. The BEM computes the forward model by calculating the interface between each tissue and segmenting them using MRI information, which can come from either a template or an individual MRI. EEG-MRI co-registration grants access to more realistic and complete forward models, making use of the exclusive information of each technique.

The inverse problem is defined by determining which intracranial sources contribute to the signal that arises over the scalp. Considering all possible solutions, a key aspect in inverse models is the presence of a priori constraints over sources, which reduce dimensions to be considered so that a mathematical estimation is possible. Therefore, models differ depending on which constraints are incorporated, with neurophysiological, biophysical, anatomical and mathematical knowledge contributing to these a priori constraints (Michel & He, 2019). Making use of this information, dipoles are computed in the source space accordingly. One popular inverse solution is LORETA (low resolution electromagnetic tomography) (Pascual-Marqui et al., 1994), which employs a minimum norm constraint to assume that current distribution has minimum energy, and that forward solution optimally explains that distribution. Additionally, LORETA considers the Laplacian of the sources rather than the sources directly, reducing the dimensionality of the data while maintaining spatial information. This feature results in a smoothed reconstruction with low resolution, occasionally creating blurring or over-smoothing reconstructions if neighbouring voxels have distinct activities. A similar approach is found in the Beamforming method (Vrba & Robinson, 2001), in which the signal from the scalp is refocused over all possible locations in the source space, adjusting weights so that the variance of the current dipole is minimal. While sharing part of the smoothing issue with LORETA, beamformers are becoming more and more popular because of their ability to capture deeper sources while suppressing external noise (Westner et al., 2022). Finally, an alternative solution to the inverse problem is offered by the Independent Component Analysis (ICA). ICA is a statistical method that transforms a multidimensional vector into a set of separate, independent subcomponents (Painsky et al., 2014). ICA can be applied to EEG source imaging by computing the sources of ICA components and then back-projecting components coefficients into the source space. Main advantages of the ICA method are its ability to efficiently separate source from a mixed signal, and to correctly identify artifacts as components to be later removed.

Different forward and inverse solution methods have been applied to localize which brain regions were mostly responsible for the observed EEG scalp signal. However, imaging studies in cognitive neuroscience have been focused on understanding brain functions through its communication and interaction rather than on the role of specific and isolated regions. Functional connectivity, defined as the statistical correlation of activity between functionally connected brain regions (Passamonti al., 2019), has indeed emerged as a main topic in neuroscientific research, as this approach has changed how we conceptualize both brain and mind. Considering brain regions as nodes and hubs of networks allows us to recognize the importance of interactions between regions belonging to the same (or distinct) functional networks that are found in both resting and task conditions. An example of the importance of brain networks in PM research can be found in the AToDi model: the contributions of the Dorsal and Ventral Attention Networks are fundamental for the regulations of bottom-up and top-down attentive mechanisms necessary for intention maintenance and execution, and the integration of functional connectivity in this framework enriches and integrates this model with exclusive information. While many methods have been devised to compute functional connectivity for EEG, none was applied to PM to date. By characterizing functional connectivity with EEG in PM, it would be possible to assess how functional networks contribute to PM processes while also implementing the exclusive temporal information over networks dynamic interaction. One promising method to measure transient oscillations of cortical networks is Hidden Markov Modelling (HMM), an unsupervised machine learning technique that can capture recurrent patterns of brain spontaneous activity (Toffoli et al., 2024). HMM can be used to describe a time-series as a set of states, each of which has its own model of the described data (Vidaurre et al., 2016). As it can be understood from *Figure 2.3*, a K-number of states (x1, x2, x3) are decided a priori so that they can effectively describe the observable data we already have (y1, y1, y3, y4).

Considering brain activity as the observable data, HMM can produce a set of neural networks as hidden states to explain the measured signal. HMMs have been used to infer dynamic properties from a range of different neuroimaging techniques, such as fMRI

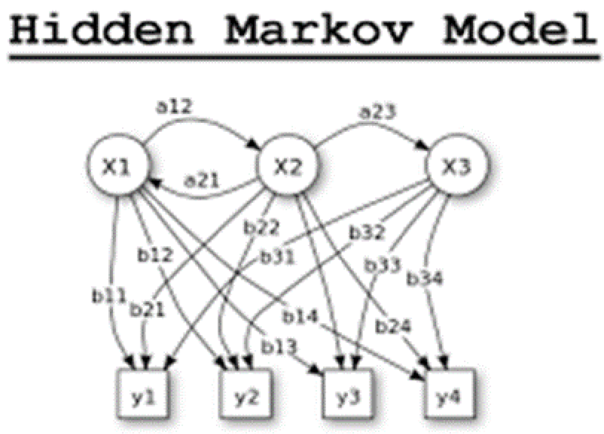


Figure 2.3 A graphical illustration of Hidden Markov Model, where the observable data (y1, y2, y3, y3, y4) at the bottom of the network are used to infer and build the hidden states (x1, x2, x3) that generated the observed data.

(Dang et al., 2017; Hussain et al., 2023), MEG (Baker et al., 2014; Hawkins et al., 2020) and EEG (Obermaier et al., 2001; Williams et al., 2018; Dash et al., 2020; Marzetti, 2023). Implementing EEG data for HMM could provide fundamental information regarding PM processes, as the temporal characterisation offered by this model could grant insights into fine-grained dynamics underlying different aspects of PM.

3. Chapter 3

Functional connectivity patterns of Time-based and Event-based prospective memory

3.1 Introduction

The ability to remember to perform intentions after a delay of time (time-based) or after a cue is presented (event-based) is defined as Prospective Memory (PM) (McDaniel & Einstein, 2007). PM constitutes one of the most important and peculiar functions of the mind, allowing us to exceed the limits of the *hic et nunc*, as allocating an intention in the future permits us to operate outside the limit of what we can keep in our working memory. Delaying the execution of an intention, even of hours, days or weeks, increases our range of actions and flexibility consistently, resulting in PM having a profound impact on our daily life. The importance of PM has been acknowledged by the scientific community and it is reflected by an average of 1,600 articles per year in the last ten years according to PubMed. The focus of research has varied greatly in the PM field, focusing on the underpinnings of event-based and time-based PM tasks and processes involved in PM such as strategic monitoring and spontaneous retrieval (Cohen & Hicks, 2017; Rummel & McDaniel, 2019) or focusing on how PM is characterized in neurological conditions, mood disorders and across the lifespan (Tse et al., 2023; Kliegel et al., 2016; Zhou et al., 2018; McFarland et al., 2016).

Notwithstanding the rising importance gained by PM in the scientific literature, not all aspects of PM have been consistently described and investigated, leaving room to complete and better PM research. Obtaining a deeper understanding of PM could give us a better insight into an ability that greatly affects our daily living, along with better tools to help individuals that lost their ability to prospective remembering.

The scarcity of studies and models including time-based tasks can make a good example of a needed improvement. In fact, while theoretical models conceptualize PM tasks as divided into event-based and time-based, most studies focused on investigating the processes and the correlates underlying the former but not the latter (Einstein et al., 2005; Guynn, 2003; McDaniels & Einstein, 2000). Even if they subserve the same goal, which is the fulfilment of the PM intention, time-based and event-based tasks require different resources and processes. In time-based tasks, the fulfilment of the intention depends on our ability to monitor the passing of time, so that the execution of the intended action happens at the appropriate moment. Since external cues signalling the necessity to retrieve the intention may not be available, time-based tasks are considered self-initiated and relying on internal cues. Conversely, event-based tasks are dictated by the appearance of an external cue acting as a reminder of the PM intentions. The difference between the allocation of cues (internal vs external) and the necessity for time-based PM to rely on executive functions such as shifting and controlled monitoring result in time-based tasks usually having a higher cost compared to event-based tasks, even though few time-based studies exist to support this (Henry et al., 2004; Matos et al., 2020). Additionally, a clear dominance of time-based PM tasks was reported by two studies set in a naturalistic environment (Holbrook & Dismukes, 2009; Schnitzspahn et al., 2020). The results obtained in ecological settings indicated a preference for time-based tasks and a remarkable absence of event-based tasks, in contrast to what is usually reported in lab-based studies.

As these two naturalistic studies demonstrated, a gap between lab-based and real-life PM can sometimes exist and PM research must acknowledge it to get the best out of the two approaches. In fact, PM posits as a theoretical construct with a marked “ecological” component, since it manifests in a wide variety of daily tasks, from taking medicines at the right time to changing diapers when it is needed. Importantly, translating real-life PM into experimental paradigms set in laboratories is not always straightforward and can sometimes create contrasting results. The most famous example is offered by the age-PM paradox (Rendell & Thomson, 1999), which consists in older adults performing worse than younger adults in lab-based PM tasks but performing better in naturalistic contexts. Apart from the already-mentioned absence of time-based PM studies, other factors in PM research contribute to this gap between real-life and lab-based PM. Firstly, PM intentions are usually maintained for hours to even days to make our plans work out properly, while lab settings require multiple intentions to be formed and executed in a limited amount of time, so that intention maintenance usually lasts seconds. Secondly, the ongoing tasks on top of which PM tasks are engaged can be far from realistic. For instance, a standard ongoing task is a Lexical Decision task (Rummel & McDaniel, 2019), which bears plenty of advantages as an experiment, but is rarely experienced outside of a lab. Experimental stimuli are crucial in creating a context that resembles real life, and attention to their ecological validity must be utmost.

However, studying PM in laboratories has undoubtedly its perks. It allows researchers to investigate PM efficiently and robustly, as a multitude of PM responses can be observed in a single session. Moreover, it permits to study a wide range of factors relevant to PM, which can be easily manipulated (e.g., type of PM task, focality/saliency of targets, ongoing-task complexity, etc.), while still reproducing the most critical features of real-life PM tasks (e.g., delayed intention-execution, self-initiated retrieval requirements) (Rummel & Kvavilashvili, 2019). Finally, laboratories often include facilities such as neuroimaging and neurophysiological techniques that can be used in naturalistic settings only to a limited extent (see Soto et al., 2018 for an example). Neural dynamics are a fundamental piece of information to understand PM processes and phenomena, as they can offer new insights into PM and its association with other cognitive functions. Furthermore, observing brain activity permits to link theoretical models to biological constraints, so that complete and realistic models of PM can be achieved.

Considering the importance of ecological validity in PM and the advantages offered by experimental settings, the solution may consist in the design of lab-based experiments that maintain a high degree of "naturalness" (Kvavilashvili & Ellis, 2004). Therefore, in the present study we propose a novel pseudo-naturalistic PM paradigm featuring time-based and event-based tasks, with the aim of filling the gap between lab-based and real-life PM. Specifically, the ongoing task involves watching movie excerpts, asking participants to pretend they are in their home watching TV. Instead, the PM task consists in "Virtual cooking", which is cooking different dishes with an imaginary oven by means of a smart TV. In time-based tasks, participants are told that potatoes are cooking in the virtual oven, and they have to press a key of the "smart TV" every two-minutes in order to turn them and prevent them from burning. In event-based tasks, participants are told to regulate the temperature of the virtual oven to correctly cook a cake, by pressing a key every time a red circle appears (the red circle is similar to the light that regulates temperature in ovens). This paradigm sought to create a familiar environment, proposing a situation that participants could have experienced before, while still being in a laboratory. Importantly, movie excerpts also allow the collection of PM responses within blocks of approximately 10 minutes, which is considerably longer than classical paradigms.

This pseudo-naturalistic paradigm is also compatible with the application of EEG technique, which was chosen for its excellent temporal resolution, in the order of milliseconds, and its ability to capture transient and dynamic information while remaining relatively comfortable for participants. Additionally, to increase spatial resolution, a High-Density (256 channels) EEG system was chosen, and individual structural MRI (sMRI) were collected for each participant for subsequent co-registration. To analyse EEG data while also addressing the relatively long experimental blocks featured in this paradigm, it was necessary to find a method that could capture fine-grained transitions intrinsic to the EEG signal embedded in a continuous segment of time. A promising novel approach that was used to satisfy these demands is Hidden Markov Modelling (HMM), an unsupervised machine learning method that can identify mutually exclusive patterns of whole-brain activity without any prior knowledge over the data (Vidaurre et al., 2018). HMM allows segmenting observed data into a set of discrete patterns of activity that are recurrent over a time-series. For instance, if a song (observed data) was given to HMM as input, one of the main outputs would most likely be the chorus (hidden state), because it would occur repeatedly over the song, even if HMM has no information about the concepts of chorus or verses. In this context, HMM can be used to obtain functional states that are recurrent over the EEG time series, so that task-related dynamic activity can be inferred if it is sufficiently stable and coordinated (Quinn et al, 2019; Toffoli et al., 2024). The main advantage of the HMM method is that the resulting functional brain states are not biased by any *a-priori* knowledge, because they are simply a configuration of regions that produced coordinated activity a consistent number of times. In addition, by obtaining functional states of coordinated whole-brain spontaneous activity, this study would constitute the first functional connectivity PM study using EEG.

In summary, the aim of this study consists in investigating time-based and event-based PM tasks with a pseudo-naturalistic design while recording EEG for the implementation of Hidden Markov Modelling. We hypothesize that some of the functional networks inferred from HMM will show the activation of regions significantly involved in PM processes, such as the anterior prefrontal cortex, the parietal cortex, and that states resembling frontoparietal networks may manifest (Cona et al., 2015; McDaniels et al., 2015). Specifically, we expect that time-based PM activity may show a stronger involvement of a network close to the Dorsal Attention Network, while event-based PM activity may result in the engagement of regions of the Ventral Attention Network, as suggested by the AtoDI model (Cona et al., 2015; see Chapter 1.5).

3.2 Materials and methods

3.2.1 Participants

A total of 31 healthy young adults voluntarily took part in the study. All participants had normal or corrected-to-normal vision and expressed their informed consent before the beginning of the study. The experiment was approved by the Ethics Committee of the IRCCS San Camillo Hospital and followed the guidelines of the Helsinki Declaration. The EEG data of 3 participants presented an excessive number of electrical/biological artifacts and were thus excluded from the analyses. Furthermore, in the final steps of pre-processing, 6 participants were excluded because the quality-check parameters necessary for the HMM analyses were not satisfied. In summary, the pre-processing led to the exclusion of 9 participants and to a final sample of 22 participants (9 males; mean age = 30.56, SD = 5.33).

3.2.2 Procedure

The experiment was conducted in a silent room in the Neurophysiology lab at the IRCCS San Camillo Hospital. A session lasted approximately one hour. Participants were first introduced to laboratory settings and were then seated in a comfortable chair approximately 60 cm from a 15-inch display in which tasks were presented. Before the beginning of the experiment, participants read and voluntarily compiled the informed consent. Afterwards, the EEG cap was positioned on the head of the participants while the structure of the experiment was explained.

The experimental paradigm was composed of four distinct blocks. The first block consisted of a resting state condition: participants were instructed to stare at a cross at the center of the screen for 5 minutes, without moving and trying not to let their mind wander. In the meantime, the recording of their brain activity at rest was collected.

In the other three blocks, a 10-minute movie excerpt from The Simpsons Movie was presented, during which participants were asked to relax and to act as if they were at home watching TV. These constituted the only instructions for the wing condition, since the interest was in the activity associated with the passive vision of a video clip and participants just had to watch the clip while trying to stay still. Conversely, the two other blocks were associated with an event-based or a time-based PM task.

The PM instructions for both event-based and time-based tasks were involved with everyday life activities to mimic a realistic situation. Namely, participants were asked to engage in a 'virtual cooking' activity, where they had to pretend to have food cooking in the oven. Then, they would monitor it by noticing a red light appearing on the computer (event-based PM task) or every 2 minutes (time-based PM task). The choice was justified by the fact that watching TV while a dish is cooking in the oven is a common activity that most people have experienced. Specifically, in the event-based PM condition, the ongoing task was represented by watching the TV, while the PM tasks involved remembering to raise or lower the temperature of the oven, depending on the position of a stimulus occurring on the screen, to cook the food properly or to prevent a cake from burning. The appearing stimulus was a pale red circle resembling the light that signals the temperature in the oven. Participants were asked to pay attention to the appearance of the stimulus below or above the center of the screen, while watching the movie excerpt, and to virtually change the temperature by pressing the corresponding key (either the up or down arrow) as soon as they noticed the red circle. The position of two subsequent PM cues (up, down) and the intervals between them (1.5, 2, and 2.5 minute) were counterbalanced across participants. In the time-based PM condition, in addition to the ongoing task, participants were asked to turn the potatoes in the oven every two minutes, by pressing either the up or bottom arrow key. When the key was pressed, a red digital clock was displayed for two seconds, reporting the time at which they “turned the potatoes” (the time would always reset after a 2-minute interval). Furthermore, participants were allowed to monitor the passage of the time by pressing either the up or bottom arrow key (the opposite arrow key to the one used for turning the potatoes). Doing so, a white digital clock would appear for two seconds at the center of the screen. Participants could check the clock for a maximum of three times within each 2-minute interval, to limit movement artifacts in the EEG signal. The PM and the monitoring keys were counterbalanced across participants.

Before the beginning of the time-based PM task, a 1-minute practice version was presented to participants to make them familiarize with the task and with the appearance of the timers.

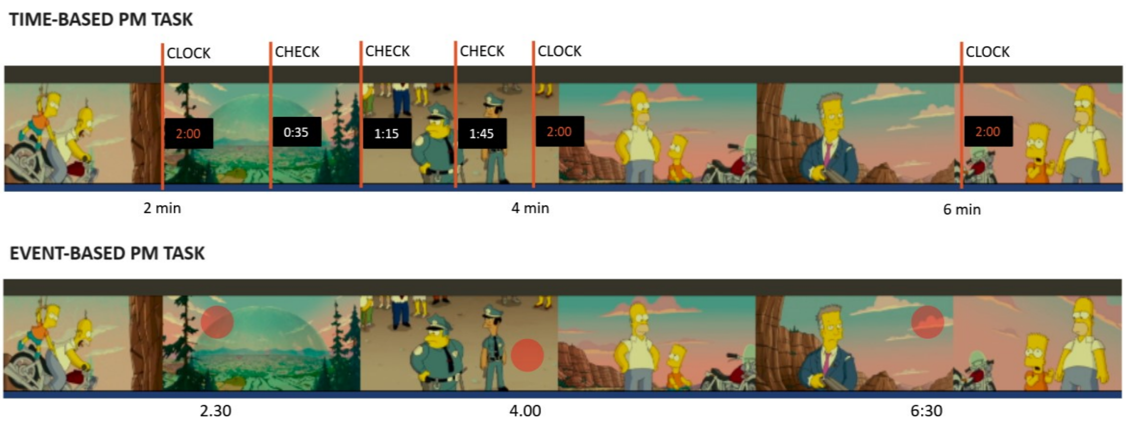


Figure 3.2.1 An illustration of the experimental design.

The PM tasks involved a total of 5 PM cues for each condition. Participants were not aware of the duration of the clips. The three movie excerpts used in the Passive Viewing, event-based, and time-based conditions were counterbalanced between participants. While the Passive Viewing condition was always presented right after the resting state condition, the order of presentation of the event-based and the time-based PM blocks was counterbalanced between the third and the fourth positions.

3.2.3 EEG data pre-processing

Neurophysiological data were acquired using a High-Density (256 channels) EEG system (EGI, Electrical Geodesic Inc). Data were sampled continuously during each experimental condition with a sampling rate of 1000 Hz. Additionally, neuroimaging data were collected using MRI Philips Achieva (1.5 Tesla). Specifically, a T1-weighted whole-head anatomical image was collected for each participant to obtain data necessary for the realization of an individual structural MRI.

The pre-processing of the EEG signal was conducted using a semi-automatic pipeline in MATLAB created in the Padua Neuroscience Center. First, recordings were down sampled to 250 Hz and filtered in the 1-30 Hz band. Secondly, EEG recordings were visually inspected to identify and remove bad segments. Additionally, channels whose activity was considered too different from the neighbouring sensors or presenting evident electrical artifacts were manually removed. Afterwards, MARA Independent Component Analysis (ICA) approach was used to identify components corresponding to biological or electrical noise. The pipeline returned a list of 60 components labelled with a suggested source, although the final decision over the removal of components was always corroborated by visual inspection. Finally, two variations of Artifact Subspace Reconstruction (ASR) were used to smooth and adjust the quality of the signal.

3.2.4 Co-registration

Co-registration was performed in SPM12 (Henson et al., 2019). Firstly, the pre-processed EEG file was uploaded, along with a file containing the electrodes coordinates in the same coordinate system as the individual sMRI. These two files were used to create a sensor space composed by the electrodes of the EEG cap. Secondly, a head model was constructed by uploading the individual sMRI. Thereafter, the nasion and the two auricular points were chosen as fiducial points, and co-registration was performed. Finally, a Boundary Element Method (BEM) forward-model was implemented.

3.2.5 Hidden markov modelling

The OHBA Software Library (OSL v2.0.3; OHBA Analysis Group, 2017) and OHBA's Hidden Markov Model Library (HMM-MAR; Vidaurre et al., 2016) were used to perform the final steps of pre-processing. Firstly, a covariance matrix was computed across the whole-time course for each participant and the obtained matrix was regularized using PCA rank reduction. A minimum variance beamformer was then applied to compute a whole-brain source-space activity in an 8mm grid. Afterwards, a 38-node cortical parcellation was used to reduce the EEG data following the approach used by Toffoli et al. (2024). Finally, the parcellation was 13inarized to estimate a single time-course per node from the first principal components across voxels.

Prior to the Hidden Markov Model initialisation, detrending, signal standardization and corrections for signal leakage were applied. First, detrending removed linear trends in the data for each channel separately; second, participants' concatenated time-courses were standardized. Next, signal leakage introduced by source reconstruction with zero temporal lag was corrected using multivariate orthogonalization (Colclough et al., 2015). Then, the

Hilbert transform was applied to estimate the absolute signal amplitude estimation for each source at each time point.

After the final steps of pre-processing, the HMM-MAR toolbox was used to compute a set of functional brain states that were recurrent in the EEG time series, considering all three conditions as one concatenated dataset. Then, an index of fractional occupancy (i.e., the fraction of the total time spent in a specific state) was computed for each state and for each participant.

3.2.6 Statistical analyses

Statistical analyses have been performed using JASP, an open-source software for statistical analysis (Version 0.19; 2024).

Behavioral analyses

The accuracy of the participants was collected in both event-based and time-based PM tasks. For the event-based PM task, a response was considered correct if participants were able to successfully detect the PM cue and press the key corresponding to the stimulus' position (i.e., the up arrow if the stimulus was above the center of the screen; the down arrow when it was below the center of the screen). In the time-based PM condition, a response was considered correct if they pressed the correct key within a range of ± 6 seconds from the target time (2 minutes). It corresponds to the 10% of the total target time's interval, in accordance with the methods of Laera et al. (2021). The accuracy between the two tasks was confronted with a repeated measure ANOVA (rm-ANOVA), and an effect size was calculated using partial η^2.

Fractional Occupancy analyses

For each state, descriptive statistics over fractional occupancy (i.e., the fraction of the total time spent in a specific state) were computed for all conditions and for the 3 different block conditions separately (Passive Viewing, Event, Time). Then, the presence of effects for block conditions was investigated using rm-ANOVA for each state, so that each rm-ANOVA presented a 1 (FO) x 3 (Condition: PV, Event, Time) within-subjects design. An effect size estimate for each rm-ANOVA was calculated using partial η^2. Finally, post-hoc analyses were conducted to investigate the effect of each factor separately, with the Bonferroni correction applied to compensate for multiple comparisons.

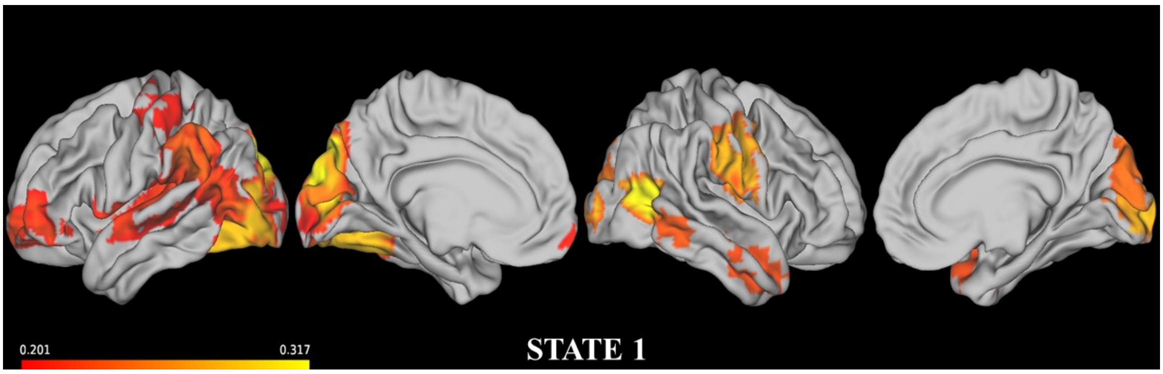
3.3 Results

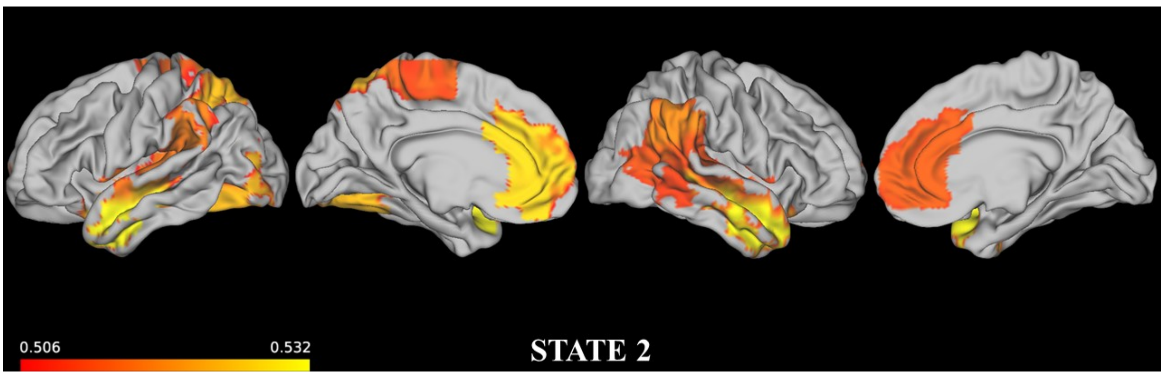
3.3.1 Hidden markov modelling

The whole EEG time-course, with all three conditions concatenated into a single dataset, was decomposed into six separate states, similarly to the method used in Toffoli et al. (2024). The decision over the number of states was based on the fact that, for M/EEG data, this number is usually between 2 and 10 (Baker et al., 2014; Quinn et al., 2018), and because it allowed the identification of distinct spatiotemporal patterns while limiting a redundancy effect caused by higher number of states.

The resulting six states can be observed in *Figure 3.3.1*. States represent the EEG signal of all participants (with the three conditions considered as one concatenated dataset) divided into stable, recurrent patterns of activity that can effectively explain the original data. Each state presents a heatmap with the average activation of the 38 parcels the brain cortex was divided in. Activations are plotted on a red-to-yellow color scale. State 1 showed activations primarily in occipital areas, involving bilateral Middle Occipital Gyrus (MOG), Superior Occipital Gyrus (SOG) and fusiform gyrus, with activations over the

Supramarginal Gyri (SMG). These areas are all significantly involved with the visual system, suggesting that State 1 may be representing a “visual network”. Additionally, weaker activity over temporal and frontal regions was present. State 2 showed activations over frontal areas, involving Anterior Cingulate Cortex (ACC) and prefrontal cortex, along with activations over the superior temporal gyrus and over parietal areas. State 3 and 4 showed strong activations in the precuneus, the cuneus and the Posterior Cingulate Cortex (PCC), which constitutes a pattern overlapping the posterior components of the Default Mode Network (DMN), a network deeply involved in memory-processes and internal processing. State 5 showed activations of the PCC and the precuneus as well, along with activity over the right angular gyrus, indicating an even greater similarity with the DMN configuration. State 6 showed activations in occipital, parietal areas and dorsal frontal areas, involving areas of the Dorsal Attention Network (DAN) such as bilateral intraparietal sulcus, bilateral premotor areas, left frontal eye fields (FEF), and left Dorsolateral Prefrontal Cortex (DLPFC).





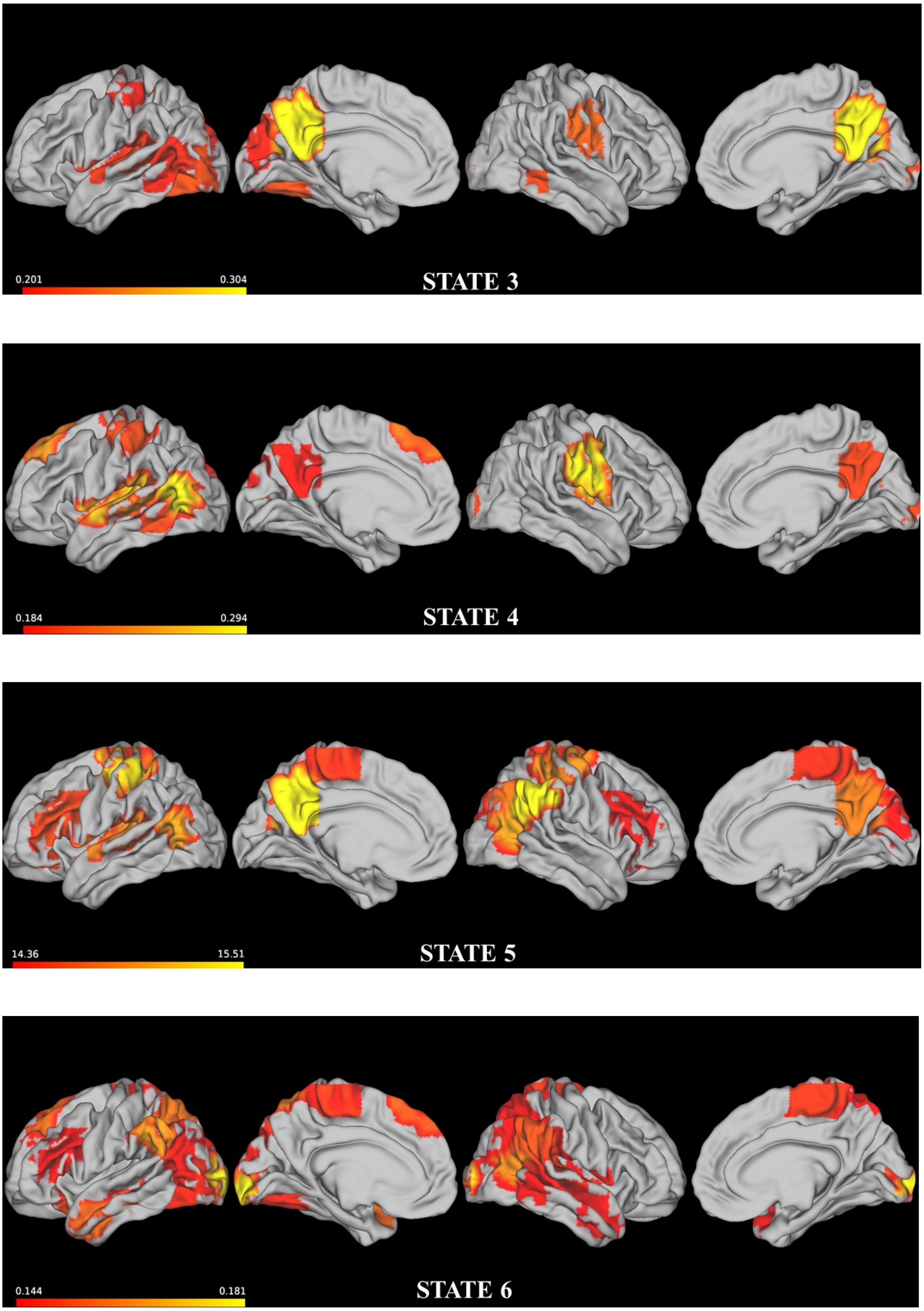


Figure 3.3.1 The heatmaps of the six Hidden States obtained with HCP workbench GUI. As evident in the colorbar, the strength of the activations in each state is plotted in a scale ranging from red (weakest reported activations) to yellow (strongest activations).

3.3.2 Behavioral analyses

The difference in the accuracy rates between the Event and Time condition was confronted with a repeated-measure ANOVA. It revealed a significant difference between the accuracy rates ($p = 0.004$; $\eta^2p = 0.240$). Participants were more accurate in detecting the PM cues in the Event condition ($M = 93.55$; $SD = 11.98$) condition than in targeting the 2-minute interval in the Time condition ($M = 74.84$; $SD = 33.05$).

3.3.3 Fractional occupancy analyses

Descriptive statistics of Fractional Occupancy are summarized in *Table 1*.

In the concatenated dataset, participants spent the most time in state 6 (i.e., the state with parietal and dorsal frontal activations, with a pattern similar to the DAN network), with a mean FO of 0.318 (0.1), indicating that, on average, participants spent 32% of the total time in this state. Conversely, participants spent the least time in State 5 (i.e., the state that resembled DMN) with a mean FO of 0.032 (0.012), indicating that, on average, 3% of the total time spent in the state. State 1, 3 and 4 all showed a mean FO of approximately 0.17/ 17%, meaning they were visited a similar proportion of time across conditions, while State 2 showed a mean FO of 0.136 (0.021).

Considering data divided into 3 subsets depending on condition, State 6 and State 5 remained the most and less visited states, respectively. Interestingly, in the Passive Viewing condition, the mean FO in states 1, 3 and 4 was higher than in the Event and Time condition. Conversely, the pattern was the opposite for State 5 and 6, in which both PM conditions had a higher mean FO, with the Time condition showing the highest mean FO for both states.

Fractional occupancy						
	State 1	State 2	State 3	State4	State 5	State 6
Mean	0.171	0.136	0.173	0.170	0.032	0.318
Std. Deviation	0.038	0.021	0.041	0.039	0.012	0.100
Minimum	0.081	0.094	0.087	0.090	0.011	0.142
Maximum	0.242	0.190	0.251	0.262	0.057	0.547
Passive Viewing Mean	0.187	0.138	0.183	0.181	0.028	0.283
Event Mean	0.167	0.140	0.168	0.167	0.031	0.327
Time Mean	0.160	0.131	0.167	0.161	0.036	0.345

Table 1 The table presents the descriptive statistics for fractional occupancy, including mean FO, standard deviation, minimum and maximum FO value for each of the six states considering all conditions. The last three rows report the mean FO for each state considering the three conditions separately.

The six repeated-measure ANOVAs showed significant effects for State 1, State 5 and State 6, while they did not reach a significant value for State 2, 3 and 4 ($p > 0.05$) (see *Figure 3.3.2*). Specifically, a robust effect was found for the FO of State 1 ($p = 0.001$; $\eta^2p = 0.280$), with participants in the Passive Viewing condition spending on average 2% more time in State 1 compared to the Event condition and 2.8% more compared to the Time condition. A significant effect was also found for State 5 ($p = 0.006$; $\eta^2p = 0.217$), as well as for State 6 ($p = 0.006$; $\eta^2p = 0.216$), with participants in the Time condition spending on average 0.5% more of their total time in State 5 compared to the Event condition and 0.8% more compared to the Passive Viewing condition, and participants in the Time condition spending on average 2.5% more of the total time in State 6 compared to the Event condition and 7% more compared to the Passive Viewing condition.

Post-Hoc analyses revealed that for State 1, both the Time and Event conditions differed significantly from the Passive Viewing condition in terms of FO (*pbonf* = 0.006 and *pbonf*= 0.009, respectively), but no significant difference was found between the two conditions. For State 5, FO in the Time condition and in the Passive Viewing condition resulted significantly different (*pbonf* = 0.014), with other conditions not reaching a significant value. Finally, for State 6, FO was significantly different for Time condition and Passive Viewing condition (*pbonf* = 0.014), and for the Event condition and Passive Viewing condition (*pbonf* = 0.011).

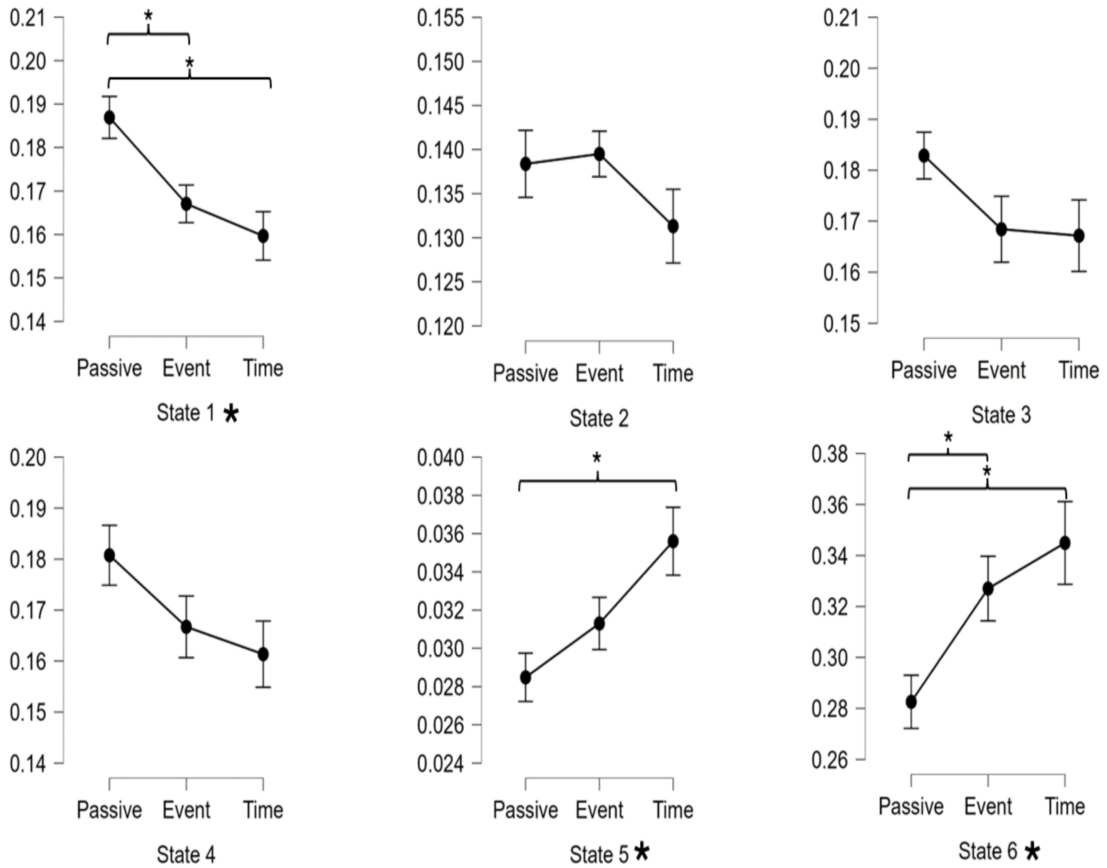


Fig 3.3.2 This figure shows the mean FO of different block conditions for all the six states, with FO value on the Y axis and the Passive Viewing, Event and Time conditions on the X axis. An asterisk is present next to State 1, 5 and 6, indicating that the three conditions showed a statistically significant difference after a rm-ANOVA for those states. Additionally, an asterisk was also used to signal statistically significant differences between two conditions after post-hoc analyses with Bonferroni correction for multiple comparisons.

3.4 Discussion

In the present study, we implemented a pseudo-naturalistic design with the aim of investigating connectivity patterns associated with time-based and event-based prospective memory, establishing, to our knowledge, the first study to use EEG and HMM to investigate functional connectivity in the context of Prospective Memory (PM). Results from Hidden Markov Modelling (HMM) and from the repeated measures-ANOVA (rm-ANOVA) analyses led to interesting findings. Namely, the six brain states, which correspond to recurrent pattern of activity intrinsic to the collected EEG data, showed prominent activations from some key areas of PM processing, including regions of the Dorsal Attentional Network (DAN) and the Default Mode Network (DMN). Additionally, the proportion of time spent in 3 out of 6 states was significantly different among conditions, with the states that presented the largest number of regions associated with PM being visited the most when participants were in PM conditions.

After performing rm-ANOVA on the fractional occupancy (FO) between the Passive Viewing, Event and Time conditions, it was found that the FO of State 1, 5 and 6 were significantly different between these three conditions. State 1's prominent activations were mostly localized in the occipital gyri, especially in the bilateral middle occipital gyrus (MOG) and superior occipital gyrus (SOG). These regions are part of the occipital complex, which is deeply involved in the visual processing of objects (Naidich et al., 2013). Therefore, these activations may signal a state of engagement towards the visual content proposed by the movie excerpts. Additionally, activations in this state were found in the fusiform and supramarginal gyrus, regions that are well-known for their involvement in face processing and empathy (Kawasaki et al., 2020; Silani et al., 2013), further suggesting the association between State 1 and engagement to the movie clip. Generally, State 1 may represent a state of visual attentional engagement with the ongoing activity, as many areas of the visual pathway were strongly involved. The rm-ANOVA showed this state to be significantly different among conditions, and post-hoc analyses revealed that participants visited State 1 considerably more during the Passive Viewing condition compared to the PM conditions. This difference may be interpreted as a greater engagement with the ongoing activity in the Passive Viewing compared to the Event and Time conditions, because the cognitive resources directed towards intention maintenance in the PM conditions may have limited full engagement with the ongoing activity.

State 5 involved strong activations in posterior and medial portions of the parietal lobe. Particularly, it showed a significant contribution from Posterior Cingulate Cortex (PCC), the precuneus and the right angular gyrus, which are key regions of the Default Mode Network (DMN). The DMN plays a fundamental role in human cognition, as it activates when we are not engaged in other activities (hence *Default*), and it has been reported to mediate internal processing, mind-wandering, social cognition, semantic, episodic and autobiographical memory. (Fox et al., 2015; Menod, 2023; Buckner et al., 2004). In a recent study by Hsu and colleagues (2022), the DMN has been shown to play an important role in PM, as the functional connectivity of the precuneus/PCC with frontal and parietal regions significantly correlated with PM performance in both normal and pathological aging. Furthermore, in the AtoDI model proposed by Cona and colleagues (2015), PCC would support bottom-up mechanisms necessary for switching from the external cue to the internal representation of the PM cue and the intention stored in memory. Then, it is important to note that State 5 was the least visited state, as participants spent an average of 3% of total time in it. This could indicate that the state may be providing a configuration that supports an isolated phenomenon, which may occur rarely but with a significant impact. Taken together, the spatial and temporal characteristics of State 5 may suggest a role in intention retrieval, perhaps supporting the moment we realize the link between the external/internal cue and the intention we previously encoded. Hypothetically, the strong activations of the PCC and DMN regions in State 5 could indicate an association with memory processes and specifically with memory retrieval, while the rare occurrence of the state may reflect the limited frequency of intention retrieval. This interpretation is supported by the statistical analyses of FO, in which the three conditions were found to be significantly different in terms of time spent in State 5. In fact, post-hoc analysis revealed that participants in the Time condition visited this state significantly more than those in the Passive Viewing condition. A greater use of State 5 by participants in the Time condition would fit well with a "Retrieval-State" interpretation, because the absence of explicit external cues may require additional resources to retrieve the intention internally and thus a greater occurrence of the activation pattern displayed in State 5.

State 6 involved primarily activations in frontal and parietal areas, specifically in regions that are part of the Dorsal Frontoparietal/Attentional Network (DAN). The DAN network is responsible for top-down control and goal-directed attention and is composed of the Dorsolateral Prefrontal Cortex (DLPFC), frontal eye fields (FEF), premotor regions, precuneus, and intraparietal sulcus (Corbetta and Shulman, 2002). Given the activations of bilateral intraparietal sulci, premotor areas, and left DLPFC and FEF, it is possible to assume an overlap between the DAN and State 6. The importance of DAN in PM has been widely discussed in the scientific literature, with a crucial role for the network proposed both in the Dual Pathways theory and in the AtoDI model (McDaniels et al., 2013; Cona et al., 2015; see Chapter 1.5 for further details over the two models). According to these two theoretical models, DAN primarily supports the maintenance of PM intention, as well as the monitoring of the passage of time or the monitoring of potential cues in the environment (i.e., Strategic monitoring). During strategic monitoring, a state of readiness is maintained by keeping the representation of the intention active in working memory.

By allocating cognitive resources to maintain this “retrieval-mode” through the activation of the DAN, it is possible to effectively monitor time or the occurrence of external cues, to retrieve the associated intention and to appropriately execute it. The role of the DAN in PM is confirmed by the results of our investigation, which revealed a recurrent dorsal frontoparietal configuration within State 6. Additionally, the importance of the DAN and strategic monitoring is highlighted by the fact that State 6 was the most visited state, with participants spending a third of their total time in it. A significant difference was observed in the FO of the three conditions from the rm-ANOVA, and post-hoc analyses showed a significant preference for State 6 during the Time condition. Finally, participants in the Event condition spent significantly more time in State 6 compared to the Passive Viewing condition. The association between time-based PM and State 6 confirms our initial hypothesis and supports the proposal of Cona and colleagues (2015), which suggests that time-based PM is more significantly supported by strategic monitoring and the DAN compared to event-based PM. This study presents the first EEG functional connectivity evidence of the DAN's involvement in PM.

3.5 Conclusions

The current study investigated EEG functional connectivity patterns of prospective memory with a Hidden Markov Modelling approach, using a lab-based experimental paradigm characterized by a pseudo-naturalistic design. Our initial hypothesis regarding the functional involvement of the Dorsal Frontoparietal/Attention Network in PM was confirmed, as one of the six hidden states, State 6, presented a large overlap with the network while being the most visited state. Furthermore, a “retrieval-state” reflecting a configuration supporting the retrieval of the PM intention was also found in State 5, indicating a functional importance for the Default Mode Network in PM. Additionally, the re-allocation of attentional resources from an external to internal focus during PM tasks was confirmed by participants spending less time in the "visual engagement-state" (i.e., State 1) during PM conditions. The results did not confirm our initial hypothesis over the involvement of the Ventral Attention Network in the retrieval phase and in event-based tasks. The absence of this association, which was present in other studies, could result from the fact that this study proposed a novel, pseudo-naturalistic design to provide the most realistic conditions to study PM in a lab setting. Moreover, it has been the first EEG functional connectivity study in PM research to date, therefore many factors distance this project from previous literature and empirical differences could be caused by the novelty of the method. Indeed, future studies implementing ecological design and functional connectivity are needed to confirm or confute the results we obtained. Finally, the hidden states that were more visited during PM conditions always had participants in the Time condition visiting them the most, indicating the importance of time-based processes and the necessity of more studies featuring both time-based and event-based tasks.

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