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EEG Correlates of Spatial Navigation in Patients with Right Hippocampal Lesion: A Mobile Brain/Body Imaging (MoBI) Study

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Abstract

Spatial navigation is a fundamental cognitive function that consists of different cognitive processes such as learning and decision making as well as physical locomotion. In the literature, there is a tendency to focus on cognitive elements of human spatial navigation while the presence of the body and embodied agents are neglected. Being that sensory and motor systems are integrated into the brain mechanisms according to embodied cognition theory, integrating physical movement into navigation research is crucial to investigate brain dynamics underlying human spatial navigation. Using Mobile Brain/Body Imaging (MoBI) approach, this study aims to understand electroencephalographic (EEG) activity during spatial navigation in actively moving humans. In the present study, 27 participants (9 patients with right hippocampal lesions and 18 healthy matched controls) performed a spatial navigation task in a human virtual analogue of the Morris Water Maze. Subjects were tested in both desktop and MoBI setups. In both study setups, frontal-midline (FM) theta (4-8 Hz) oscillations were examined with high-density EEG. In MoBI, EEG activity was recorded synchronously to motion capture, and the virtual environment was presented by a head-mounted display. EEG data were analyzed by using the event-related desynchronization/synchronization (ERD/ERS) method. Association between FM theta activity and spatial navigation performance was analyzed. Further, we also tested the effect of the study setup on the participant group. By comparing desktop and MoBI setups, the study aims to reveal how dynamics of the brain with hippocampal lesions change under action during spatial navigation compared to a healthy brain.

Keywords: spatial navigation, EEG, hippocampus, mobile brain imaging, theta power

Chapter 1: Introduction

1.1 Spatial Navigation

As one of the most fundamental dimensions experienced by perception and cognition, the very idea of space has been central to debates since the inception of philosophy (Postma & Koenderink, 2016). In 1781, Kant wrote "Space is a necessary a priori representation that underlies all outer intuitions (Der Raum ist eine notwendige Vorstellung a priori, die allen äußeren Erscheinungen zum Grunde liegt)". According to him, every material object that we perceive in the outer intuition domain occupies a place in the space and possesses a specific shape (Stolorow, 2005). As the space is occupied by objects, taking their positions into account is essential to interact with the environment and navigate (Herweg & Kahana, 2018; Tommasi & Laeng, 2012).

Spatial navigation can be described as a process by which organisms use different strategies and cue sources to travel to a specific location through coordinated and goal-directed behavior (Brodbeck & Tanninen, 2012; Montello, 2005). From the lower evolutionary level to primates, animals are required to navigate from one location to the next efficiently and accurately in both familiar and new environments for survival. Although all mobile animals share some similarities in terms of basic navigation strategies, different animal species possess some differences as they develop their own strategies suitable for their distinctive nervous system structure, their environment, and their survival instincts (Ito, 2018; Kelly & Gibson, 2007). For example, salmon and sea turtles use the magnetic field of the Earth as a directional cue to return back to their nest area after a long period of time while desert ants find their nest location by estimating the distance and direction according to their movement (Lohmann et al., 2008; Wehner & Wehner, 1986). On the other hand, in humans, spatial navigation is a complex cognitive process that is subserved by a complex system that requires the engagement of different processes including not only spatial representation but

also higher order cognitive processes as well as lower order processes common with the other species (Guariglia & Pizzamiglio, 2006).

In The Cambridge Handbook of Visuospatial Thinking, Daniel R. Montello (2012) discusses human spatial navigation in terms of two key components as locomotion and wayfinding. While he defines locomotion as a coordinated body movement to the proximal surroundings, he describes wayfinding as a coordinated decision making and planning process to both the local and distal surrounds. However, according to him, wayfinding is more related to distally coordinated planning, whereas locomotion mostly consists of proximally coordinated movements. In 1986, Pick and Palmer noted that "Locomotion is guided both perceptually by current sensory information and cognitively by previously acquired information". Unlike Pick and Palmer, Montello (2012) approaches the concept of locomotion as a process that is guided by mostly sensory information, and he approaches wayfinding as a process that is guided by cognitive information processing. Therefore, he differentiates these two components and noted that while action and perception systems are involved during the locomotion component of navigation, planning and memory are more involved during wayfinding.

It is important to note that clear distinction between two components can be hard to make as they are part of an integrated system that can be separated only conceptually (Montello & Sas, 2006). In the literature, some researchers tend to describe the term "navigation" synonymously with "wayfinding", and the locomotion component is disregarded while investigating the navigation process especially among human subjects (Montello & Sas, 2006; Taube et al., 2013). However, even though the amount of involvement of these components can vary, both components are essential for the vast majority of spatial navigation (Montello, 2012). Therefore, it is important to integrate both components to the experimental setups to study human spatial navigation.

1.1.1 Locomotion

Human locomotion is the action of the body that moves around an environment which can be aerial, aquatic, or terrestrial. It refers to the coordinated real-time movements of the body parts which are controlled by the neuro-musculoskeletal system (Medved, 2001). During locomotion, the movement is toward the proximal surroundings that can be accessed by the motor and sensory systems (Montello, 2012). Locomotion is an important part of the human spatial navigation. While locomoting, we process and acquire knowledge and information about the environment that we are moving around as well as information about our body at a given moment such as the position of our body and head (Montello, 2012; Rossignol et al., 2006). In most of the studies in the literature, navigation is investigated with virtual movements in which physical locomotion is missing (Ekstrom et al., 2018). These study setups lack of providing relevant information related to the body to be used as a cue (Taube et al., 2013). Moreover, even though it is possible to acquire knowledge about the virtual environment, the obtained information is inconsistent with the self-motion cues (Wang & Spelke, 2002). Therefore, investigating spatial navigation without physical locomotion provides only an incomplete picture of the human spatial navigation (Taube et al., 2013).

Information obtained from different sensory systems during locomotion plays an essential role in human spatial navigation (Nardini & Cowie, 2012) and can be divided into two categories as idiothetic and allothetic information/cues in terms of whether it is acquired internally or externally (Loomis et al., 1999). Vestibular cues, proprioceptive cues, which are the sensory information derived from the joints and muscles, and motor efferent signals are internal/idiothetic cues that are generated by self-motion of the body in the space. On the other hand, during locomotion, we also benefit from external environmental information which is called allothetic cues. They indicate the outside world inputs such as auditory and visual information (Loomis et al., 1999). Even though unimodal contribution of these

idiothetic and allothetic cues sheds light on our understanding of the navigation mechanisms, spatial navigation is a multimodal process in which different sensory modalities are integrated for necessary calculations during different stages of the process (Karimpur & Hamburger, 2016). Revealing the multimodality of navigation is crucial to understand the real nature of this complex process as in everyday life, humans encounter continuous multimodal inputs which can be contradictory or concurrent to each other from various senses and need to successfully integrate this information (Ehinger et al., 2014).

Visual cues are generally considered as one of the most critical environmental information that facilitates locomotion as it plays an important role in updating the spatial relationship with the environment and ensuring correct orientation and stable balance (Patla, 1997). Although a number of studies have demonstrated that locomotion can be carried out accurately without vision (Farrell & Thomson, 1999; Sun et al., 2004; Terrier & Reynard, 2015), visual perturbation and deprivation can alter the length and frequency of stride, walking speed and kinematic response (e.g., increased knee flexion in foot contact and backward leaning position of the trunk) as more cautious walking strategy is adapted (Hallemans et al., 2009a, 2009b). These findings suggest that vision plays an important role in controlling dynamic stability and balance which are the fundamental motor skills for locomotion (Iosa et al., 2012).

Another most important facilitatory sensory systems to the locomotion and navigation in humans is the vestibular system (Bent et al., 2005). Even though the vestibular system does not conduct the locomotion itself, it is crucial for functions like updating eye position according to head movements, computing the head direction, informing the brain for the position of the head as well as balance which is a prerequisite for most of the body movements (Ekstrom et al., 2018). The vestibular system involves three semicircular canals that are critical for head direction computation in the inner ear. These canals are filled with

extracellular fluid that moves with the movement of the head and they are orthogonal to each other. Because of their perpendicular positions to each other, all possible orientation in the three-dimensional space is covered by them; thus, any angular direction of the head will activate one of the semicircular canals in the inner ear leading to the detection of head rotation direction (Ekstrom et al., 2018; Goldberg et al., 2012). Moreover, the vestibular system is also evolved to detect the linear motions of the head. While semicircular canals are responsible for the detection of the angular movement, two otolith organs in the vestibular system which are utricle and saccule detect the linear motions. The upper layer of the otoconial membrane consists of calcium carbonate crystals which lead to a greater density in the otoconial membrane than the outside. Thus, any linear head movement results in an opposite displacement of the otoconial membrane relative to the skull because of the density difference (Goldberg et al., 2012).

It is possible to examine the significance of vestibular cues together with other idiothetic cues in spatial navigation tasks by comparing performance on different measurement tools and study setups (Chance et al., 1998). Conducting spatial navigation research in real-world settings can be challenging due to significant limitations. In real-world navigation studies, it is hard to control the extent of the exposure to the tested environments which is called familiarity effect (Ekstrom et al., 2018). As the level of the exposure to the environment may vary among different participants and it is hard to discriminate between exposure levels and the types, it may mislead the results. Therefore, using virtual environments can offer a solution to overcome such limitations as it provides controlled laboratory circumstances (Ekstrom et al., 2018; Kuliga et al., 2015).

In the literature, different study setups for virtual environments are used to study spatial navigation in humans such as desktop-based virtual environment, walking in place, joystick controlling, teleportation, and redirected walking in virtual reality (Kim et al., 2021).

There is considerable evidence in the literature indicating that study setups with poor idiothetic cues demonstrate lower navigation performance results compared to full physical movement conditions. Langbehn and his colleagues (2018) designed a study to evaluate three locomotion methods used in virtual reality and found that participants outperform in redirected walking in comparison to teleportation and joystick locomotion which do not involve physical motion. Other experiments which compare physical motion and joystick navigation in virtual reality have also drawn similar conclusions (Riecke et al., 2010; Ruddle & Lessels, 2006). Although in Human Walking in Virtual Environments book, Waller and Hodgson (2013) remark that despite the involvement of idiothetic systems in immersive VR, idiothetic cues are limited and not accurate as much as real-world walking, Ruddle and Lessels (2009) found comparable performance results for immersive VR and real world conditions. Moreover, their findings also suggest that navigation performance is worse in virtual locomotion setups compared to physical motion in both VR and real-world environments. In the literature, it was also found that vestibular loss is associated with impaired spatial navigation (Brandt et al., 2005; Brandt & Dieterich, 2017; Hüfner et al., 2007; Nuti et al., 2017w; Smith et al., 2005). Therefore, these findings provide evidence for the importance of proprioceptive and vestibular cues, which can be acquired through physical locomotion for spatial orientation and navigation.

So far, the locomotion component of navigation and the importance of sensory modalities obtained during physical locomotion is discussed. Although sensory information acquired during movement contributes to the locomotion component itself, it is also utilized for the cognitive processes during wayfinding as these two components of navigation are interconnected to each other (Darken & Paterson, 2001; Symonds et al., 2017). Embodied cognition theory also emphasizes this effect of locomotion on wayfinding and their interaction (Woods et al., 2020). According to embodied cognition theory, cognitive processes are

directly influenced by the motor and sensory processes (Foglia & Wilson, 2013). This theory approaches the brain as a part of a broad system that also involves the body and the environment and emphasizes their interaction instead of considering the brain as a system that mainly creates representations of the outside world and uses that knowledge for behavioral outputs (Varela et al., 2016). Embodied cognition theory claims that cognition is directly affected by our experience and interaction with the physical world. Therefore, the way we think is shaped by our bodily experiences (Schneegans & Schöner, 2008). Accordingly, the construction of our experience of space is also strongly influenced by sensory-motor systems and the interaction of our body, brain, and the environment (Rohrer, 2007). Thus, locomotion is one of the key components of spatial navigation as it is an embodied process, which has roots in our actions (Konig et al., 2018).

In the literature, there is a tendency to focus on cognitive elements of human spatial navigation while the presence of the body and embodied agents are neglected (Symonds et al., 2017). However, cognitive elements of navigation, which can be considered under the wayfinding component of navigation, can be understood most correctly when embodied activity including re-orientating and physically moving the body is involved (Lueg & Bidwell, 2005). For example, instead of choosing the shortest route, people tend to choose longer and more comfortable paths in everyday life. This can be only explained by considering the body at the center of the navigation experience as wayfinding strategies are affected by the sensory experiences and the interaction with the environment (Symonds et al., 2017). According to Gramann and his colleagues (2011), to study human spatial navigation, it is important to involve natural movement, which provides idiothetic information, and allow participants to freely move and interact with their environment for receiving information from all relevant modalities.

To sum up, it can be concluded that during locomotion, the information about linear and angular head movement together with the other sensory information such as visual and proprioceptive are used to calculate the current and subsequent positions in the space for successful locomotion (McNaughton et al., 2006). Although locomotion is possible without all idiothetic and allothetic cues, locomotion, as well as navigation, are multimodal processes in which integration of different multisensory information contributes (Berthoz & Viaud-Delmon, 1999). Furthermore, this multimodal information that is acquired during locomotion by the different sensory systems is also integrated and utilized during wayfinding for later computations (Akay & Murray, 2021).

1.1.2 Wayfinding

Wayfinding refers to a goal-directed and planned behavior in an environment for exploring, searching, and route planning from one place to a goal destination (Farr et al., 2012). In wayfinding, cognitive processes such as information processing and decision making play a critical role as it requires solving some problems such as which route should be chosen and where the distal landmark is located relative to another landmark, etc. (Montello, 2012; Iftikhar et al., 2020). During wayfinding, different forms of sensory information that are acquired during locomotion are integrated to make representations of the environment for different cognitive strategies and store them in the memory for later recalls (Passini, 1980).

There are two fundamental representation forms related to the navigated environment that are used in human spatial navigation as egocentric and allocentric representations (Gramann, 2013). Egocentric representation indicates the spatial location of the individual in the environment, and it encodes spatial information of other objects in the environment relative to one's position. Therefore, egocentric representation depends on one's current position. On the other hand, in allocentric representation, spatial information of the landmark positions is encoded relative to each other (Ekstrom et al., 2018). Yet, successful navigation

does not include the engagement of one single representation strategy (Bosch et al., 2010). Instead, for successful navigation, combining and switching different spatial reference frames efficiently depending on the requirements of the navigation task is necessary (Gramann et al., 2012). Interestingly, there is great variability between individuals in terms of the preference of egocentric/allocentric strategy usage during navigation (Colombo et al., 2017; Marchette et al., 2011).

In humans, two important mechanisms which are path integration and cognitive map play an essential role in the spatial navigation process and they can be considered under the wayfinding component of navigation (Allen, 1991; Montello, 2012). While path integration strongly influences egocentric representations, it is possible to approach cognitive map as it is more related to allocentric representations (Ekstrom et al., 2018). Nevertheless, both representation systems interact with each other during navigation and both cognitive map and path integration mechanisms involve allocentric and egocentric reference frames (Ekstrom et al., 2014).

Path integration can be defined as an ability to compute updated positions in the space by keeping track of self-motion and traveled distance relative to start location (Fortin, 2008). Necessary information to calculate updated position is derived from idiothetic cues generated by locomotion; therefore, path integration is sometimes also referred to as internal cue processing. However, external cues such as optic flow are also used for path integration to correct errors (Savelli & Knierim, 2019). Besides internal cues and visuospatial knowledge, path integration also requires working memory to encode and maintain path integration signals (Chrastil et al., 2016).

Path integration has some limitations; therefore, it is generally considered a primitive form of the navigation system (Wang, 2016). Since spatial navigation abilities of humans and other animals go beyond these limitations, navigation abilities exceeding path integration

mechanism are generally believed to rely on cognitive map mechanism (O'Keefe & Nadel, 1978; Tolman, 1948; Wang, 2016). Cognitive map which refers to a neural representation of relative locations in a traveled environment was firstly proposed by Tolman (1948) to explain navigational behaviors of rats (Breed, 2012). He proposed that spatial knowledge of traveled routes are combined to form an integrated map of the environment. Apart from traveled paths, information about the routes that are not directly traveled is inferred from the spatial knowledge of traveled routes and included in the mental representation of the environment. Therefore, it is possible to navigate through inferred paths that are not traveled before by using the information of a single representation of the environment. This idea was also supported neurobiologically by O'Keefe and Dostrovsky (1971) with the discovery of place cells in the hippocampus of rodents. Although cognitive map theory was originally derived from behavioral and neuroanatomical rodent studies, recent works have also supported a similar navigation mechanism for humans (Epstein et al., 2017). Moreover, even though path integration and cognitive map mechanisms are generally considered as two distinct mechanisms, path integration plays an important role in cognitive mapping as it provides useful information for its integration (Gallistel 1990). In the literature, it was also suggested that cognitive maps are generated from basic path integration systems (Wang, 2016).

As it was discussed earlier, while locomotion mostly involves action and sensory systems, higher-order cognitive functions of memory and planning systems are more prevalent in wayfinding (Montello, 2012). Therefore, instead of considering wayfinding as a simple process, it is important to approach it as a complex process that consists of the involvement of different cognitive processes such as perception, decision making, memory, and spatial learning (Dalton et al., 2019; Sternberg & Ben-Zeev, 2001). The contribution of these different cognitive systems in wayfinding and navigation process is discussed in numerous articles (Giannopoulos et al., 2014; Passini, 1984; Tenbrink & Wiener, 2007).

Specifically, spatial memory and learning have drawn great attention in the literature as navigation depends on learning and remembering landmarks and locations (Broadbent et al., 2004; Chrastil & Warren, 2012; Vorhees & Williams, 2014).

The process of spatial memory indicates both long-term and working memory (Giudice et al., 2012). In the context of navigation and wayfinding, long-term spatial memory specifies the permanent representation of landmarks and locations that are available even in less attended situations (Morris & Mayes, 2004). Most of the navigational tasks that we need to perform in our daily activities take place within environments that are familiar to us such as workplace, school, market, etc. Long-term memory allows us to navigate in these familiar environments that we learned in the past and to recognize known landmarks and locations (Giudice et al., 2012; Spiers & Maguire, 2007). On the other hand, working spatial memory enables us to keep spatial information actively and perform mental transformations of this information for a relatively short period of time (Giudice et al., 2012).

The topic of spatial memory and how it differs from other memory mechanisms are also well studied in the neuroscience literature. It is also important to note that in order to reveal the mechanisms of spatial navigation and the role of memory and learning, benefitting from neural measures and finding links between behavioral and neural signals is also necessary as behavioral studies may not always explain and reflect how the brain works.

1.2 Neuroanatomical Bases of Spatial Navigation

Studying neural mechanisms of navigation has a long history in the neuroscience field. One of the first remarkable findings in navigation history was made by John O'Keefe and his colleague Jonathan Dostrovsky in 1971 with the discovery of place cells several decades after Tolman's assertion of the cognitive map. In 2014, John O'Keefe was awarded the Nobel Prize of Physiology and Medicine for his discovery together with May-Britt and Edvard Moser, who discovered grid cells (Hafting et al., 2005). Their revolutionary findings on the place and

grid cells in the hippocampus, which constitutes the so-called "inner GPS" in the brain demonstrate a neural basis for the spatial navigation process. Since then, spatial navigation has been a hot topic in the academic community.

In the current study, participants were selected from patients with hippocampal lesions and their healthy controls to reveal the differences between their brain mechanisms during the navigation process. The main purpose of the study is to understand frontal-midline theta power which generally reflects the activity in the prefrontal cortex under presence and absence of hippocampal activity. Moreover, how the brain activity changes during physical and virtual movement is investigated. Therefore, in this section, the role of hippocampus and prefrontal cortex as well as their contribution to the multisensory information processing in spatial navigation will be discussed.

1.2.1 Hippocampal Formation

After O'Keefe and Nadel (1978) introduced the idea of the main involvement of the hippocampus in cognitive map, hippocampus, prominent C shape structure located in the medial temporal lobe, has been associated with spatial navigation and has been central to navigation research. O'Keefe and Dostrovsky (1971) observed rat's behavior in a box by simultaneously recording electrodes placed in rat's hippocampus and discovered that pyramidal cells, also known as place cells, located in the main output region of the hippocampus fired whenever rat moved into a specific place in the environment. Each place cell fired when the rat was in a different part of the box such that the activity of the local neurons represented the entire environment in a similar way to the cognitive map argument of Tolman (1948). It was suggested that representation of allocentric space and one's position in that space were provided by these cells (Moser et al., 2008). For different environments, the same place cells appeared to fire, but provided different firing relationships (Wilson & McNaughton, 1993). Place cells were found in the CA1 and CA3 regions of the hippocampus

(Gothard et al., 1996; Hasselmo et al., 1995; Jensen & Lisman, 1996; Leutgeb, 2004; O'Keefe, 1979). Early recordings of the place cells were acquired from the dorsal region of the hippocampus; however, later on, they have been also found in the ventral hippocampus (Jung, 1994; Knierim, 2015).

In further discussions after the discovery of place cells, it was also suggested that the hippocampus is a well-suited structure to subserve multisensory information related to the environment through its connection with other regions and sensory control over place cell firing (Arleo & Rondi-Reig, 2007; Muller, 1996). O'Keefe and Speakman (1987) tested the idea of sensory control by placing rats into a 4-arm maze in one of which a reward is presented. The location of the goal-arm was changed from trial to trial and indicated by 6 different controlled cues. While cues were presented throughout the whole trial duration in spatial reference memory trials, they were partially presented in the spatial working memory trials. Rats were able to find the goal location even in the condition that cues were withdrawn from the environment. In both conditions, most of the firing fields of place cells had significant relations to the controlled cues. Others were found to be associated with static background cues. Furthermore, in control trials, experimenters did not provide any cues, so there was not any correct goal location. In such trials, the relationship between the firing field and the rat's goal choice was still present. These findings suggest that where a place cell will fire critically depends on both sensory inputs presented in the environment and the behavior of the animal.

Another part of the hippocampal formation called the medial entorhinal cortex, the gateway between neocortex and hippocampus, also shows spatial firing similar to place cells, except multiple firing fields are observed in each cell (Fyhn et al., 2004). Specifically, Hafting et al. (2005) found that fields of these nerve cells in the entorhinal cortex formed a grid that activated in a unique pattern across the entire environment that a rat explored. Grid cells

provide information about the traveled distance by forming a coordinate system (Moser et al., 2008). However, encoding of space related information is not unique to the entorhinal cortex or hippocampus. Ranck (1984) observed specific cells which code directional information. It was discovered that particular head direction cells fired for a specific direction that a rat faces but remained silent for other directions. Head direction cells provide information to the hippocampus, and they have been found in the different regions of the brain including the anterior thalamus and dorsal tegmentum (Taube et al. 2007).

Similar to rats, extracellular recordings with microelectrodes in humans also indicate the role of the hippocampal formation in spatial navigation (Redish & Ekstrom, 2013). In 2003, Ekstrom and his colleagues recorded 317 neurons in different brain regions of epileptic patients while they were navigating using a computer keyboard in a two-dimensional virtual environment. They found increased neural firing rate in the hippocampus as a response to a specific location in the virtual environment and increased neural firing rate in the parahippocampus as a response to views of landmarks. Later, Jacobs et al. (2010) replicated the findings of place cell like firing in humans by recording neurons of epileptic patients. However, although they also recorded neurons of the entorhinal cortex, they could not find neural activity similar to grid cells in rats. Nevertheless, according to Redish and Ekstrom (2013), this finding may not constitute evidence against the grid cells in humans given that whether there is a human homologue of the medial entorhinal cortex is not clear.

Extracellular recording of the human brain with microelectrodes is rare in the literature due to several difficulties. However, other non-invasive methods such as fMRI also provide some evidence on the neuroanatomy of spatial navigation even though it does not indicate direct but correlational results. Consistent findings with Ekstrom et al. (2003) were also found in fMRI literature. Epstein and Kanswiher (1998) introduced a specific location in the parahippocampus, called parahippocampal place area (PPA) which showed more

activation during passive viewing of environmental scenes compared to seeing objects or faces. Similarly, Hassabis et al. (2009) conducted fMRI recording while subjects navigated in two connected rooms in a virtual environment and observed different patterns of hippocampal activation correlated with the navigation to the corners of the rooms, while parahippocampal activation pattern differed between the two rooms which also suggest scene processing of parahippocampus. Moreover, Maguire and her colleagues (2000; 2003) compared MRI scans of London taxi drivers with their age-matched controls and with people who have high navigational expertise. Taxi drivers showed greater grey matter volume in the posterior hippocampus than both of the control groups. In the follow-up study, the comparison between London taxi drivers and London bus drivers who use constrained set of routes also showed greater grey volume in the hippocampus of taxi drivers (Maguire et al, 2006).

Studies presented above were conducted either among healthy participants or collected data from healthy parts of the brain. Another way to examine the neuroanatomy of navigation is through patient studies. Patients who suffer from selective brain damage, which can occur as a result of various reasons, including viral infections, surgery to treat epilepsy or tumors, can inform us about the role of a particular brain region in navigation since it allows observing how brain functionality and behavior change in the absence of that particular region (Ekstrom et al., 2018). In a study that was conducted in a virtual water maze paradigm, patients who have bilateral hippocampal damage showed impairment while navigating in the non-visible platform condition indicating that they had difficulty remembering new spatial locations. Patients also showed longer search durations and took longer paths to find the hidden platform compared to healthy controls. In the same study, another interesting result was found. Although navigational impairment was observed in non-visible trials, when the platform was visible, their performance result was similar to controls, displaying intact procedural navigation strategies (Goodrich-Hunsaker et al., 2010).

To examine the functional asymmetry of the hippocampus and its role in navigation, Spiers and his colleagues (2001a; 2001b) tested spatial abilities and episodic memory of patients with both bilateral and unilateral hippocampal damage in a large-scale virtual reality town. Navigational tasks included navigation in different locations in the town, recognition of visited locations, and drawing the map of the navigated town while episodic memory was tested by asking context and object related questions about the traveled virtual town. Patient who has bilateral hippocampal damage was impaired in navigational tasks as well as recall of the context-dependent questions. However, his memory related to objects was intact. On the other hand, patients who have right hippocampus damage were impaired only in navigational tasks whereas patients with left hippocampus damage showed decreased memory results on context-dependent episodic memory but showed better navigational performance compared to right hippocampal patients. These results provide evidence of hippocampus involvement in navigation. More specifically, while spatial memory is mainly mediated by the right hippocampus, the left hippocampus is more involved in the context-dependent aspects of episodic memory.

Yet, there are also confronting results in the literature. In some cases, preserved spatial memory and navigation abilities were observed among patients with bilateral medial temporal lesions in allocentric navigation tasks suggesting against the view of the hippocampus as an area necessary for all types of allocentric representations (Bohbat et al., 1998; Kolartik et al., 2015; Rosenbaum et al., 2000). Ekstrom et al. (2017) addressed this issue and emphasized the involvement of different regions in the spatial navigation process.

1.2.2 Prefrontal Cortex

The prefrontal cortex has been seen as a key structure for executive functions including working memory, goal-directed behavior, flexible thinking, planning, and decision making (Pryor & Veselis, 2006). Given that spatial navigation requires high order cognitive

processes, it is no surprise that increased activation in prefrontal areas correlated with navigational activity was reported in various functional neuroimaging studies (Gron et al., 2000; Hampstead et al., 2014; Hartley et al., 2003; Rodriguez, 2010). The contribution of the prefrontal cortex in spatial navigation is mostly attributed to its role in goal-directed behavior and working memory (Spiers, 2008).

Animal studies show that inactivation of the prefrontal cortex leads to an interruption in spatial navigation performance (Lacroix et al., 2002; Vafaei & Rashidy-Pour, 2004). Specifically, the orbitofrontal cortex, subregion of the prefrontal cortex, in rats encodes not only the motivational value of the task but also spatial variables such as location and required action to reach the goal remarking the essential role of the prefrontal cortex in goal-directed behavior (Feierstein et al., 2006). Functional MRI results also underlie the prefrontal cortex for goal processing. The medial prefrontal cortex (mPFC) was found to be correlated with proximity to goal destination in the virtual simulation of London (Spiers & Maguire, 2002) while other distinct areas of the prefrontal cortex were also found to be associated with different aspects of spatial navigation such as route planning, violation of expectations about the setting of environment, dealing with unexpected obstructions, arousal and perception of internal state (Spiers & Maguire, 2006). Moreover, the case study of patient LG, who has bilateral ventromedial prefrontal cortex damage and experiences difficulties while navigating, exemplifies the necessity of the prefrontal cortex for navigation. Although his topographical knowledge of his town was intact, his performance on describing routes between familiar locations in the town was poor. However, he showed similar performance results compared to healthy controls when the goal destination was reminded every 15 seconds indicating the role of the medial prefrontal cortex in keeping the goal in mind (Ciaramelli, 2008).

Not only maintaining the goal destination in working memory but also a more general aspect of working spatial memory was examined in the literature. Shrager et al. (2008) found

that patients with hippocampal lesions could keep track of reference location by benefiting from idiothetic cues on paths up to 15 meters whereas in the conditions that requirements of the task exceeded working memory they showed impaired performance. Kim et al. (2013) demonstrated similar results among patients with medial temporal lobe damage even though this finding was not replicated in rats (Kim et al., 2013; Sapiurka et al., 2016). According to the authors, the involvement of the medial prefrontal cortex (mPFC) in spatial working memory is the main reason for intact navigation performance in hippocampal patients. Accordingly, damage to the dorsolateral prefrontal cortex by cerebral stroke cause impairment in the ability to keep spatial information online in working memory, while stroke patients with hippocampal lesion showed impairment in transferring spatial information from working memory into long term memory (van Asselen et al., 2006). However, it would not be correct to attribute these results to the independent processing of the hippocampus and prefrontal cortex in spatial working memory. In order to make inferences about the processes in the prefrontal and hippocampal cortex, investigating only behavioral results may not be enough. Therefore, it is needed to look into the brain network for navigation which leads us to the next part.

1.2.3 The Navigation Network

Unlike localizationist perspectives on spatial navigation, which mostly focus on particular brain regions and their independent computations on the different aspects of the space, Ekstrom and his colleagues (2017) emphasized the importance of parallel interactions and involvement of different brain regions including the hippocampus, parahippocampus, entorhinal cortex, thalamus, posterior parietal cortex, occipital place area, precuneus, and prefrontal cortex. Although due to the multimodal and dynamic nature of spatial navigation, distinct regions contribute to the human navigation network, only the interaction between the

prefrontal cortex and hippocampus will be addressed in this section for the sake of the relevance to the topic of the current study.

While the hippocampus and the medial prefrontal cortex of rats interact with each other to coordinate the spatial memory processing at longer delays, it is suggested that these regions may represent spatial information independently in working memory tasks at short delays (Churchwell & Kesner, 2011). Some patient studies also suggest the same argument for the prefrontal-hippocampal network in humans as it was discussed in the last section (Kim et al., 2013; Shrager et al., 2008). However, in some cases, reorganization of the brain after the brain damage would induce such misleading conclusions indicating independent processes of the hippocampus and prefrontal cortex as intact spatial short-term memory among hippocampal patients is related to compensation of preexisting memory network in the neocortex, specifically in parietal and prefrontal cortex (Finke et al., 2013). Furthermore, damage to the hippocampus or the prefrontal cortex may affect the connectivity between these two regions totally or partially. This would also make it hard to draw conclusions about the independent functions of these regions. Nevertheless, with careful interpretation, patient studies can be very informative about the differential or common roles of the prefrontal cortex and hippocampus to navigation as patients with brain lesions can behave differently (McCormick et al., 2018).

According to Laroche et al. (2000), functional interaction between the hippocampus and the prefrontal cortex areas plays an essential role in spatial learning and memory. Spellman et al. (2015) found evidence of the role of the direct hippocampal-prefrontal pathway in spatial working memory in rats. Specifically, ventral hippocampus and medial prefrontal cortex afferents are critical in updating task-relevant spatial information such as location cues. Furthermore, their findings suggest the importance of this pathway for encoding; however, they couldn't find similar results for the storage and retrieval of task-

critical spatial cues. Accordingly, human studies also point out the interaction between these two regions for spatial memory. Subjects whose spatial abilities were tested in a rich virtual town showed increased hippocampal activation in the initial few seconds of route planning to reach a goal destination along with increased medial prefrontal cortex activation (Spiers & Maguire, 2006).

Some scientists found evidence of the representation of future positions and subsequent route choice in hippocampus place cells aside from the representation of current position (Johnson & Redish, 2007; Wikenheiser & Redish, 2015). According to Hiroshi Ito (2018), considering the function of the hippocampus, a possible explanation of how the hippocampus represents information about future positions is that the medial prefrontal cortex provides inputs about the goal representations to the hippocampus. Even though there are no direct known return connections from the medial prefrontal cortex to the hippocampus, the thalamic nucleus reuniens (NR), midline nuclei of the thalamus, provide an indirect pathway between these two regions. However, projection of thalamic nucleus reuniens is only possible to the CA1 region of the hippocampus. This prefrontal-thalamo-hippocampal circuit plays an important role in goal-directed navigation (Ito, 2018; Ito et al., 2015).

Moreover, Hugo Spiers and Sam Gilber (2015) also emphasized the role of prefrontal-hippocampal interaction during a detour as a response to blockage in a learned route by reviewing the relevant lesion, single-unit recording, and functional neuroimaging studies in the literature. According to their proposed model, the lateral prefrontal cortex responds when there is a change in the path, superior and frontopolar prefrontal cortex involve in making changes in route planning according to the new subgoals, and finally, the simulation of the new path is taken place in the hippocampus.

1.3 Electrophysiology of Spatial Navigation

So far evidence for theories on the mechanism and neural basis of spatial navigation has been addressed by referring to extracellular recording, structural and functional neuroimaging, behavioral, and focal brain damage patient studies in the literature. Although an introduction about the electrophysiology of spatial navigation has been made with rat and limited human studies of extracellular recording with microelectrodes, brain oscillations were not mentioned. Thus, this section will mostly focus on brain oscillations related to spatial navigation in humans. Moreover, as the main aim of the present study is investigating brain dynamics of navigation under physical movement, relationship between body movement which provides idiothetic information and navigation related brain oscillations will be also discussed under this section.

1.3.1 Frontal-Midline Theta

Scalp EEG studies in humans have reported prominent theta power observed at a frequency of 4-8 Hz over frontal regions (Cavanagh & Frank, 2014; Hsieh & Ranganath; 2014; Ishihara & Yoshi, 1972; Klimesch, 1999). This scalp recorded theta oscillations, also known as frontal-midline (FM) theta has a focal distribution that is maximal around the frontal-central electrodes, especially the electrode position Fz (Mitchell et al., 2008). Frontal-midline theta has been associated with working memory, sensorimotor integration, attention, and spatial navigation in the literature (Aftanas & Golocheikine, 2001; Cruikshank et al., 2012; Gevins et al., 1997; Onton et al., 2005; Plank et al., 2010). It was suggested that it is generated in bilateral medial prefrontal cortices including the anterior cingulate cortex consistent with its associated functions (Ishii et al., 1999).

Previous electrophysiology studies associated frontal theta with working memory encoding and retrieval (Friese et al., 2013; Hsieh & Ranganath, 2014; Itthipuripat et al., 2013; Kaplan et al., 2014). Similarly, during a virtual navigation task, frontal-midline theta was

found to be linked to the learning of the maze presented in the task (Nishiyama et al., 2002). Another evidence to the frontal-midline theta and spatial working memory encoding association was provided by a study conducted by Jaiswal et al. (2010). In the experiment, 12 healthy participants were tested in a realistic virtual corridor. Participants were able to navigate virtually by using their right thumb. According to the results, while theta activity increased during the encoding phase, it decreased during the retrieval, suggesting that encoding of spatial information is more demanding than retrieval period as the encoding process is cognitively more challenging. Authors drew this conclusion according to the literature often suggesting that frontal midline theta increases depending on the demand of the working memory task (Fernández et al., 2021; Gevins et al., 1997; Jensen & Tesche, 2002). Moreover, increased theta activity was found to be correlated with performance. Some studies showed that larger theta activity during the learning phase is associated with the high success rate in retrieval (Klimesch et al., 2001, Weiss et al., 2000).

In a few articles, the involvement of frontal-midline theta in goal-directed behavior was also discussed. Cavanagh and Frank (2014) pointed out the role of frontal-midline theta in cognitive control. They discuss cognitive control of this theta activity according to goal adjustment and goal relevant decision making. The relationship between frontal-midline theta activity and goal-directed behavior was also tested in a simulated driving task (Laukka et al., 1995). In the experiment, participants were asked to choose the correct road according to the presented signs by driving a car in a computer game which consists of a set of different roads. As Cavanagh and Frank (2014) suggested, increased frontal-midline theta associated with goal-directed behavior was found. Moreover, as it was suggested in the earlier studies mentioned above, this increase was observed during the learning phase and was associated with successful task performance.

According to the sensorimotor integration hypothesis, sensorimotor integration in goal-directed wayfinding behavior is coordinated by cortical theta activity (Caplan et al., 2003). Kober and Neuper (2011) designed a virtual maze experiment to test this hypothesis. In the maze, there were 18 decision points. 9 of the decision points in the maze contained a landmark in a hidden box that opened automatically 1 second after the arrival of the subject. After the exploration phase, subjects needed to find the shortest way to a target landmark presented on the screen. Authors found higher FM theta activity during the landmark processing at decision points on the way to the goal. Furthermore, theta activity increased when the box is opened, and landmark was visible. According to Kober and Neuper (2011), it might be because of the updating of motor plan toward a goal according to incoming sensory information from the landmark. In general, their results may confirm the involvement of FM theta activity in sensorimotor integration.

Although studies presented above reflect the role of FM theta in spatial navigation, they do not involve the locomotion component of navigation. Thus, Liang et al. (2018) wanted to examine movement-related FM theta by testing participants in an omnidirectional treadmill. The experiment consisted of 4 different tasks in which participants were asked to alter between moving on the treadmill and standing still or opening and closing eyes with the beep sound. Tasks were classified as "eyes open, alternating movement", "eyes closed, alternating movement", "moving, alternating eyes open" and "moving, alternating eyes closed". During the experiments, participants navigated in a virtual city displayed by a VR headset. Results showed that FM theta oscillation was higher in the movement condition compared to standing still regardless of the presence of visual input. The interaction effect was also found between movement and eyes open condition as when there is visual input, FM theta activity was even more prevalent. According to Liang et al. (2018), their finding

confirms the effect of movement via combination of vestibular, proprioceptive, and visual information on frontal-midline theta oscillations.

1.3.2 Hippocampal Theta

Slow rhythmic oscillations around 4-12 Hz were firstly observed in rodents' hippocampus during arousal, locomotion, and spatial memory process (Green & Arduini, 1954; O'Keefe & Nadel, 1978; O'Keefe & Recce, 1993; Vanderwolf, 1969). The speed of locomotion was also found correlated with the frequency of hippocampal theta in rats (Czurko et al., 1999; Sławińska & Kasicki, 1998). Moreover, rats with lesions in the area generating hippocampal theta were not able to complete the spatial task even though the electrolytic lesions were made after the learning trials suggesting the importance of hippocampal theta for spatial navigation (Winson, 1978).

Intracranial electroencephalogram (iEEG) studies in epilepsy patients also reveal that humans exhibit low frequency oscillations, called theta rhythm in the hippocampus during virtual movement (Caplan et al., 2001; Ekstrom et al., 2005; Kahana et al., 1999). However, hippocampal theta frequency observed in humans peaked at lower frequencies, around 3.3 Hz compared to rodents, exhibiting a peak around 7.7 Hz (Watrous et al., 2013). According to Jacobs (2014), who reviewed iEEG studies in the literature, hippocampal theta oscillations observed in humans during spatial navigation are slower than in rodents. Yet, another study that measures the theta rhythm of rats in both real-world and virtual reality, where vestibular cues were not provided found that the frequency of hippocampal theta in local field potential was lower during virtual locomotion compared to real-world locomotion (Ravassard et al., 2013). This finding suggests that lower frequency theta rhythm in humans related to spatial navigation might be due to the lack of vestibular, motor, and proprioceptive inputs. Similarly, Bohbot et al. (2017) reported similar hippocampal oscillations during real navigation and lower frequency hippocampal oscillations during virtual navigation by testing patients with

depth electrodes. The findings on hippocampal theta power in humans indicate the important role of the hippocampus and multimodality in spatial navigation.

EEG monitoring with depth electrodes is suitable to measure activity from deep structures of the brain. On the other hand, scalp electroencephalogram (EEG) can capture the aggregate neural activity of the brain, that generates electrical signals, but it is generally used to measure activity in the outer layers of the neocortex. Even though some recent articles reported that it is possible to measure and localize the activity from deep structures like the hippocampus using high-density EEG (Fahimi Hnazaee et al., 2020; Seeber et al., 2019), capturing and isolating hippocampal theta with scalp EEG is a difficult task. However, although it is hard to investigate hippocampal theta in human subjects via EEG recordings from the surface of the skull, literature of hippocampal theta that has been extensively investigated in rats may provide perspective on the role of frontal midline theta, which is one of the most studied human EEG rhythms, in working memory and spatial navigation (Mitchell et al., 2008). In an article that reviews the frontal midline theta studies in the literature, Mitchell and his colleagues (2008) discussed whether FM theta is related to the theta rhythm generated by the hippocampus. According to them, it is possible that there is a functional relationship between hippocampal and FM theta due to activation of hippocampo-cortical loops.

1.4 Methods to Study Human Spatial Navigation

As it was demonstrated throughout the paper, different methods to investigate brain dynamics of spatial navigation in humans were used in the literature. Even though various articles highlighted many key points associated with spatial navigation, there is still much to discover about how spatial navigation is being processed in the human brain. In order to reveal more about its neural basis, choosing the right method by considering the nature of the spatial navigation mechanism along with the research question of interest is needed.

1.4.1 Challenges

One of the major challenges in navigation research is how to study human spatial navigation in a laboratory setting given that humans need to navigate through large scales in their everyday life. Even though it is possible to examine the memory of navigational experiences, this method cannot be used to investigate the encoding phase of the spatial memory. Moreover, testing participants while navigating in a real environment such as navigating in a city would mislead the result because of the familiarity effect (Ekstrom et al., 2018). As briefly mentioned in the locomotion section, in order to overcome these limitations, the virtual reality (VR) approach is widely used in the literature (Kuliga et al., 2015). Virtual reality provides constructing large-scale complex environments which can be presented on computers, larger screens, or VR headsets (Schubert et al., 1999). However, there are some points needed to consider while working on VR environments.

Burgess et al. (2002) discussed the effect of dimensionality on spatial representation in their review article and differentiate between the representation of 2D scenes and 3D space. They suggest that involvement of the brain regions differs according to dimensionality as 2D scenes are associated with the activity in the parahippocampus whereas, for representation of 3D locations, involvement of the hippocampus is required. Kober and her colleagues (2012) measured participants' sensation of "being there" during a spatial navigation task in virtual environments displayed on a computer screen with 2D view and 2x2 meter projection screen with the 3D view and examined cortical activity associated with them. 3D view led to a more intense spatial presence experience than the 2D view. They also found increased parietal brain activation associated with the feeling of presence and stronger functional connectivity between frontal and parietal brain regions with the lower presence experience. Similarly, Slobounov et al. (2015) also compared fully immersive 3D VR with less immersive 2D VR in a spatial navigation task and found a higher sense of presence associated with 3D VR like

Kober and her colleagues (2012). Moreover, Slobounov and his colleagues (2015) showed increased FM theta activity during the encoding and greater postural instability in 3D view compared to 2D view. These results indicate that immersive 3D VR environments require the allocation of more sensory and brain resources for spatial navigation tasks.

Besides the effect of dimensionality, there is another key point that has an impact on the findings related to spatial navigation mechanism which is the navigation type (Langbehn et al., 2018). In most of the virtual reality experiments, participants are asked to navigate virtually by using a computer keyboard or a joystick (Nilsson et al., 2018). This may lead to drawing missing conclusions about the nature of spatial navigation as there are major differences between virtual and real-world navigation (Gramann et al., 2011). Real-world navigation contains physical movement, which corresponds to the locomotion component of navigation. As it was discussed in the first section, during physical locomotion, the brain integrates sensory information from multimodal sources (Montello, 2012). This multimodal sensory integration constitutes one of the key aspects of spatial navigation that has been well studied in the literature (Arleo & Rondi-Reig, 2007; Campos et al., 2012; Eimer, 2004; Karimpur & Hamburger, 2016; Ravassard et al., 2013); however, during virtual navigation, idiothetic sensory information that is generated from self-movement is missing.

Taube et al. (2013) discussed the differences between virtual and pyhsical navigation and pointed out that even though there are some similarities between these two navigation types, they are not identical. According to them, missing vestibular and proprioceptive information as well as efferent copies of motor signals in virtual navigation may lead to a mismatch between the visual cues viewed by the participants. Inference of the need for involvement of physical movement in navigation research has been addressed throughout the paper by means of evidence for the significance of idiothetic cues in navigation (Brandt et al., 2005; Brandt & Dieterich, 2017; Hüfner et al., 2007; Langbehn et al., 2018; Nuti et al., 2017;

Riecke et al., 2010; Ruddle & Lessels, 2006; Smith et al., 2005). Accordingly, Taube and his colleagues (2013) also remark on the importance of physical movement while studying human spatial navigation and suggest that spatial perception is more accurate when idiothetic information and motor signals are present.

1.4.2 Mobile Brain/Body Imaging (MoBI)

According to embodied cognition theory, brain dynamics underlying cognitive processes have a close link with the motor actions with a physical body in an environment (Schneegans & Schöner, 2008). Therefore, cognition can be altered by physical motion and associated sensorimotor signals. Being that sensory and motor systems are integrated into the brain mechanisms, integrating of active movement into navigation research is crucial not only to study cognitive mechanisms but also to investigate brain dynamics underlying human spatial navigation (Gramann et al., 2011). However, due to constraints of neuroimaging methods like functional MRI, positron emission tomography (PET), and magnetoencephalography (MEG), most of the neuroscientific experiments designed to study brain dynamics of spatial navigation has been conducted stationary (Cornwell et al., 2008; Maguire et al., 1999; Rodriguez, 2010). Moreover, in fMRI studies, participants need to lie supine in the scanner which might result in conflicting signals from the orientation of the head and the visual information presented on the screen (Taube et al., 2013). Challenges with traditional neuroimaging techniques limit our understanding of the brain dynamics of spatial navigation under natural movement.

Given that EEG sensors are quite light compared to other neuroimaging methods mentioned above, it is a more suitable technique to use during active movement (Makeig et al., 2009). However, most of the traditional EEG studies were also conducted immobile such that participants were not even allowed to move their heads and had to restrain their eye movements. (Bischof & Boulanger, 2004) The reason behind this movement restriction is the

fact that movement and muscle activity may create fluctuation in EEG data. Traditional signal processing methods were not able to handle the contamination of these artifacts on the interested brain signals (Miyakoshi et al., 2021). However, recent approaches such as independent component analysis have successfully addressed this issue and dissociated electrical activity related to the brain from non-brain signals (Gwin et al., 2010; Pion-Tonachini et al., 2019). Therefore, together with the new signal processing approaches on EEG data, using EEG during active movement becomes more possible. In fact, mobile EEG technologies have been started to be used in laboratory and clinical settings to study real time brain activity under motion (Lau-Zhu et al., 2019).

Mobile Brain/Body Imaging method also benefits from mobile EEG technology. It is a relatively new technique that is proposed to overcome the challenges of traditional neuroimaging methods (Park et al., 2018). It combines high-density mobile EEG with a synchronized whole body motion capture system. Moreover, it is also possible to use immersive head-mounted virtual reality in MoBI experiments (Jungnickel et al., 2018). High-density EEG recording distinguishes MoBI from mobile EEG studies as low-density recordings is generally preferred to improve mobility in mobile EEG studies (Jungnickel et al., 2018). Moreover, MoBI differs from mobile EEG studies as it tries to understand not only the brain dynamics but also its relationship with movement as body movements are also considered as an informative input in MoBI setups (Jungnickel et al., 2018; Makeig et al., 2009). In order to identify links between brain activity and body movements, data from multiple modalities including EEG, body motion capture and eye tracking is recorded wirelessly and synchronously by benefiting from a dedicated software architecture such as The Lab Streaming Layer framework (https://github.com/sccn/labstreaminglayer) (Gramann et al., 2014).

First MoBI experiment was conducted to test the feasibility of mobile brain/body imaging approach by investigating brain activity of participants walking or standing on a treadmill while performing a cognitive task (Gramann et al., 2010). In the experiment, target (20%) and non-target (80%) stimuli were presented to the subjects, and they were expected to respond whenever a target was appeared on the screen while they were performing different movement conditions (standing, slow walking, fast walking and running) on a treadmill. By using a well-known paradigm known as visual oddball paradigm, the study investigated whether it is possible to replicate oddball P3 in the event related potential during whole-body movement. The results demonstrated that EEG brain activity accompanying cognitive processing can be analyzed during physical motion through spatial filtering and ICA decomposition.

Considering the mobile and multimodal nature of the spatial navigation process, this technique is well suited to study brain dynamics underlying human spatial navigation under active locomotion (Do et al., 2021; Jungnickel & Gramann, 2016; Lin et al., 2015; Miyakoshi et al., 2021). Recently, Gramann and his colleagues (2021) investigated heading computation mechanism which is crucial for spatial orientation by using MoBI setup. In the experiment, subjects performed a spatial orientation task in both stationary and full-body rotation conditions. Behavioral results showed that heading estimation of participants were more accurate during physical rotation compared to stationary setup. Interestingly, they reported differences in EEG activity from the retrosplenial complex (RSC), which has a central role in heading computation in navigation. During MoBI setup in which participants performed physical rotation, wide frequency range synchronization which was modulated by the velocity of the rotation was found in the retrosplenial complex as well as the occipital and parietal cortices. However, desynchronization in the alpha band was only found in the stationary setup. Therefore, authors suggested that frequently reported alpha desynchronization in

navigation studies which were conducted in traditional stationary setups might not be related to heading computation but rather reflects contradiction of sensory information from proprioception and vision.

1.4.3 Morris Water Maze

So far challenges of studying brain dynamics of spatial navigation and importance of using a suitable approach like MoBI for navigation research are discussed. However, choosing the experimental paradigm that is most appropriate for the question of interest is also important as much as choosing the neuroimaging method and the setup. Therefore, to study spatial learning and memory, understanding interested components of the process and choosing paradigm accordingly is crucial to reveal brain dynamics associated with them (Craver & Darden, 2001).

In the memory and learning process, there are three necessary stages which are encoding, storage, and retrieval (Melton, 1963). While initial learning of information takes place in the encoding phase, retrieval refers to the ability to access information learned during the encoding phase. In order to retrieve information from memory, it is important to maintain it over time. Storage indicates this phase of maintenance (Murdock, 1974). Accordingly, spatial memory tasks are generally decomposed into encoding, maintenance and retrieval phases in the literature (Jaiswal et al., 2010).

To study the specific phases of spatial memory and learning, numerous different tasks have been presented in spatial navigation research; however, Morris Water Maze is one of the most widely used ones. The maze was originally developed by Richard Morris (1981) to assess spatial learning in rats. In the task, rats are placed in a large circular pool filled with water which includes a hidden platform that allows rats to escape from the water. In the original maze, there are no cues indicating hidden platform and representation points. During training trials, rats learn to escape from water by finding the hidden platform. After the

training trials, the spatial memory of rats is tested in the same maze (D'Hooge & de Deyn, 2001; Vorhees & Williams, 2006). In further studies, Morris also evaluated hippocampal dependent of spatial learning by using the same paradigm (Morris et al., 1982; 1986; 1984). He reported impaired landmark navigation due to hippocampal damage and this finding is replicated by other studies (Morris et al. 1982; Sutherland & Rudy, 1988).

Since its introduction, Morris Water Maze has become one of the most popular behavioral assay as it provides flexible protocols and controlled environment for landmark manipulation (Thornberry et al., 2021). Therefore, even though the procedure of Morris Water Maze is relatively simple, it has been successfully used in neuroscience experiments to assess neurobiology and neuropharmacology of spatial memory and learning of rats (Brandeis et al., 1989; D'Hooge & de Deyn, 2001). Malek et al. (2009) used Morris Water Maze to investigate the effect of Growth Hormone (GH) injection to hippocampus on the treatment of Alzheimer's Disease. Their results suggested that intra-hippocampal injection of GH could improve impaired spatial cognition in rats with dementia type of Alzheimer's Disease.

Although the Morris Water Maze was originally developed for rats, human analogues of the maze were also successfully adapted in navigation research (Thornberry et al., 2021). Laczó et al. (2010) designed an experimental setting similar to Morris Water Maze for human subjects at risk of Alzheimer's Disease. The experimental room setting was a circular tent with 2.8-meter high and 2.9-meter diameter. Target location was marked by a laser pointer during the experiment, and movements of participants were recorded by a tracking system. On the other hand, Cornwell and his colleagues (2008) adapted the maze in a virtual environment where participants could move in by a fiber optic joystick and projected it onto a screen while neuromagnetic activity was recorded via MEG. They found that theta activity from hippocampus and parahippocampus predicts the performance of participants on the Virtual Water Maze.

1.4.4 The Present Study

In the present study, Mobile Brain/Body Imaging method is used to investigate the electrophysiology of spatial navigation. Participants are selected from both patients with unilateral hippocampal damage and healthy controls. In order to compare brain dynamics under mobile and immobile conditions, participants are tested in both desktop setting in which they navigate virtually and in MoBI setup where they can freely move and interact with the environment. The current study aims to investigate how the dynamics of the brain with hippocampal lesions change under action during spatial navigation compared to a healthy brain. The focus of the current study is frontal-midline theta power as it has an important role in encoding and retrieval of spatial information, locomotion, and goal-directed behavior (Cavanagh & Frank, 2014; Friese et al., 2013; Kaplan et al., 2014; Liang et al., 2018). Therefore, the current study also aims to answer questions like how hippocampal damage affects the frontal-midline theta and how this effect changes according to the presence and absence of idiothetic information.

In the literature, frontal-midline theta was found to be associated with both encoding and retrieval of spatial information (Friese et al., 2013; Kaplan et al., 2014). Accordingly, it is expected that FM theta will differ significantly from a population with mean equal to zero in both encoding and retrieval phases of spatial navigation. Even though frontal theta power among hippocampal patients was not studied in depth in the literature, because of the functional connectivity between hippocampus and prefrontal cortex, which is suggested to be the source of frontal-midline theta (Ishii et al. 1999; Ito, 2018; Laroche et al., 2000), it is hypothesized that FM theta power will differ significantly depending on being in the control or patient group. Moreover, it is also expected to see the effect of idiothetic cues on FM theta considering that information obtained from body movements plays an important role in navigation (Diersch & Wolbers, 2019). Specifically, it is hypothesized that FM theta activity

will differ significantly also depending on being tested in MoBI or desktop conditions. The difference between patient and control subjects is expected to be lower in MoBI condition compared to desktop condition. Consistent with the literature, the association between performance and theta activity during encoding should be present if the brain activity during encoding predicts retrieval success (Klimesch et al., 2001). Finally, as it was discussed earlier, several articles remark that FM theta power increases with respect to workload (Fernández et al., 2021). In the current study, in order to increase the task demand, participants start the spatial navigation task rotated in some retrieval trials. Therefore, increased activity in rotation trials is also expected to be observed in the current study.

Chapter 2: Method

2.1 Participants

11 patients with a unilateral partial resection of the medio-temporal lobe (MTL) including the removal of the right hippocampus were recruited for the current study. Resections were performed either due to hippocampal sclerosis and intractable epilepsy or due to the removal of a benign tumor. Time passed after the surgery varied between 9 months to 17 years. The age of patients was ranged between 22 to 61 ($M = 38$) and the years of education that they received varied between 12 to 20 ($M = 16$). All patients were recruited via the department of neurology at the Charité-Universitätsmedizin Berlin. For each patient, two healthy controls who matched with the patient in age, sex and education level took part in the study. Controls were recruited via the intranet of the Charité-Universitätsmedizin Berlin and online-advertising. All participants gave written informed consent, and all procedures were approved by the local ethics-committee of the Charité-Universitätsmedizin Berlin. Two patients were excluded from the analysis due to excessive noise and detected psychosis symptoms of the patient after the experiment as well as their matched controls. Therefore, all the analyses were based on 9 patient and 18 control subjects.

2.2 Apparatus

The experiment was conducted at the Berlin Mobile Brain/Body Imaging Lab (BeMoBIL). All participants were equipped with high-density electroencephalography (EEG) with 128 channels synchronized to the virtual or physical motion streams using the lab streaming layer (LSL, C. Kothe (2014), https://github.com/sccn/labstreaminglayer) (see Figure 1). EEG data was recorded with a nominal sampling rate of 1000 Hz and band-pass filtered from 0.016 Hz to 500 Hz (BrainAmp Move System, Brain Products, Gilching, Germany). An elastic cap with an equidistant layout (EASYCAP, Herrsching, Germany) was used and the data were referenced to an electrode located closest to the AFF6h electrode of

the extended 10% system. Impedances were kept below 20kΩ in most electrodes and electrode locations were digitized using an optical tracking system (Polaris Vicra, NDI, Waterloo, ON, Canada). Experimenters monitored the performance and safety of the participants via the ceiling camera, shared screen view, and audio stream. To this end, participants were equipped with a microphone and earphones during the task.
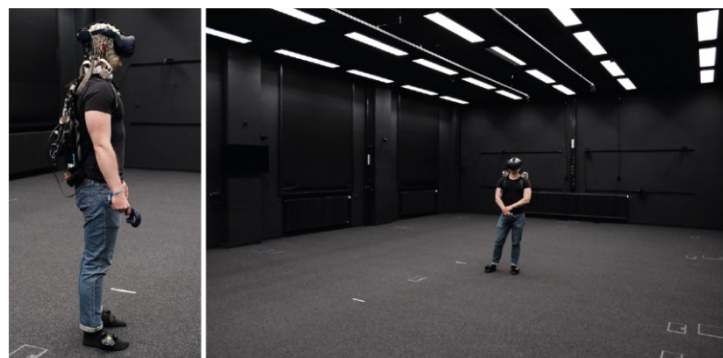
Figure 1

Experimental Setup

Desktop   Virtual reality

    A   **B**

Note. photo credit Lukas Gehrke, modified from Iggena et al. (in prep). (A) Desktop setup with joystick rotation, displaying a virtual environment presented with a first-person view on a wall-mounted screen. Joystick was place on a desk in front of the participant. (B) Mobile Brain/Body Imaging (MoBI) setup with a participant equipped with motion trackers, head-mounted VR, and high-density EEG.

2.2.1 Mobile Brain/Body Imaging (MoBI) Setup

In the MoBI session (see Figure 1B), a virtual environment created with Unity 3D was presented to the participants using a head-mounted immersive VR display (HTC Vive Pro, 90 Hz refresh rate, 110 degrees field of view). To enable wireless navigation within the room, a wearable gaming PC, powered by portable batteries, was used to generate the graphical input

to the HMD. Participants were equipped with three HTC Vive motion trackers. One of the trackers were placed on top of the PC on their back and other two were placed on their left and right foot respectively. The position and orientation data were recorded using the HTC lighthouse tracking system with sampling rate of 90 Hz and were streamed via Wi-Fi to the LSL on the recording PC. While performing the tasks, participants held an HTC Vive controller and pressed the trigger key to respond or to terminate breaks between blocks. The navigable area in the room was approximately 15 x 9 meters. However, participants were instructed to always stay within the boundary of the virtual arena (a walled circle with 3.8 meters radius). As participants were able to move physically within the room, MoBI setup enable them to use idiothetic cues (i.e., motor, vestibular, and proprioceptive) in addition to visual flow to complete the task. During the task, there were no external cues (sound or air flow) that may have informed participants of their position in the room.

2.2.2 Desktop Setup

In the desktop session (see Figure 1A), the virtual environment was presented with a first-person view on a wall-mounted screen (HD resolution, 60 Hz refresh rate, 40″ diagonal size) in the same room as in the MoBI session. Participants viewed the screen while standing approximately 1.5 meters away and navigated virtually in the VR environment by simulating movement using a joystick placed on a desk in front of them. Thus, their physical movements were constrained, and only visual flow information was available for completing the task. The heights of both the screen and the desk were adjusted according to the height of the participant. To navigate in the virtual environment, participants rotated their perspective around the up-down axis (yaw) by tilting the joystick to the left or to the right. Likewise, forward, and backward translation was controlled by tilting the joystick forward or backward. The speed of translation was 1.4 virtual meters per second and the rotation speed was 50 degrees per second. The time series of positions and orientations of the virtual camera was

sampled at 60 Hz and streamed to the LSL. Participants pressed a red button on the joystick with their thumb to respond or to terminate breaks between blocks.

2.3 Experimental Design

Participants were tested in both the MoBI and the desktop sessions using the identical experimental protocol. They performed a spatial memory task analogous of Morris Water Maze in a virtual environment. Two different versions of the virtual environment were created and assigned to the MoBI and desktop sessions, respectively (see Figure 2). In both versions, participants stayed within a circular arena enclosed by a wall that was 1.7 (virtual) meters high. The floor inside the arena was covered with fog. A skybox featuring clouds was rendered in the background and the arena was surrounded by a hilly terrain. Three building objects were placed in a triangular formation around the arena. However, the identity of the building objects and a number of other features such as the sky background, wall color, the texture and shape of the terrain varied between the two versions to avoid transfer effect across sessions (see Figure 2).

In each session, 6 experimental blocks were presented, with each consisting of 3 "learning" trials and 4 "probe" trials. A block was defined by a set of spatial parameters, namely the location of the origin and the target. First, the 6 origins were located on each end of the radial axes equally dividing the circle into 6 areas (at 0, 60, 120, 180, 240, and 300 degrees). For each origin, the corresponding target was located on one of the center axes of the four quadrants defined with respect to the origin (relative angles +- 45 degrees or +-135 degrees). The distance of the target location from the center was randomly sampled from a uniform distribution over the interval of [0.2, 0.8] × arena radius (3.8 (virtual) meters). The 6 sets of block-specific spatial parameters (see Table 1) were generated once and used for all participants and both of the sessions. However, the order of the blocks was randomly permuted for each session.
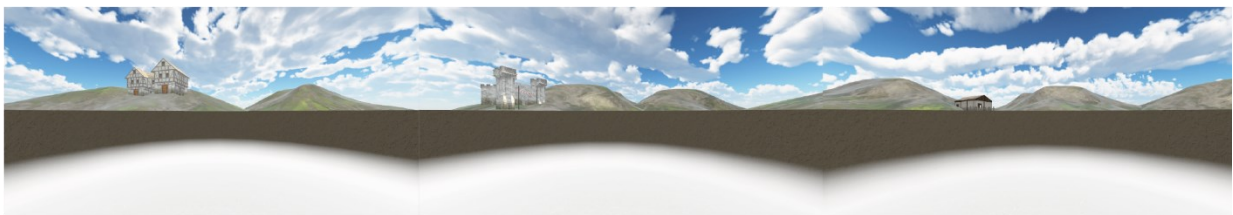
Figure 2

Virtual Environment

Panorama view scene A
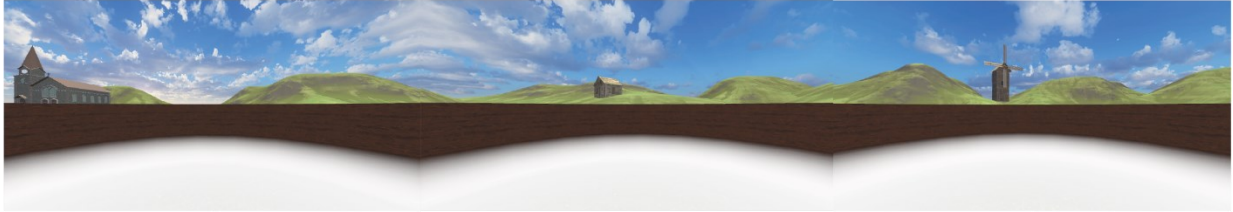
Panorama view scene B

Note. photo credit Lukas Gehrke, modified from Iggena et al. (in prep). The two scenes were counterbalanced across the MoBI and desktop sessions.

Table 1

*Spatial configuration of the 6 presented blocks*

Block	Origin angle	Target angle	Angle between origin and target	Target distance from center (meters/virtual meters)
1	0	315	-45	2.63
2	300	165	-135	2.77
3	240	15	135	2.52
4	180	225	45	2.03
5	120	75	-45	2.68
6	60	195	135	2.75

Note. Retrieved from Iggena et al. (in prep). The order of the blocks was randomized across each session.

12 different object models were used as targets, half of which were randomly assigned to the blocks in the desktop session and the other half to those in the VR session. The presentation order for desktop and MoBI sessions and scene versions were counterbalanced between participants in the patient group. All randomized parameters, including the presentation order of the blocks and target object models, matched within each set of patient and controls.

Figure 3

Session Trials

| Learning trial | Disorientation | Probe trial |
| A | B | C |

● Start location   ● Target location
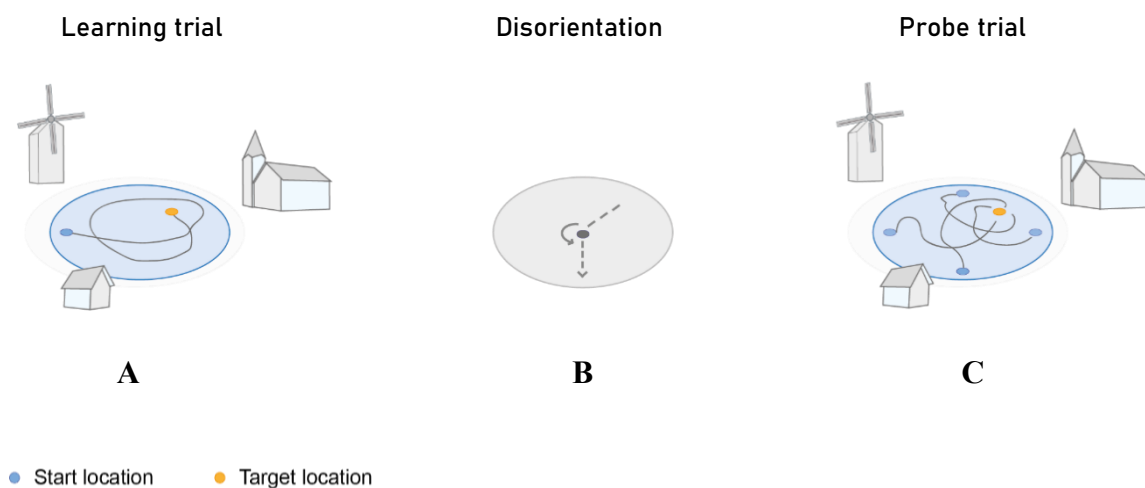
Note. photo credit Lukas Gehrke, modified from Iggena et al. (in prep). Each session consists of 3 learning and 4 probe trials. Disorientation task was presented between consecutive trials.

2.3.1 Learning Trials

Each experimental block started with three learning trials (see Figure 3A), in which the participant had to search for a hidden object in a circular arena with the floor covered with fog. The target object started to gradually appear when approached (< 1.2 (virtual) meters) and was registered as found when the participant was closer than 80 (virtual) cm from the center of the object while facing it. The target object remained on display for maximally 20

seconds and the participant was instructed to remember the location. This phase was optionally terminated earlier by a key press.

2.3.2 Probe Trials

The training trials were followed by four probe trials (see Figure 3C), in which the participant was asked to navigate back to the remembered location of the target object. The starting points were defined as rotations of the origin around the center by 0, 90, 180, and 270 degrees in each of the four trials, and they were presented in a randomly permuted order. In probe trials, the target object stayed hidden, and the participant completed the task by pressing the key after having positioned themselves at the remembered location of the target.

2.3.3 Disorientation Task

A disorientation task (see Figure 3B) was inserted between all pairs of consecutive trials or after termination of a break between blocks. In the task, all visual features that could be used as a spatial cue were hidden, including the sky. Participants were first asked to navigate to a waypoint at the center of the arena. Then a white sphere appeared in the viewing direction, which guided the participant to turn their body following a sequence of three rotations. The rotation sequence was randomized between right-left-right and left-right-left, with angles of 90, 180, and 90 degrees, each of which jittered by a random error sampled between ± 20 degrees. After following the sequence of rotation, they were asked to walk straight to the starting point of the next trial indicated by a way point. Only then the sky and other spatially relevant features in the virtual environment were revealed again. In the MoBI session, this prevented participants from walking straight back and forth between the starting point and the target location in the learning trials or from simply tracking back their steps to the rotated starting points in the probe trials. The rotation of starting points in the MoBI session was achieved by means of rotation of the virtual space with respect to the physical space. This way, in the physical space, the participant always started from the same location

within the room. However, the virtual environment was rotated, placing them at the rotated starting points. The reasoning behind this manipulation was that the representation of the location of oneself formed in a trial should be "reset" at the beginning of the next one. As it is physically challenging to "teleport" participants in real world, we have rotated the virtual environment and masked the potential dissonance with the disorientation task. In the desktop session, the disorientation task was included as well to match the participants' experience with the MoBI session.

2.4 Analysis

All data analyses were done in MATLAB (R2020b version 9.9; The MathWorks, Inc., Natick, MA, USA), using custom scripts based on the EEGLAB toolbox (version 2021.0; Delorme & Makeig, 2004) and the BeMoBIL pipeline (Klug et al., in prep).

In order to preprocess the EEG data, the BeMoBIL pipeline was used (Klug et al., prep). The BeMoBIL pipeline was designed for mobile EEG datasets to improve the signal-to-noise ratio. As it provides a standardized protocol with automatization of most preprocessing steps, the preprocessing procedure can be easily replicated in other studies (Delaux et al., 2021). The raw data was downsampled to 250 Hz, and spectral peaks at 50 and 90 Hz were removed by using Zapline (Cheveigné, 2020) to reduce the power line artifacts. Noisy channels were detected for rejection via an automated function which has the same algorithm as the PREP pipeline (Bigdely-Shamlo et al., 2015). Rejected channels were reconstructed by interpolation of neighboring channels and re-referenced to the common average. High pass filter with cutoff frequency of 1 Hz was applied to the data to suppress slow drifts in EEG activity as removing slow drifts before independent component analysis improves the decomposition (Klug & Gramann, 2020). Independent component analysis (ICA) using adaptive mixture independent component analysis (AMICA) algorithm (Palmer et al., 2008) was performed to decompose the clean EEG dataset into independent

components (ICAs). For each independent component, an equivalent current dipole model was computed by performing dipole fitting procedure. ICLabel algorithm (Pion-Tonachini et al., 2019) which considers seven categories (brain, muscle, heart, line noise, channel noise and other) was used to classify ICs. Classification of brain ICs was based on the default version of ICLabel algorithm which uses majority voting. Therefore, the final dataset included sources that are very likely to be brain sources and their projections to the channels.

As the study was interested in theta power, 4-8 Hz bandpass filter was applied to the preprocessed data by using filtering function from BeMoBIL pipeline (Klug et al., in prep). After the bandpass filter, the data was segmented into 4 seconds epochs. Epochs were selected as two seconds before and after from the start of both learning and probe trials as well as the point that the target was found in the learning trials. While epochs of learning trials in which target location was found represented encoding, epochs which include the starting points of learning and probe trials were used for analysis related to retrieval, where they retrieved the location of the hidden target from memory and navigated back. Moreover, continuous baseline data which were recorded before each session was also segmented into 4 seconds of consecutive epochs.

To analyze non-phase-locked theta oscillations (4-8 Hz), event-related desynchronisation/synchronisation (ERD/ERS) (Pfurtscheller, 1989; Pfurtscheller & Lopes da Silva, 1999) was calculated. ERD/ERD calculation was confined to frontal-midline area, and AFz, AF3, AFF1h, AFF2h, and AF4 electrodes were clustered for the analysis. To avoid the effect of event-related potentials (ERPs) which reflects the phase-locked EEG activity on ERD/ERS, the intertrial variance method was used to calculate ERD/ERS (Kalcher & Pfurtscheller, 1995 & Kober & Neuper, 2011). Intertrial variance is defined as:

$$IV_{(j)} = \frac{1}{N-1} \sum_{i=1}^{N} (X_{f(i,j)} - \bar{X}_{f(j)})^2$$

Where, N is the total number of trials, $X_{f(i,j)}$ is j^{th} EEG sample of the ith trial of the bandpass filtered data, and $\overline{X}_{f(j)}$ is the average of all filtered trials at the jth sample (Kalcher & Pfurtscheller, 1995; Shahlaei et al., 2018). In the current study, firstly, average of bandpass filtered data across trials was calculated. Afterwards, to compute the point-to-point intertrial variance, the average was subtracted from each data samples separately. Finally, the calculated difference scores were squared and averaged over trials. Intertrial variances were calculated using the same steps for all encoding and retrieval epochs as well as baseline. Later, ERD/ERS was calculated as:

$$ERD/ERS = \frac{IV_{Event} - IV_{Reference}}{IV_{Reference}} \times 100\%$$

Where, IV_{Event} represents the variance of the event related period, and $IV_{Reference}$ is the variance of the reference period (Kalcher & Pfurtscheller, 1995 & Kober & Neuper, 2011). Therefore, in the present study, baseline variance was subtracted from variance of encoding and retrieval epochs separately and the results was multiplied by a hundred to calculate the ERD/ERS for encoding and retrieval epochs. Furthermore, rotated (90°, 180° and 270°) and non-rotated conditions presented in probe trials were segregated and ERD/ERS calculation was conducted by using the same intertrial variance method steps described above.

Chapter 3: Results

One sample t-test was performed to compare theta power values during encoding phase, retrieval phase in learning trials, and retrieval phase in probe trials against zero separately. It was found that theta power during encoding phase ($M = 13.58$, $SD = 31.74$) differ significantly from zero, $t(53) = 3.14$, $p < .01$. Mean of theta activity during retrieval phase of probe trials ($M = 16.40$, $SD = 23.05$) was significantly higher than the population with mean equal to zero, $t(53) = 5.23$, $p < .001$. Statistically significant result was also found for the retrieval phase during the learning trials ($M = 12.08$, $SD = 33$), $t(53) = 2.69$, $p < .01$. Therefore, null hypotheses were rejected at the 5% significance level.

In order to determine whether there is an effect of the type of the experiment setup (MoBI vs desktop setup) and the subject group (patient vs control group) on the theta activity, 2-Way Repeated Measures ANOVA was conducted for retrieval in both probe and learning trials and encoding separately (see Table 2).

Table 2

ERD/ERS Theta Table

		Patients		Controls	
		MoBI	Desktop	MoBI	Desktop
Encoding θ	Mean	4.604	27.69	7.213	17.38
	SD	35.23	30.80	37.20	22.81
Retrieval (probe) θ	Mean	11.09	18.80	4.868	29.39
	SD	14.65	15.60	27.66	18.42
Retrieval (learning) θ	Mean	3.630	11.59	0.292	28.35
	SD	26.62	10.63	26.26	43.04

Note. Means and standard deviations of theta was presented separately for each conditions.

For encoding phase (see Figure 4), participants did not show significant difference in FM theta oscillations in MoBI setup ($M = 6.34$, $SD = 35.89$) compared to desktop setup ($M = 20.82$, $SD = 25.63$), $F(1, 25) = 2.27$, $p = .14$. Main effect of subject group was also not significant as difference between FM theta power of patients ($M = 16.15$, $SD = 34.23$) and controls ($M = 12.30$, $SD = 30.85$) was not found, $F(1, 25) = 0.13$, $p = .72$. Moreover, interaction effect of subject group and experimental setup was not statistically significant, $F(1, 25) = 0.36$, $p = .55$.
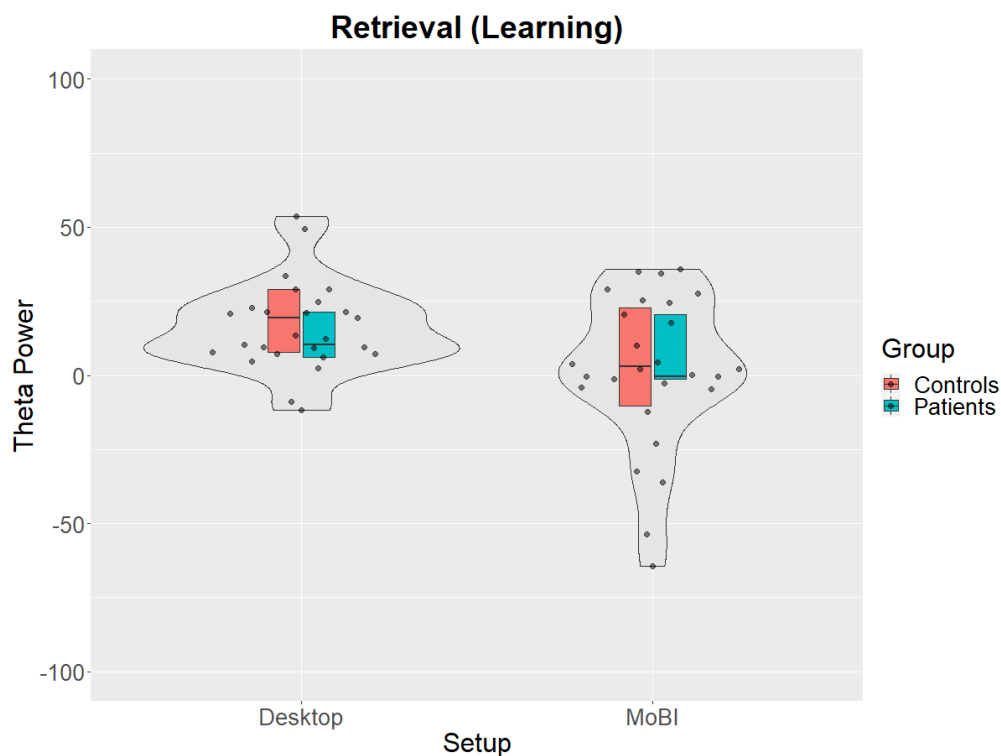
Figure 4

Encoding ERD/ERS Theta Graph
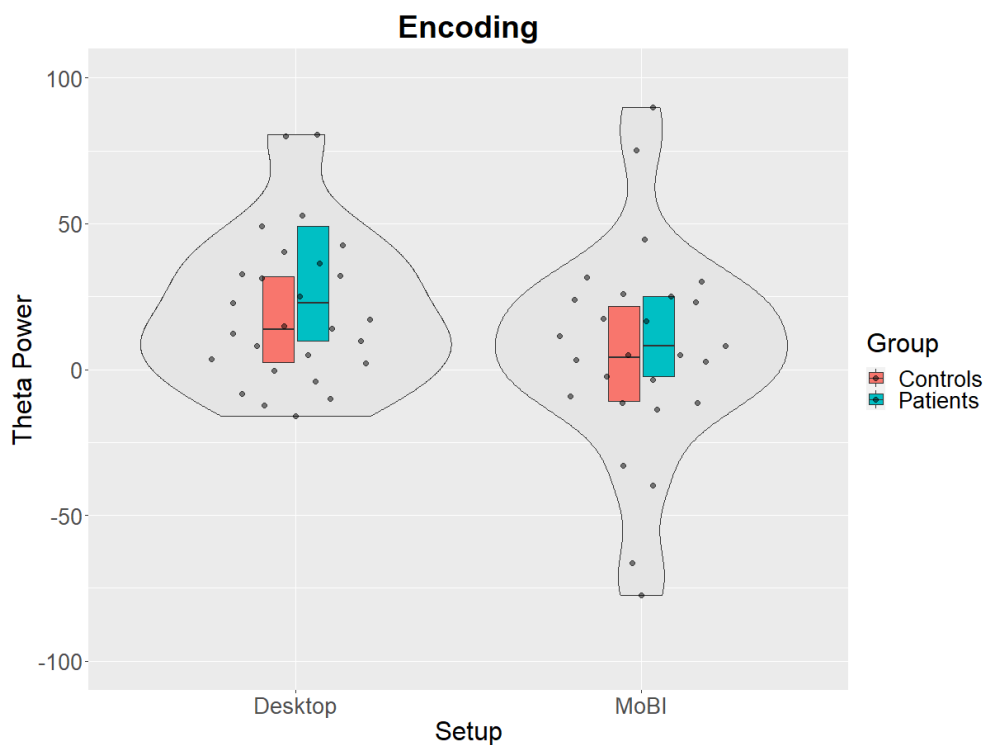
Note. While boxplots show the distribution of ERD/ERS theta power of subjects during encoding in MoBI and desktop setups separately for patient and controls, violin plots show the distribution of theta activity in MoBI and desktop setups for all participants.

During retrieval phase of probe trials (see Figure 5), repeated measures of ANOVA could not confirmed a main effect of setup on ERD/ERS theta, $F(1, 25) = 1.26$, $p = .27$.

Therefore, participants did not show statistically different theta activity in MoBI setup ($M =$ 6.94, $SD = 23.98$) compared to desktop setup ($M = 25.86$, $SD = 17.96$). Main effect of subject group was also not significant as difference between FM theta power of patients ($M = 14.94$, $SD = 15.21$) and controls ($M = 17.13$, $SD = 26.29$) was not found, $F(1, 25) = 0.12$, $p = .72$. There was not any interaction effect between the levels of subject group and setup $F(1, 25) = 0.74$, $p = .40$.
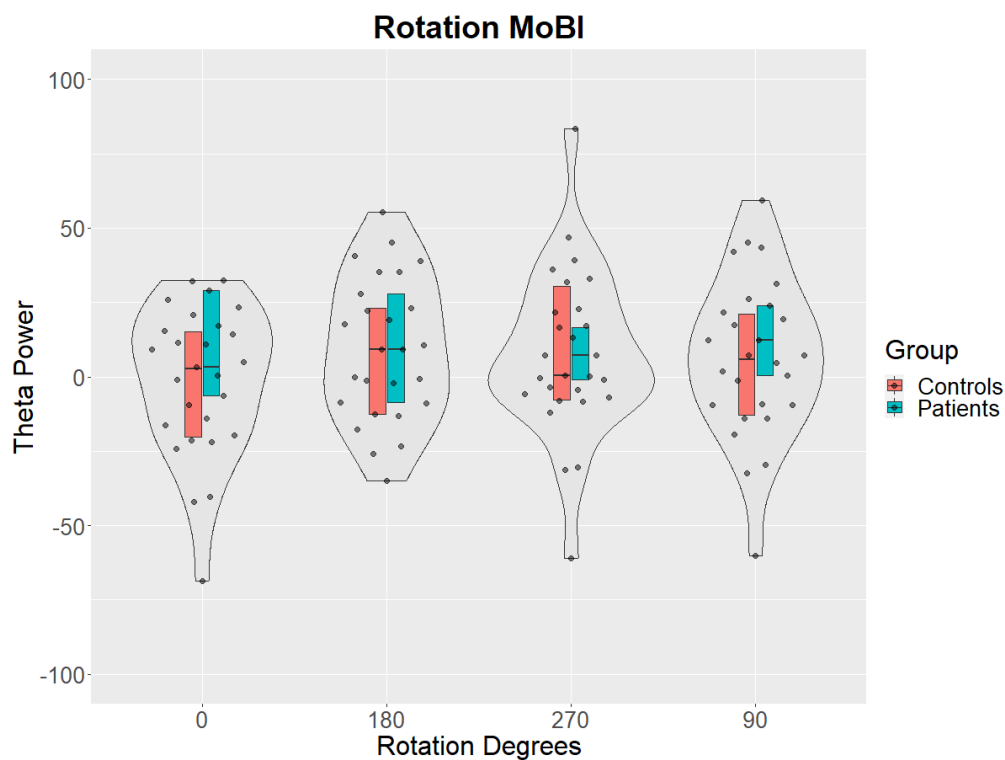
Figure 5

Retrieval (probe) ERD/ERS Theta Graph
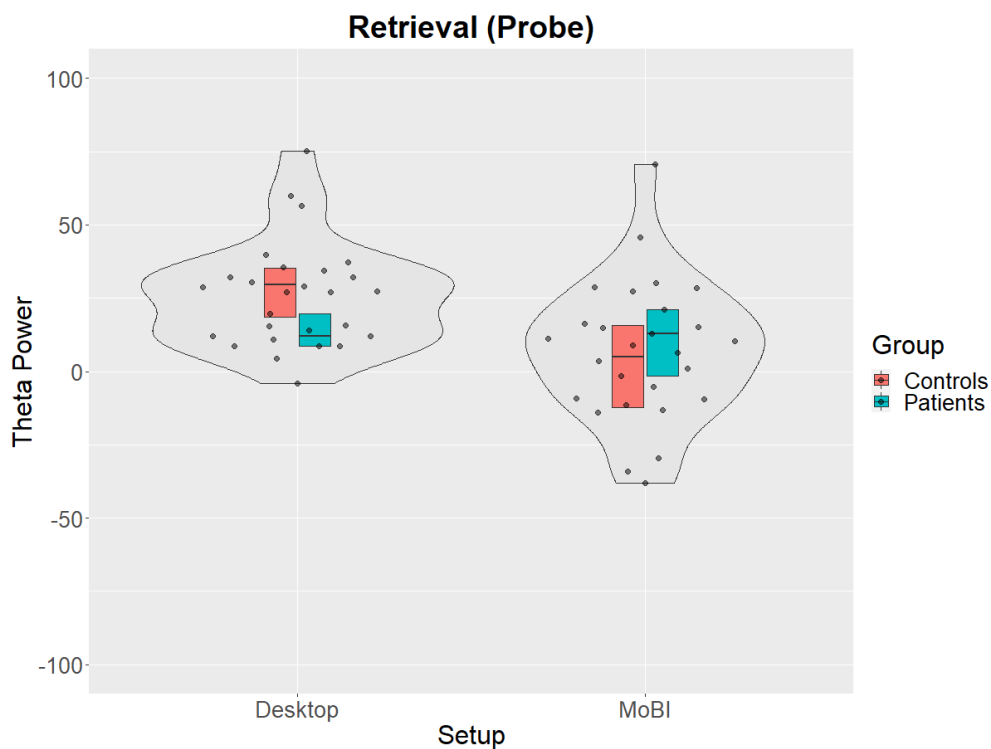
Note. While boxplots show the distribution of ERD/ERS theta power of subjects during the retrieval phase of probe trials in MoBI and desktop setups separately for patient and controls, violin plots show the distribution of theta activity in MoBI and desktop setups for all participants.

Similar results were found for retrieval phase during learning trials (see Figure 6). Theta activity of participants did not change significantly between MoBI ($M = 1.41$, $SD =$

25.92) and desktop setups (M = 22.77, SD = 36.20), $F(1, 25)$ = 0.004, p = .95. Although

controls (M = 14.32, SD = 37.91) show higher theta activity tendency compared to patient

subjects (M = 7.62, SD = 20.09), this effect was not statistically significant, $F(1, 25)$ = 0.61, p

= .44. Also, repeated measures of ANOVA analysis did not reveal significant interaction

effect between setup and study group for retrieval phase during learning trials, $F(1, 25)$ = 1, p

= .33.

Figure 6

Retrieval (probe) ERD/ERS Theta Graph

Note. While boxplots show the distribution of ERD/ERS theta power of subjects during the

retrieval phase of learning trials in MoBI and desktop setups separately for patient and

controls, violin plots show the distribution of theta activity in MoBI and desktop setups for all

participants.

Further analyses were preformed to understand the effect of rotation during probe

trials on ERD/ERS theta. The interaction effect of rotation, experimental setup and subject

group was tested by 2x2x2 repeated measures ANOVA (see Figure 7 and 8). While experimental setup and subject group has two levels as MoBI vs. desktop setup and patient vs control group, levels of rotation variable were defined as rotated vs unrotated trials. Repeated Measures ANOVA did not show main effect of rotation. Difference between theta powers during unrotated (M = 2.65, SD = 25.90) and rotated trials (M = 20.70, SD = 17.34) was not confirmed, $F(1, 25)$ = 0.67, p = .42. However, even though interaction effect of rotation and setup ($F(1, 25)$ = 1.03, p = .32) as well as interaction effect between all 3 variables ($F(1, 25)$ = 0.18, p = 68) was not found, the data showed significant interaction between rotation and subject group, $F(1, 25)$ = 4.80, p < .05. Yet, further post-hoc analysis did not show any significant effect of neither rotated trials (p = .24) nor unrotated trials (p = .27) on the subject group.

Figure 7

Rotation (MoBI) ERD/ERS Theta Graph

Note. Distribution of ERD/ERS frontal midline theta activity in different rotation degrees during MoBI session.

Figure 8

Rotation (Desktop) ERD/ERS Theta Graph

Note. Distribution of ERD/ERS frontal midline theta activity in different rotation degrees during desktop session.

Regression analyses were conducted in order to reveal whether theta power values during encoding and retrieval predict performance results of the spatial navigation task. FM theta activity of control participants during encoding significantly predicted duration that participants spend to find the target in learning trials in both MoBI ($\beta = .06$, $t(16) = 2.26$, $p < .05$) and desktop setup ($\beta = .21$, $t(16) = 2.14$, $p < .05$). Also, encoding FM theta activity of control participants explained significant proportion of variance in search duration for both MoBI ($R^2 = .24$, $F(1, 16) = 5.1$, $p < .05$) and desktop ($R^2 = .23$, $F(1, 16) = 4.65$, $p < .05$) setups. However, the analysis for encoding FM theta power of patients did not indicate significant prediction of search duration results for neither MoBI setup ($\beta = -.08$, $t(7) = -.74$, $p = .48$) nor desktop setup ($\beta = .06$, $t(7) = -.11$, $p = .91$) (see Figure 9). Theta activity during

encoding also predicted distance error to the target value in retrieval trials significantly for control group ($\beta = .008$, $t(16) = 2.12$, $p < .05$) and marginally for patient group ($\beta = .02$, $t(7) = 2.23$, $p = .06$) in desktop setup (see Figure 10). Increase in theta values corresponded to higher error in estimating target position in both conditions. However, significant prediction results for MoBI setup were not found for both patient ($\beta = -.001$, $t(7) = -.55$, $p = .60$) and control ($\beta = .001$, $t(16) = .72$, $p = .48$) subjects. Lastly, retrieval theta values in both probe and learning trials did not predict distance error for any conditions (see Table 3 & Figure 11 and 12)

Table 3

Regression Results

DV	IV	Condition	β	*p*	R^2	F
Encoding θ	Search Duration	Patients - MoBI	-.088	.477	.281	2.73
		Controls - MoBI	.064	.038*	.242	5.1
		Patients - Desktop	.589	.91	.272	2.61
		Controls - Desktop	.216	.048*	.225	4.65
Encoding θ	Distance Error	Patients - MoBI	-.001	.595	.105	.821
		Controls - MoBI	.001	.484	.031	.514
		Patients - Desktop	.022	.061	.418	5.02
		Controls - Desktop	.007	.049*	.377	9.69
Retrieval (probe) θ	Distance Error	Patients - MoBI	-.010	.171	.364	4
		Controls - MoBI	.002	.354	.054	.921
		Patients - Desktop	-.021	.401	.103	.801
		Controls - Desktop	.007	.221	.186	3.66
Retrieval (learning) θ	Distance Error	Patients - MoBI	.005	.356	.127	1.02
		Controls - MoBI	.001	.829	.003	.048
		Patients - Desktop	-.048	.177	.244	2.26
		Controls - Desktop	.004	.093	.234	4.89

Note. Values of regression coefficient (β), p, coefficient of determination (R^2), and F are presented for each condition separately. * $p < .05$

Figure 9
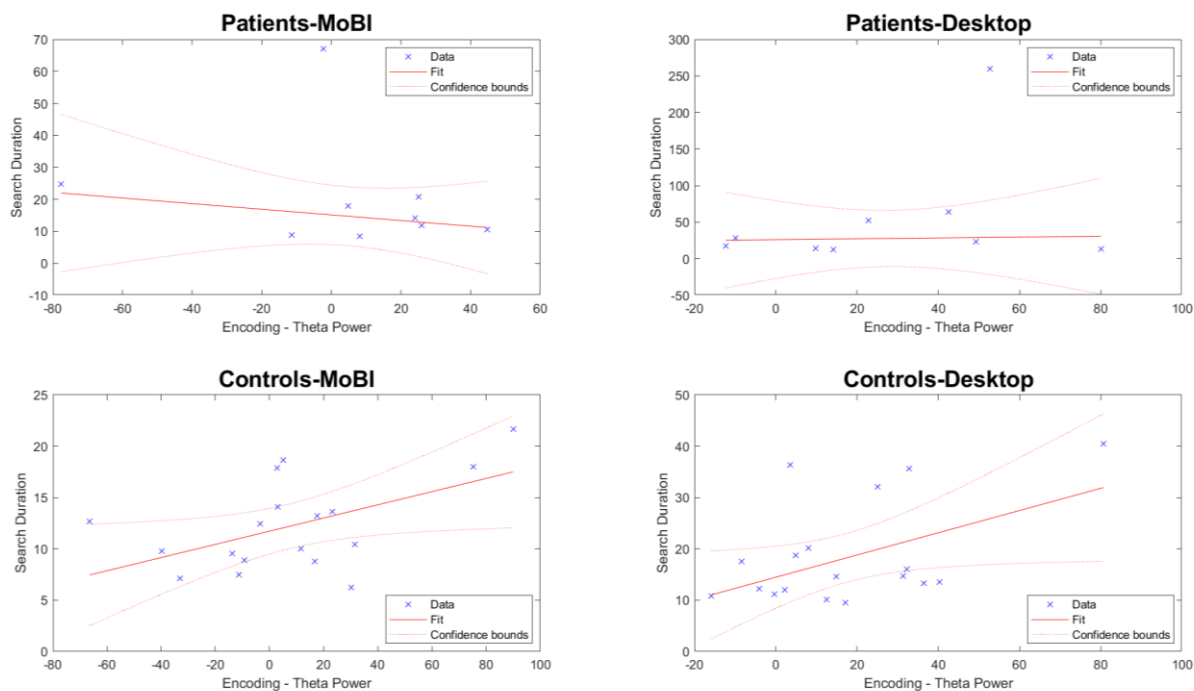
Regression Graph (Encoding Theta & Search Duration)

Figure 10

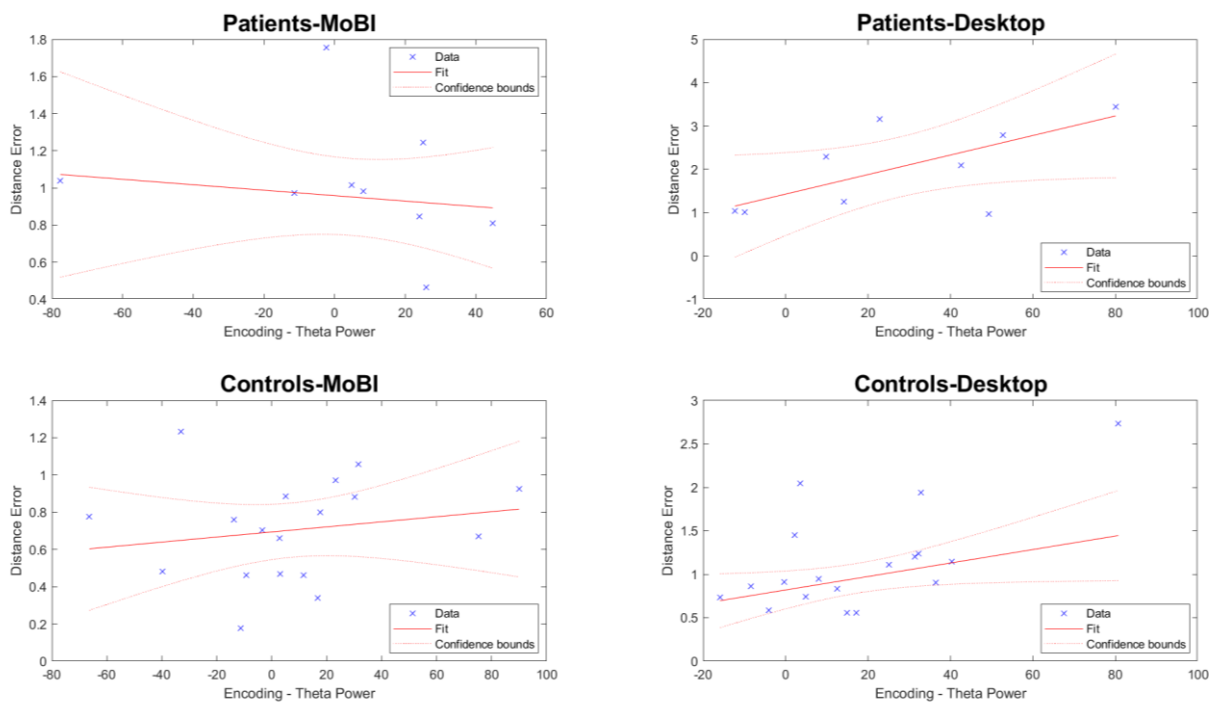*Regression Graph (Encoding Theta & Distance Error)*

Figure 11

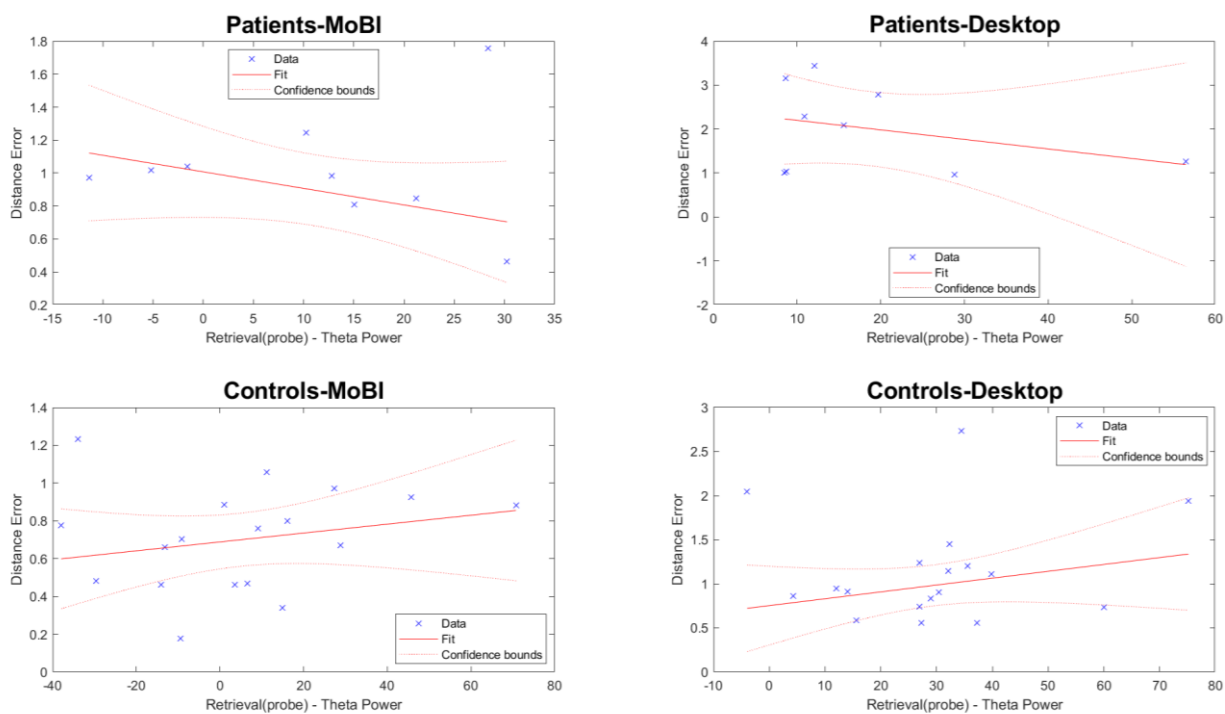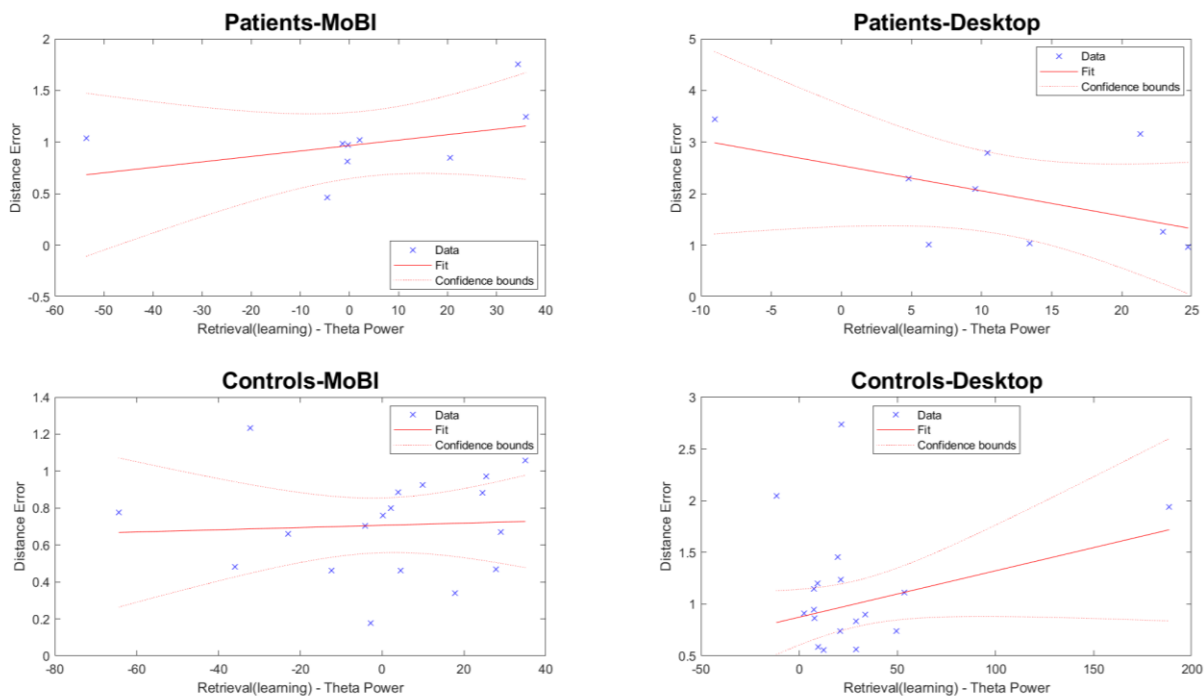*Regression Graph (Retrieval-Probe Theta & Distance Error)*

Figure 12

Regression Graph (Retrieval-Learning Theta & Distance Error)

Chapter 4: Discussion

The current study aimed to reveal how brain dynamics of spatial navigation of patients with hippocampal lesions change under active movement which provides idiothetic cues compared to healthy controls. In order to study the brain under active movement, Mobile Brain/Body Imaging (MoBI) approach was used. In line with our hypothesis, an association between performance and theta power was found in some conditions. Although neither the main effects of setup (MoBI vs desktop) and group (patients vs controls) nor the interaction effect of these two variables could not be found statistically significant, change in the differences between ERD/ERS theta power of the variables in different conditions might explain the behavioral results (Iggena et al., in prep). Potential reasons and limitations for non-significant results are also discussed in this section.

Frontal-midline theta activity is associated with goal-directed behavior, landmark processing, spatial navigation, and working memory during both encoding and retrieval (Cavanagh & Frank, 2014; Jaiswal et al., 2010; Kober & Neuper, 2011; Laukka et al., 1995). Similarly, the current data also showed significant theta activity at the frontal-midline site during both the encoding and retrieval phase of the spatial navigation task based on the t-test results. Therefore, it could provide evidence for the association between spatial memory and frontal-midline theta. Although localization analysis was not conducted, given that FM theta power generally represents activity from the medial prefrontal cortex (mPFC) and anterior cingulate cortex (ACC), involvement of mPFC and related structures in spatial memory might be also considered (Ishii et al., 1999). FM theta is found to be related to the encoding phase of spatial navigation which represents the process of learning a spatial environment (Friese et al., 2013). The results showed that retrieval of the spatial information in order to reach a target location in a specific environment might be also associated with the activity in the frontal

midline area. Therefore, it is also possible to remark on the relationship between goal-directed navigation and FM theta activity.

Even though a significant effect of the study setup was not found, it can be seen that theta activity increased in the desktop setup compared to MoBI in both encoding and retrieval phases. As it was discussed throughout the paper, while physically locomoting in an environment in order to navigate from one location to another, proprioceptive and vestibular information are integrated with other sensory cues (Karimpur & Hamburger, 2016). Therefore, in the MoBI setup participants might benefit from sensory information from multiple sources including body related information, while in the desktop setup, idiothetic cues may not be available for subjects. Moreover, participants might still rely on information coming from the body in the desktop session, but it might contradict the other sensory information such as visual information. Therefore, instead of providing useful information for successful navigation, they would even obstruct the process (Dolins & Mitchell, 2010; Taube et al., 2013). Thus, either in the case of absent idiothetic cues or in the case of contradicting information, navigating in the desktop setup might be considered a harder task compared to navigation in the MoBI setup. As cognitively more demanding tasks induce more FM theta activity, an increase in the theta power in desktop setup might be attributed to the high cognitive demand (Gevins et al., 1997; Jensen & Tesche, 2002).

One of the possible explanations for the association between cognitively challenging tasks and FM theta activity might be the role of attention. Tasks that are cognitively more demanding require to allocate and recruit more cognitive resources; therefore, highly focused attention is needed to complete them compared to tasks that are less challenging (Clayton et al., 2015; Sauseng et al., 2007). In the present study, the stationary condition might require participants to pay attention more to the task and induce higher frontal midline theta compared to the mobile condition which is relatively easier due to the presence of

multisensory information. The role of the anterior cingulate cortex in attention also supports this hypothesis (Ishii et al., 1999).

Another possible explanation might be the association between frontal midline theta and cognitive control (Domic-Siede et al., in prep; Sauseng et al., 2019). Based on the environment, social context, and task demand, the processing of information varies adaptively. This adaptation refers to cognitive control. Therefore, cognitive control which is also referred to as executive function can be defined as successfully monitoring and selecting behaviors, thoughts, and emotions depending on the current task demand and goals (Dixon, 2015). It includes a wide range of mental operations including attention allocation (Mackie et al., 2019). Therefore, it provides a wider perspective and explanation to the reason behind the association of cognitively demanding tasks and higher FM theta activity.

Confronting multiple task demands and conflict in information processing requires cognitive control of the process (Eschmann et al., 2018). According to conflict monitoring theory, the medial prefrontal cortex and anterior cingulate cortex play an important role in reducing and detecting conflict by a control mechanism (Yeung, 2014). Accordingly, numerous studies remarked on the relationship between FM theta and the cognitive control process, and tasks that require more cognitive control were found to be associated with higher FM theta activity (Cavanagh & Frank, 2014; Sauseng et al., 2019). Because of the discrepancy between idiothetic and allothetic information, more cognitive control on the information integration in order to learn and navigate in the maze might be the reason for higher theta activity in desktop setup compared to MoBI.

A significant result could not be found also for the main effect of the experimental group. However, a pattern seen in the mean difference between control and patient participants might explain the behavioral results of the current data (Iggena et al., in prep). The data showed different results for encoding and retrieval phases in terms of the

experimental group. During the encoding phase, while patients have higher frontal midline theta activity compared to controls, control subjects showed higher theta activity during retrieval in both probe and learning trials. In order to interpret the difference between EEG activity of two groups better, it might be beneficial to compare them with behavioral results. Behavioral analysis of the current data was not in the scope of this paper; however, Iggena et al. (in prep) have conducted a behavioral analysis of the same dataset and found that control subjects had better memory scores in the spatial navigation task compared to patients. This result replicates the literature and provides evidence of the key role of the hippocampus in spatial navigation (Jacobs et al., 2010; Redish & Ekstrom, 2013). As patients with hippocampal lesions had worse memory scores, it might show that they were less successful to encode and/or retrieve spatial information compared to control subjects. Therefore, learning the maze might be a cognitively more demanding task for patients, and require more cognitive control than controls. This might explain the higher frontal-midline theta seen among patients during the encoding phase.

Contrary results for encoding and retrieval might be due to different navigation strategies. Different trajectories to navigate to the target position between patient and control groups were found in the behavioral analysis (Iggena et al., in prep). Specifically, while control participants tended to follow the shortest path to reach the landmark, some patients preferred to go to the center first and then find the target location as they repeated their movement from the previous trial. Therefore, while controls tried to retrieve the spatial information related to the maze, patients tried to retrieve their previous movements. Because of this strategy difference, the navigation task might be harder for the controls as they need to remember more details related to the maze. Thus, higher activity during retrieval in control subjects might be also due to the cognitive control or attention process. This trajectory difference might also explain the significant interaction effect of rotation and subject group.

Because of the strategy that control subjects chose, the task might be even more difficult for them compared to patient subjects. Instead of trying to find the landmark by benefitting from environmental cues and spatial information they acquired, patients tried to replicate their previous movements; therefore, rotating the origin might not affect their response as much as the control group.

It is also possible to compare patient and control groups according to the study setup. In both patient and control groups, the absence of physical locomotion led to higher EEG activity in the frontal midline scalp site during both encoding and retrieval. Moreover, the mean difference between patient and control subjects were less in the MoBI setup compared to desktop, so participants showed more similar theta activity during physical movement condition. This finding is also parallel with the behavioral results (see figure 13). According to behavioral results, both control and patient groups benefited from physical locomotion, and it was more pronounced among patient subjects.

Figure 13

Memory score graph and memory score calculation
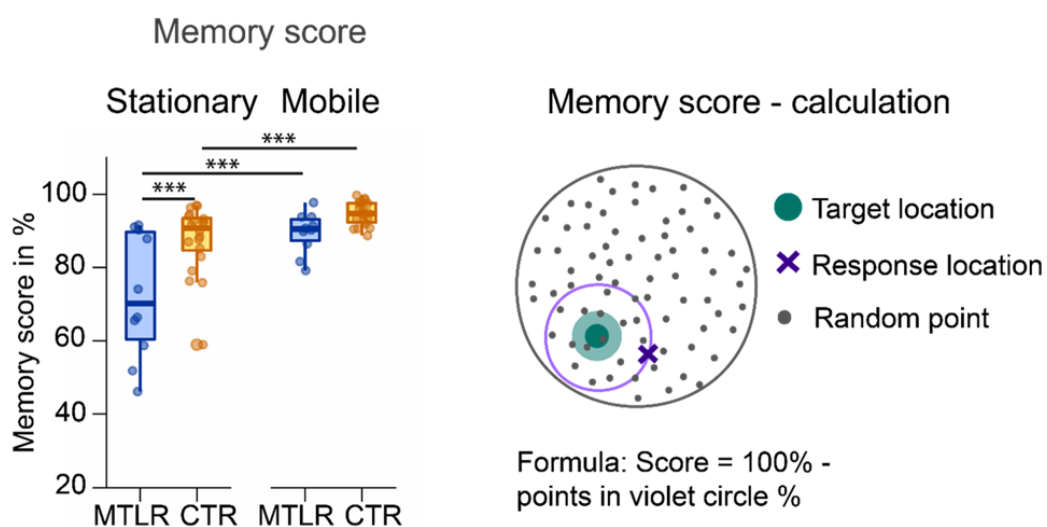
In the literature, FM theta activity was found to be positively associated with performance results (Klimesch et al., 2001, Weiss et al., 2000). In the current study, it was

found that theta activity of controls during encoding predicted the time that participants spend to search for the target location. Specifically, higher theta activity induced higher search duration time. Moreover, theta activity during encoding also predicted distance error between the response and target location in retrieval trials among control participants in desktop setup and distance error increased as there is an increase in the theta activity. An increase in the search duration and distance error means that subjects performed worse. Therefore, the results were contradictory to some literature results in which an association between FM theta and higher performance results was suggested. However, there is also some evidence for the relationship between lower performance and higher FM theta activity (Maurer et al., 2015). As the significant negative relationship was only observed in controls, the relationship might depend on the navigation strategy that control, and patient groups choose. In the behavioral analysis, it was found that while control subjects tend to use allocentric framework, patients tend to rely more on egocentric representations. Therefore, the relationship found among control groups might be related to the allocentric reference frame which activate parieto-premotor network specifically anterior cingulate cortex (Gramann et al., 2006).

Besides the strengths of the current study, there are also limitations that may lead to some non-significant results in the analysis. Firstly, two subject sets in total 6 participants were needed to be removed from the study. The sample size was relatively small as participants with hippocampal lesions were rare. Therefore, removing the data of some participants further decreased the power of the study. Secondly, even though noise detection procedure was conducted, and non-brain independent components were removed, the data was still noisy to some extent especially in the MoBI setup due to movement-related artifacts. Lastly, although some explanations of the possible brain regions related to the results were discussed, source localization was not conducted in the scope of this paper. Therefore, it is

difficult to associate the frontal midline theta power with specific brain areas without source localization.

In future studies, these limitations would be taken into consideration to draw more conclusive results. Further noise detection procedures would be conducted to remove artifacts in order to have clean data. Conducting source analysis would be also beneficial to interpret the data better. The results were interpreted based on the assumption that frontal midline theta is generally generated in the medial prefrontal cortex and anterior cingulate gyrus. However, it may not be the case for the current study. Therefore, knowing the source of the activity would lead to a better understanding of the relationship between the hippocampus and other brain areas and the spatial navigation loop in the brain. Furthermore, analyzing the activity from other brain regions and oscillations from different scalp sites would provide a better view of the role of different brain regions in spatial navigation. Finally, in the current study allocentric and egocentric navigation were not analyzed in terms of their brain dynamics. However, behavioral results showed that patient and control participants tended to have different strategies. Therefore, differences between patients and controls in terms of their brain activity associated with allocentric and egocentric navigation during physical movement would be investigated in future studies.

In conclusion, although there are some limitations, the current study may provide a view to understand the role of the hippocampus in spatial navigation and integration of the multisensory information coming from idiothetic cues. In line with the behavioral analysis, even though significant result could not be found, patient and control groups tend to show similar electrophysiological activity around frontal-midline area in MoBI setup compared to desktop. This may highlight the fact that multisensory integration facilitates the spatial navigation process even in the presence of hippocampal damage and decrease the cognitive demand needed to complete the navigation task. Moreover, significant negative association

that was found between FM theta and performance results among control participants may provide a neuroscientific explanation of different navigation strategies used by patient and controls. Finally, since it is possible to see some differences depending on whether participants were tested in a classical stationary setup or in a Mobile Brain/Body Imaging setup, it could represent the importance of including physical locomotion in spatial navigation research and the strengths of the MoBI technique.

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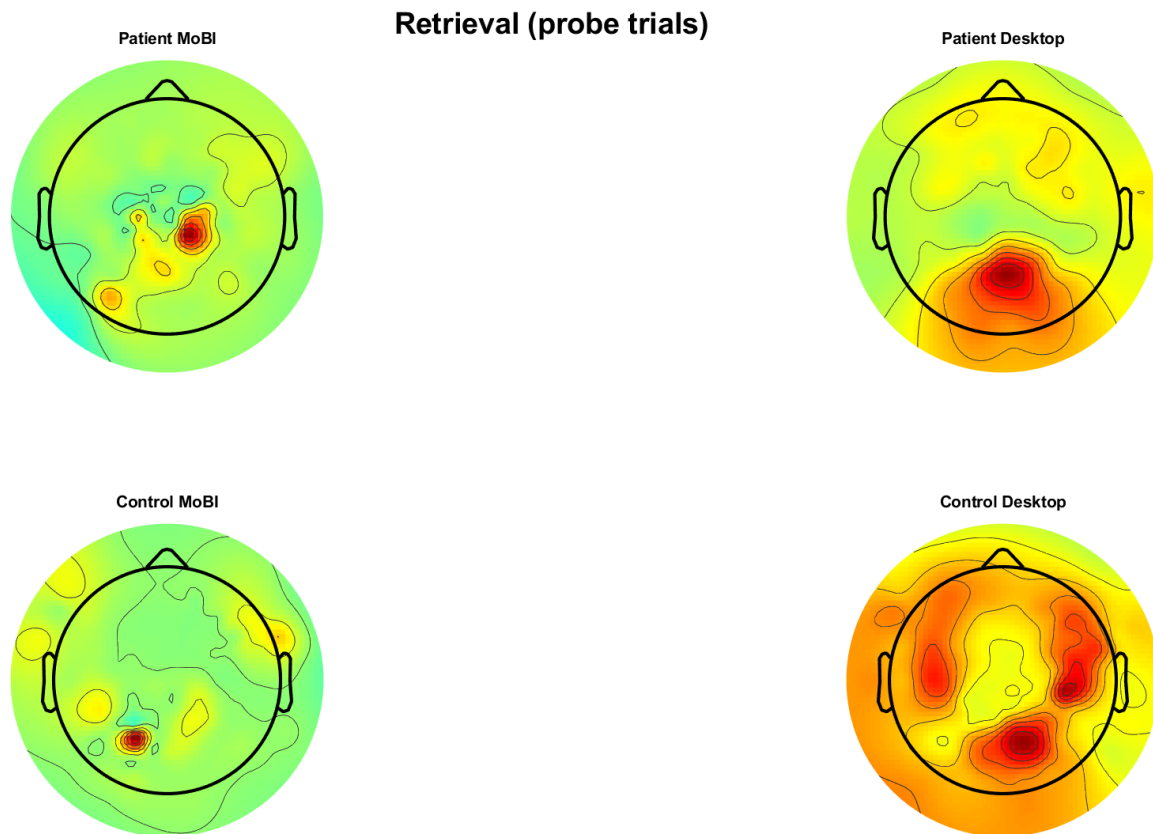   Oxford University Press.

Supplementary Materials

Figure S1
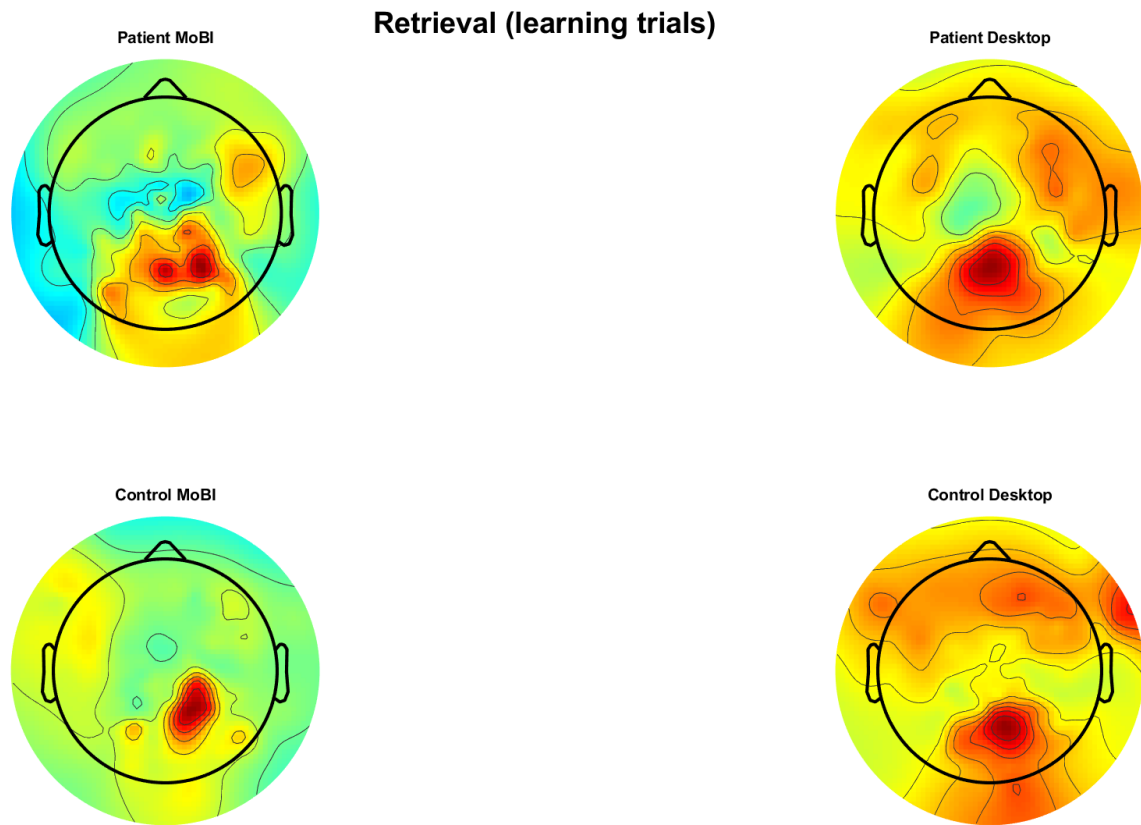
Topographic Map of Encoding Theta
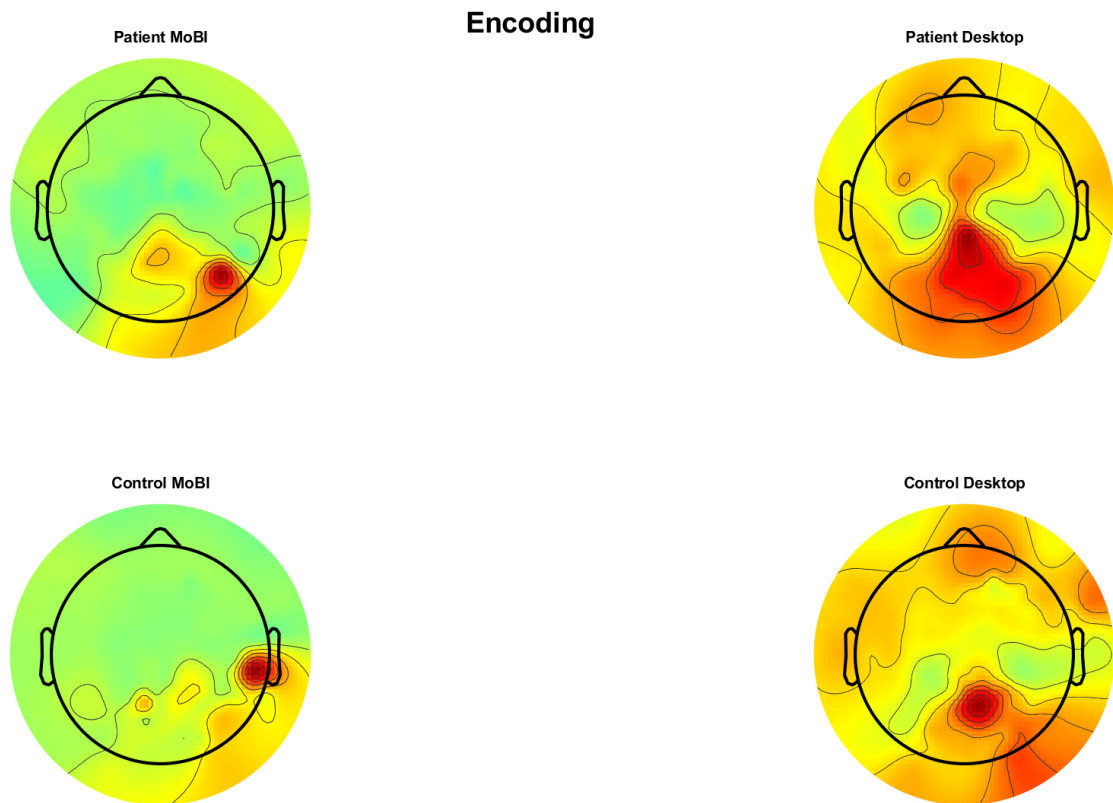
Note. The graphs show the distribution of ERD/ERS theta during encoding across the scalp.

All electrodes were included to the map.

Figure S2

*Topographic Map of Retrieval (probe) Theta*

Note. The graphs show the distribution of ERD/ERS theta during retrieval (probe) across the scalp. All electrodes were included to the map.

Figure S3

Topographic Map of Retrieval (learning) Theta

Note. The graphs show the distribution of ERD/ERS theta during retrieval (learning) across the scalp. All electrodes were included to the map.
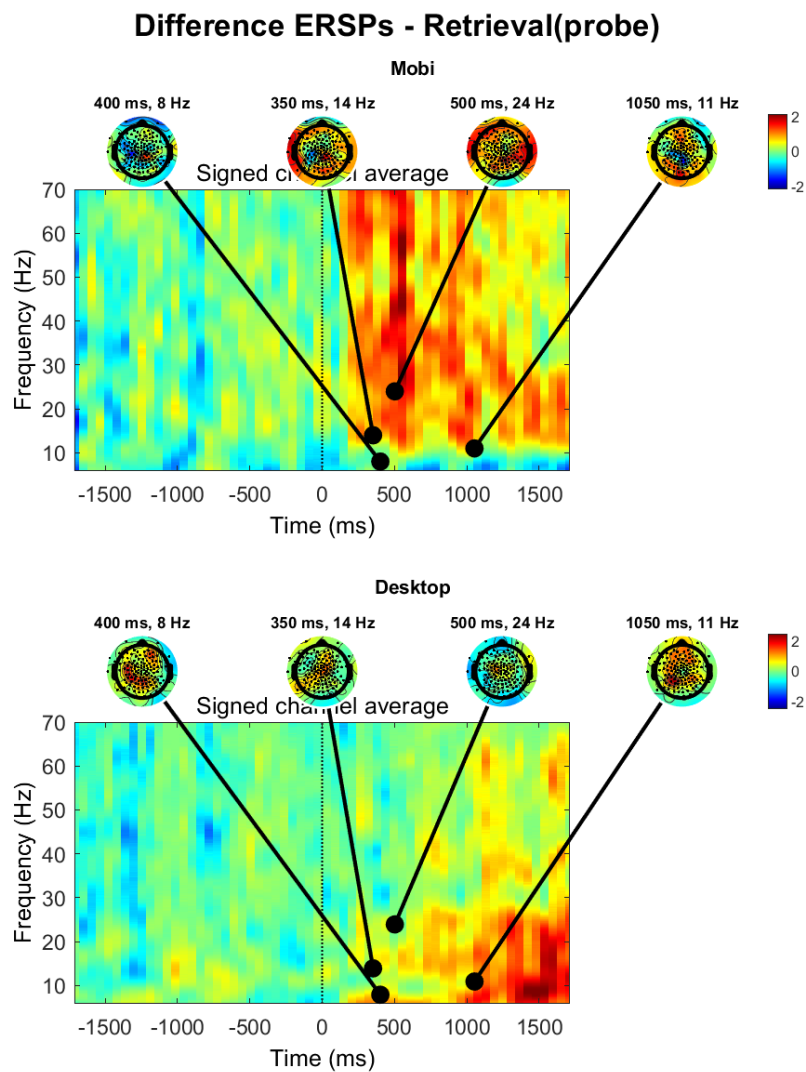
Figure S4

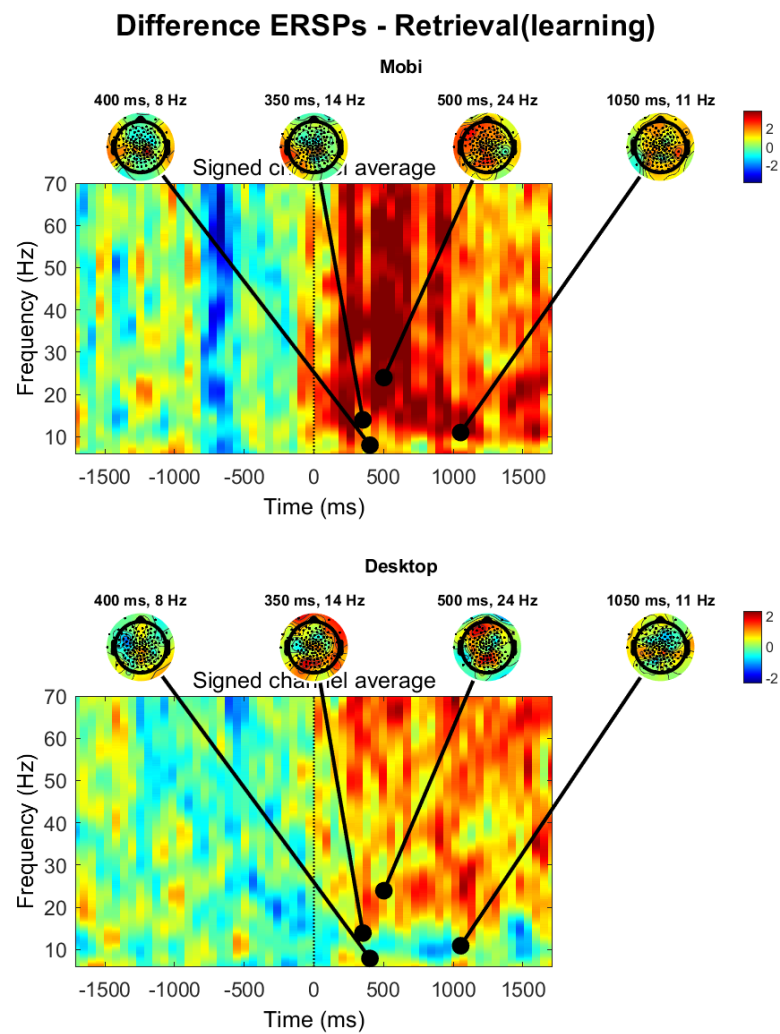*Difference ERSPs during Encoding*
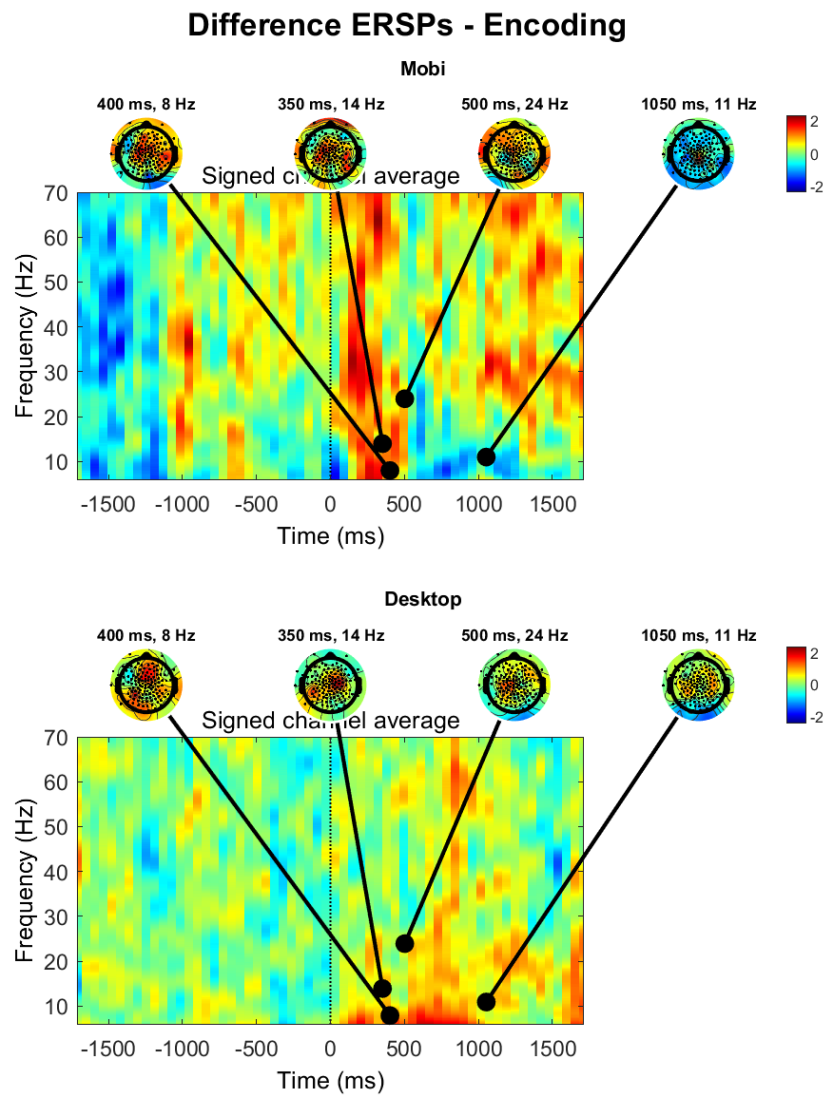
Note. All electrodes were included to the ERSP analysis. Difference ERSPs were calculated

by subtracting ERSP values of patients from controls.

Figure S5

Difference ERSPs during Retrieval (probe)

Note. All electrodes were included to the ERSP analysis. Difference ERSPs were calculated by subtracting ERSP values of patients from controls.

Figure S6

Difference ERSPs during Retrieval (learning)

Note. All electrodes were included to the ERSP analysis. Difference ERSPs were calculated by subtracting ERSP values of patients from controls.