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Dynamic Imaging of Deep Brain Structures with MEG: Contributions to Understanding Human Memory

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1. Introduction

MEG is traditionally conceived of as a tool that provides excellent temporal and spatial resolution to characterize the dynamic time-course of brain responses originating within superficial cortex, such as basic primary sensory or motor responses. However, this dynamic imaging of brain activity within specific regions could also be very useful for expanding upon our knowledge of the neural underpinning of complex cognitive processes, such as memory. Although cognitive neuroscientists are now beginning to appreciate the utility of MEG imaging to illuminate the underlying mechanisms of human cognition, there has been a considerable debate regarding whether it is feasible to apply MEG to the study of memory. This chapter will briefly outline this debate, and provide a selective review of the literature that suggests that not only can MEG be a reliable tool with which to investigate memory in multiple populations, but that the insights gained by the application of MEG technology to the field of memory research are beyond those provided by other neuroimaging tools, such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET) and electroencephalography (EEG). These insights come from the examination of the spatiotemporal dynamics of healthy brain function, as well as how these patterns are perturbed in pathological conditions such as in individuals with brain damage or psychiatric disorders. Ultimately, we suggest that recent findings from MEG have encouraged researchers to reconsider their conceptualizations of memory. For example, memory is often thought of as a modular cognitive process, distinct from other faculties such as perception. However, we will show new evidence from recent MEG studies that suggests a more distributed and interactive conceptualization of memory, and of cognition in general.

2. Detection of hippocampal signal using MEG

The difficulty surrounding the application of MEG to the study of human memory is that brain structures critical for memory are located deep within the brain. Neuropsychological and neuroimaging (MRI and PET) studies have implicated the hippocampus, a structure deep within the medial temporal lobe, as a crucial region supporting memory (e.g. for reviews see Cohen & Eichenbaum, 1993; Cohen et al., 1999; Cohen & Squire, 1980; Moses & Ryan, 2006). Specifically, bilateral damage to the hippocampus in humans leads to profound and pervasive amnesia in which the ability to remember or acquire particular classes of long-term memories is lost (Rosenbaum et al., 2008; Scoville & Milner, 1957; Tulving 1972). However, it has traditionally been assumed that reliable signal could not be obtained from deep sources such as the hippocampus, and as a result, MEG investigations have focused on recording from superficial cortices and have constrained the kinds of conceptual questions that were being investigated. Thus, in order to apply MEG technology to the study of human memory, thereby developing a new avenue of research in cognitive neuroscience, the validity of imaging hippocampal activation had to be demonstrated (for in depth discussions see Quraan et al., 2011; Riggs et al., 2009; Stephen et al., 2005).

The first challenge to hippocampal imaging with MEG lies with the structural property of the hippocampus itself. The spiral or spherical shape of the hippocampus could theoretically lead to cancellation of all signal, which would allow no detectable activation to pass outside of the hippocampus (Baumgartner et al., 2000, Mikuni et al., 1997). This type of complete cancellation would require perfect anatomical symmetry, as well as simultaneous activation of the dentate and cornu ammonis (CA) fields with equal signal intensity. However, this assumption of perfect symmetry is incongruent with studies that have demonstrated anatomical and electrophysiological asymmetries within the hippocampus (Duvernoy, 1988; Yeckel & Berger, 1990). Moreover, simultaneous recording from MEG and subdural electrodes demonstrates that strong epileptic discharges originating from within the hippocampus can, indeed, be detected using MEG (Mikuni et al., 1997). Additionally, simulation work demonstrates that MEG has the sensitivity to detect epileptic spike activity from the hippocampus and surrounding cortex (Stephen et al., 2005). Thus, cancellation of signal from the hippocampus is, at the very least, incomplete. Therefore, the imperfect symmetry of hippocampal anatomy and physiology permits activity from this structure to be detected by MEG sensors.

The second challenge to hippocampal imaging with MEG is that magnetic field strength decreases with increasing distance between neural sources and MEG sensors. Thus, there is concern that signal from deep sources, which are the furthest from the MEG sensor array, will be at least weaker than signal from superficial sources, and perhaps not detectable at all (Hillebrand and Barnes, 2002; Baumgartner et al., 2000; Hämäläinen et al., 1993). Simulation and empirical studies have been conducted to systematically investigate this issue regarding the strength of hippocampal and cortical sources (Mills et al., in review; Quraan et al., 2011). These studies have demonstrated that even weak stimulus-evoked hippocampal and cortical activity can be detected if care is taken in experimental design (i.e. appropriate behavioural and control tasks, sufficient numbers of trials) and selection of optimal analysis methods. In support of the conclusions from simulation work, an increasing body of empirical evidence demonstrates that although hippocampal activation may be more difficult to detect than superficial sources, it can be reliably detected with a range of experimental paradigms and analysis techniques (Breier, 1998, 1999; Hanlon et al., 2003, 2005, 2011; Hopf et al., 2010;

Ionnides et al., 1995; Kirsh et al., 2003; Leirer et al., 2010; Martin et al., 2006; Mikuni et al., 1997; Mills et al., in review; Moses et al., 2009; Nishitani et al., 1999; Papanicolaou et al., 2002; Stephen et al., 2005; Quraan et al., 2010; Riggs et al., 2009; Tesche, 1997; Tesche & Karhu, 1999, 2000; Tesche, Karhu & Tissari, 1996). Thus, using a well-designed paradigm and appropriate analysis techniques, stimulus-evoked hippocampal activation is detectable using MEG.

3. Insights into human memory gained from MEG

As stated above, MEG is an ideal tool to study human memory due to its excellent temporal and spatial resolution. Memory processes rely on the dynamic interaction among superficial sensory and association cortices with deep neural structures such as the hippocampus. Simulation studies and empirical findings demonstrate that MEG can reliably detect activation from the hippocampus, in addition to superficial cortical structures. The combination of this spatial resolution and high temporal resolution can elucidate at which particular stage of processing different brain regions contribute to the task, or cognitive operation, at hand, as well define the parameters (e.g. frequency) under which neural regions operate. In this capacity, MEG stands apart from other neuroimaging tools. fMRI is known for its high spatial resolution, but is not a direct measure of neuronal activity and has poor temporal resolution. EEG, like MEG, has superb temporal resolution. However, EEG is limited in its spatial resolution due to the brain, skull, and CSF smearing the electric potential patterns assessed from the scalp surface. In addition, EEG is recorded as a difference in potential between two electrode sites, with the pattern of electric potentials at the scalp surface contingent on the electrode site used as a reference for the sites of interest. Although MEG is not faced with these particular limitations of EEG, it is important to recognize that like EEG, MEG shares the uncertainties in source localization algorithms imposed by the "inverse problem". Confidence in the solutions however has been acquired through the use of simulation studies and empirical findings. Thus, overall, MEG can be used to compare the dynamics of healthy brain activation to that found in pathological conditions, such as in cases of brain damage or psychiatric disorders and as such, is well poised to provide new insights about human memory.

In this portion of the chapter, we will first discuss MEG studies that have characterized the dynamics of neural system activations involved in different types of memory processes in the healthy brain. We will then examine how facilitating the recruitment of one system over another may allow for compensation under pathological conditions. Subsequently, we will discuss studies that have used MEG to directly examine the neural basis of compensation in pathological conditions that arise due to brain lesions and schizophrenia. Lastly, we will report on applications of MEG to understanding the neural organization of memory during development.

3.1 How does the hippocampus contribute to memory?

Previous fMRI studies have documented the role of the hippocampus in the encoding and subsequent retrieval and recognition of newly learned information (e.g. Kirchoff et al., 2000; Stark & Okado, 2003; Weis et al., 2004; Kapur et al., 1995; Schacter et al., 1995; Squire et al., 1992). However, these studies could not tell us the mechanisms (e.g., frequency, timing) by which the hippocampus supports such memory processes.

MEG studies have demonstrated that theta oscillations within the hippocampus are associated with memory processing. For instance, Guderian and Duzel (2005) required

participants to study a series of faces superimposed on a background image. During a retrieval phase, faces were re-presented and participants were required to recollect the context (i.e., background image) with which the face had been paired. Recollection of the context in which a face had been learned was associated with an increase in the amplitude of theta oscillations. In a subsequent study, Guderian, Schott, Richardson-Klavehn and Duzel (2009) demonstrated that theta oscillations could be localized to the medial temporal lobes and that the amplitude of the theta oscillations observed prior to the onset of words were positively correlated with subsequent memory for the words. Using a working memory paradigm in which participants were required to maintain a series of integers in memory, Tesche and Karhu (2000) further localized theta oscillations to the hippocampus and additionally observed that such oscillations were stimulus-locked to the presentation of the memory set and that the duration of this stimulus-locked theta increased with increasing memory load. All together, these studies suggest that theta oscillations may mediate the dynamic interplay between the hippocampus and the cortex allowing for disparate cortical representations to be bound together and maintained in memory.

More recent evidence from MEG studies has suggested that via theta oscillations, the hippocampus supports memory through its dynamic interconnections with the cortex. For example, in Cashdollar et al., (2009), healthy participants and participants with bilateral hippocampal sclerosis (BHS) performed a delayed match-to-sample (DMS) task in which memory for the relations depicted within each scene stimulus had to be maintained in order for successful performance to occur. Specifically, in the non-relational condition, participants were presented with a single indoor or outdoor scene as the sample stimulus, and then were presented with the probe display in which the same exact scene was re-presented alongside a novel scene. In the relational condition, one of the scenes in the probe display was an exact repetition of the sample stimulus, and the other was again this same scene, but some relational change had occurred to the objects within the scene (e.g., an item had been added, deleted or moved in its spatial location). In healthy participants, an occipito-temporal theta synchrony was observed during the relational DMS task, whereas a frontal-parietal synchrony was observed for the non-relational DMS. Patients with left temporal lobe epilepsy (who had structurally intact hippocampi) showed similar effects to control participants; however, patients with BHS did not demonstrate the occipito-temporal theta synchrony in the relational DMS task and showed decreased accuracy on the task relative to the other participant groups, demonstrating that occipito-temporal theta synchrony critically supports relational memory.

A further specification regarding how the hippocampus supports memory concerns the timing by which the hippocampus contributes to processing. The cognitive implications of hippocampal responses that are earlier versus later in the processing stream are very different. For example, activation found later during the processing stream (e.g. 250+ ms following stimulus onset) would suggest that the hippocampus becomes involved only after the stimulus has already been perceived. This paints a modular and serial view of perception and memory processing -- first we perceive the stimulus, then we search our memory stores for a match.

In contrast, hippocampal activation found early in the processing (e.g. prior to 250 ms following stimulus onset) stream is suggestive of a role for this structure during perceptual processing. Such a finding may be interpreted as a contribution from memory in shaping and/or encoding our initial perception of a stimulus. This leads to a more distributed and interactive view of memory and perception. This integrated view of memory is expressed

nicely by McIntosh (2007): “Memory is not the domain of particular systems in the brain, but of the brain as a whole.... The act of seeing, hearing and acting makes use of the brain’s capacity for memory”. Using MEG, serial modular versus distributed interactive views of the neural organization of cognitive functions such as perception and memory can be tested. Riggs et al. (2009) conducted a MEG investigation regarding the relative timing of the contribution of hippocampal responses to scene recognition. They examined hippocampal responses during the processing of novel and recently studied indoor and outdoor scenes. In support of the distributed interactive view of cognitive organization, they found very early hippocampal responses, during the first 200 ms following scene presentation, to both novel and previously studied scenes. This early latency is within the time window within which perception is thought to occur independently of the hippocampus (Tsivilis et al., 2001). Riggs et al. also found that this hippocampal activity consistently oscillated within the theta frequency band. They concluded that the hippocampus may be involved during early perceptual processing of old and new information, or at the very least, that memory processing begins rapidly and operates in conjunction with, or parallel to, visual processing when perception is thought to occur.

3.2 Perceptual plasticity: MEG studies of the effect of memory on perceptual processing

The idea of distributed interactive memory and perceptual processing was taken one step further by Ryan et al. (2008), with their discussion of *perceptual plasticity*. Their study built on fMRI work demonstrating that the information that has come to be associated with an object over time can change subsequent brain activation patterns that are invoked during processing when the object is subsequently presented in isolation (Nyberg, Habib, McIntosh & Tulving, 2000; Wheeler, Petersen & Buckner, 2000). For instance, visually presented words, when presented in isolation, do not elicit responses in auditory regions. However, following repeated pairings between the visually presented words and auditorily presented sounds, the presentation of a previously studied word elicits activation within auditory regions (Nyberg et al., 2000). Ryan et al. (2008) point out that although these fMRI studies can tell us that memory for associated information is related to the processing of sensory inputs, they cannot tell us precisely at what stage of processing activation is observed in these associated regions. Therefore, we do not know whether prior experience results in the activation of associated information that occurs following perceptual processing, or whether prior experience results in the activation of associated information during the time of perceptual processing itself. Hence, the dynamic description of brain systems obtained using MEG can inform our overall conceptualization of memory and perception, including the relationship between these faculties and whether they are, indeed, dissociable.

3.3 When does memory modulate primary sensory activity?

The unique combination of excellent temporal and spatial resolution of MEG allows for an investigation regarding the timing of primary sensory cortical modulations, and to infer whether the influence of prior experiences, or memory, can occur early enough to affect our perceptions. Moses et al. (2005) exposed participants to an auditory noise burst that was repeatedly paired with a visual presentation of a geometric figure. Initial presentation of the visual stimulus alone did not elicit activity within auditory regions. However, following training trials in which the noise and visual stimulus were presented together, the

presentation of the geometric figure alone elicited a response within the auditory cortex. Interestingly, this response within the auditory cortex occurred early (approximately 50 ms) following the time when the presentation of the noise would have ordinarily been expected. This time interval of 50 ms coincides with the time at which sensory processing associated with tone perception occurs within the auditory cortex. In a further analysis, early responses were observed in the amygdala within 200 ms following the onset of the visual stimulus that had been previously paired with the noise compared to visual stimuli that had never been paired with the noise (Moses et al., 2007). These findings suggest that the experience of hearing a sound coincident with seeing a picture leads to changes in the way the brain processes that picture. In other words, the memory acquired by the participants within the laboratory altered their subsequent neural responses, and possibly, their perception of the items. These findings have also been replicated in the somatosensory domain (Moses et al., 2010).

3.4 Does memory alter primary perception?

Ryan et al. (2008) expanded on this question and asked whether pre-existing knowledge about an object changes the way the object is “perceived”. Specifically, they asked whether the presence of memories about an object changes the way the brain responds at the time of initial perception, or whether the changes occur following initial perceptual processing at a time when memory processing is traditionally thought to occur. In contrast to Moses et al. (2005, 2007, 2010), in which memory acquisition occurred within the experimental session, Ryan et al. (2008) used a paradigm in which the “previous learning episodes” occurred in real life prior to the experiment, and in which the learned associated information was not presented at any time during the study and was not needed in order to complete the task given to the participants. Thus, they could ask whether early changes in neural activity actually represent a long-term change in perceptual processing, or whether they are merely a short-lived artificial change induced only in the laboratory as a result of the particular experimental procedures.

Ryan et al. (2008) gave participants visual presentations of famous and non-famous (novel) faces and, and auditory presentations of famous and non-famous names while neural responses were recorded with MEG. Interestingly, responses within the *auditory* cortex were larger for *visually* presented famous versus nonfamous faces. Likewise, activation within the *visual* cortex was larger for *auditorily* presented famous versus nonfamous names. These effects were found early during processing, within 150–250 ms, which is within the time window during which most perceptual processes are thought to occur, as opposed to a later time window (e.g. 250-1000 ms) during which conceptual/semantic processes and/or the retrieval of associated information are largely purported to occur (e.g., Itier et al., 2006; Schweinberger et al., 2002; Donaldson & Rugg, 1998, 1999). These data suggested that, when a famous name is heard, there is obligatorily activation of a visual representation of the person’s face; however, this visual representation is not present for non-famous names. Similarly, the presentation of a famous person’s face obligatorily activated an auditory representation of the sound of their name. Thus, our memories, or knowledge about an individual, actually change how we initially perceive that individual during subsequent encounters. In a broader sense, Ryan et al. (2008) proposed that memories and prior experiences not only influence processing but that they may do so in an unconscious, obligatory manner. They contend that each encounter leads to a sort of “perceptual plasticity”, meaning that subsequent processing of the same item is “ever-changing”.

4. MEG studies of compensation for neural damage

Although the hippocampus plays a crucial role in memory, not all types of memory processing are mediated by the hippocampus. Hippocampal lesions in humans and non-human animals specifically lead to impairments in the ability to learn the relations among multiple items (Cohen & Eichenbaum, 1993; Sutherland & Rudy, 1989); an ability that is essential for acquiring episodic and autobiographical memory as well as semantic memories (Moses & Ryan, 2006; Eichenbaum & Cohen, 2001; Cohen & Eichenbaum, 1993). It is generally agreed upon that after a period of consolidation, semantic memories can be retrieved independently from the hippocampus, although there is currently still debate regarding whether the retrieval of episodic or autobiographical memories can ever occur independently from the hippocampus (Moscovitch, Rosenbaum, Gilboa et al., 2005). Other mnemonic functions such as skill learning and priming are considered procedural in nature, rather than relational, and can be mediated by extra-hippocampal structures (Cohen & Eichenbaum, 1993). Therefore, following hippocampal damage, extra-hippocampal structures can mediate the retrieval of semantic memory, as well as support procedural learning such as skill learning and priming (Cohen & Eichenbaum, 1993; Squire, 1992; Tulving, 1972). The recruitment of these extra-hippocampal regions during performance of a memory task may allow alternate cognitive strategies to support performance, thereby demonstrating a potential mechanism whereby one may circumvent a damaged hippocampal system. MEG can define the spatial distribution of distinct neural networks that can each support performance, and provide detail regarding when distinct networks are engaged.

4.1 Imaging the potential for compensation

Using MEG, Moses et al. (2010) investigated the conditions under which extra-hippocampal systems can facilitate performance on what has traditionally been shown to be a hippocampal-dependent relational memory task: transverse patterning. (e.g. Alvarado & Bachvallier, 2005; Astur & Constable, 2004; Driscoll et al., 2003; Hanlon et al., 2003, 2005, 2011; Meltzer et al., 2008, Moses, Ostreicher, Rosenbaum & Ryan, 2008; Moses et al., 2009; Rickard & Grafman, 1998; Rickard, Verfaellie & Grafman, 2006; Reed & Squire, 1996; Ostreicher, Ryan, Moses & Rosenbaum, 2010; Saksida et al., 2007).

The transverse patterning task is structurally analogous to the childhood game “rock-paper-scissors” (Rock crushes Scissors, Scissors cut Paper, Paper covers Rock), but uses novel stimuli (A, B, C) that have ambiguous meanings outside the context of their pairings (A beats B, B beats C, C beats A; or A+B-, B+C-, C+A-; Fig. 1A). Performance on the transverse patterning task is impaired following hippocampal damage, and is correlated with measures of hippocampal neuronal integrity (Driscoll et al., 2003). Transverse patterning deficits are also observed in conditions associated with impaired hippocampal functioning such as schizophrenia (Hanlon et al., 2005, 2011) and normal aging (Driscoll et al., 2003). Additionally, transverse patterning performance elicits hippocampal activation measured with fMRI (Astur & Constable, 2004; Meltzer, Nigishi & Constable, 2008; Rowland et al., 2010) and MEG (Hanlon et al., 2003; 2005; 2011; Hopf et al., in review; Leirer et al., 2010; Mills et al., in review, Moses et al., 2009).

However, the transverse patterning task can be solved despite bilateral hippocampal damage if the stimuli involved are designed to tap previously acquired semantic memories (Moses et al., 2008), the retrieval of which is thought to be mediated by frontal and anterior

temporal cortices (Cabeza & Nyberg, 2000). In Moses et al. (2008), amnesic patient K.C., whose damage includes the hippocampus bilaterally, was tested on four transverse patterning conditions that varied the extent to which the stimuli and relations among them were semantically meaningful, or known pre-experimentally: 1) abstract objects; 2) geometric shapes; 3) playing cards; 4) rock-paper-scissors (RPS). K.C. could solve the transverse patterning task using meaningful, but not arbitrary stimulus relations, suggesting that his successful performance was supported by an increased contribution from semantic memory (Moses et al., 2008).

In support of the notion that the transverse patterning task with meaningful stimulus relations can be solved by extra-hippocampal structures, an MEG study with neurologically intact participants revealed a bilateral decrease in hippocampal activation for the meaningful RPS condition compared to the other conditions (Moses et al., 2009). Hippocampal peaks were apparent as early as 120 ms, and maximum differentiation in hippocampal activation between the meaningful RPS and the other conditions occurred at approximately 300 ms in the right, and 550 ms in the left hippocampus. These time-course differences across conditions suggest that the meaningfulness of the stimuli affected later, conceptual, processing, rather than early perceptual processing.

Additionally, participants recruited left inferior frontal gyrus, as well as left perirhinal and anterior temporal cortices, to a greater extent for the meaningful RPS compared to the other stimulus conditions (Moses et al., 2009). Activation in left cortical regions has been shown to be involved in the processing of semantic information (Cabeza & Nyberg, 2000; Mummery et al., 2000; Taylor et al., 2006). Interestingly, the maximum differentiation between the meaningful RPS and the other conditions in these left cortical regions occurred at 500–550 ms, which coincides with the observed reduction in left hippocampal activation. This pattern of results suggests that a tradeoff can occur between two memory systems late in the processing stream; one memory system is mediated by the hippocampus and is involved in acquiring memory for novel relations and one memory system is mediated by left cortical regions and is involved in the use of semantic memory (Moses et al., 2009; Ryan and Cohen, 2003, 2004). The dynamic interplay between these two systems allows for semantic memory to be used to perform a relational memory task when stimulus relations are meaningful. Future work can investigate the extent to which alternate brain systems can be invoked to support new learning to allow for compensation in pathological conditions (e.g., Tse et al., 2007). However, such findings demonstrate that MEG can be used to examine the pattern of brain activation within specific regions or networks, such as the hippocampus and frontal cortex, as well as the latency of those activation patterns during the processing stream. This type of dynamic information regarding the temporal tradeoff between hippocampal and frontal brain networks has not been provided by other imaging modalities such as fMRI or EEG.

4.2 MEG provides direct evidence of compensation in pathological conditions

The previous work demonstrates that there is potential for dynamically interacting brain systems to allow for compensation in pathological conditions. As outlined below, numerous MEG studies have examined how neural dynamics are altered in the pathological brain, and how these changes affect cognition. Below, we focus the discussion on studies that have examined memory performance in individuals with compromised hippocampal function.

Using MEG, Hanlon and colleagues found evidence for compensation or functional plasticity in patients who have hippocampal damage or dysfunction (Hanlon et al. 2003).

During performance of the transverse patterning task using abstract pictures or “nonverbal” stimuli, neurologically intact control participants activate their right hippocampus. This is consistent with the idea that the right hippocampus is particularly implicated in nonverbal/visuo-spatial memory (Burgess et al., 2002; Smith and Milner, 1981, 1989) and left in verbal/narrative or episodic memory (Burgess et al., 2002; Frisk and Milner, 1990). Similarly, a patient with left hippocampal sclerosis also showed right hippocampal activation. In contrast, a patient with a right hippocampal lesion showed left hippocampal activation during performance of this nonverbal transverse patterning task (Hanlon et al. 2003). This increased left hippocampal activation found with right hippocampal damage may allow for behavioural compensation for an impaired right hippocampus.

The idea that the left hippocampus allowed for compensation for right hippocampal abnormalities is supported by the findings of Hanlon et al. (2005). They found that patients with schizophrenia were more likely than healthy control participants to show left or bilateral hippocampal activation during performance of a nonverbal transverse patterning task. Importantly, this increased left hippocampal activation in schizophrenia was correlated with higher performance accuracy on the transverse patterning task. In contrast, this relationship was not found in the control participants, who showed predominantly right hippocampal activation. Thus, the patients with schizophrenia who were the most successful at transverse patterning were most likely to show an atypical laterality pattern of hippocampal activation. These findings suggest that the additional recruitment of left hippocampal activation in patients with schizophrenia provided a compensatory mechanism for a dysfunctional right hippocampal system and led to improved behavioural performance.

In order to further investigate this compensation phenomenon, Hanlon and colleagues have recently developed a version of transverse patterning that uses visually presented novel verbal stimuli, or “non-words” (eg. “VULG”, “COSE”, “RINT”) to compare to the novel nonverbal abstract pictures (Hanlon et al., 2011). In healthy control participants, this verbal transverse patterning task activates the left hippocampus to a greater extent than the right (Hanlon et al., 2011), in contrast to the nonverbal transverse patterning task, which, as noted above, activates the right hippocampus to a greater degree than the left (Hanlon et al., 2003, 2005, 2011; Leirer et al., 2010; Mills et al., in review; Moses et al., 2009). This reinforces the notion that the left and right hippocampi process different information modalities, and also allows for the non-invasive evaluation of the functioning of right and left hippocampus separately.

This lateralized hippocampal activation found in control participants was not seen in patients with schizophrenia, who instead showed more bilateral or left hippocampal activation for both the verbal and nonverbal transverse patterning tasks (Hanlon et al., 2011). This result was interpreted as the left hippocampus possibly trying to compensate for a right hippocampal deficit, using a verbal strategy, although inefficiently, and the right hippocampus unable to do the same for the left deficit. In addition to lateralized hippocampal activation, prefrontal cortex activation was observed, consistent with other neuroimaging studies using the transverse patterning task (Meltzer et al., 2008; Moses et al., 2009). This prefrontal cortex activation is not surprising given that the task not only relies on relational memory, but also on working memory for maintaining the distinct relationships. Interestingly, patients and controls showed a lateralized activation difference in the prefrontal cortex. Patients activated the left prefrontal cortex during both the verbal and nonverbal transverse patterning tasks, in contrast to controls who activated the right prefrontal cortex (Hanlon et al., 2011). Thus, patients showed hyperactivation of both

prefrontal cortex and hippocampus and prefrontal cortex in the left hemisphere. Overall, this pattern of results suggests that the patients with schizophrenia were recruiting the hippocampus bilaterally in each condition in an attempt to compensate for hippocampal dysfunction.

4.3 MEG studies of the organization of memory development

The work of Hanlon et al. (2003, 2005, 2011) demonstrates that in adults with hippocampal dysfunction, recruitment of the hippocampus bilaterally may support performance for a task that typically elicits unilateral activation. However, it is unclear whether this effect may be found in developmental populations, since children show different laterality patterns than adults. In general, many cognitive operations that are lateralized to one hemisphere in adults have bilateral hemispheric representation in children. For example, the semantic processing of sentences recruits more bilateral activation in children, compared to left lateralized activation in adults (Brauer & Friederici, 2007), and increased activation of left middle temporal gyrus and inferior parietal lobule is found with increasing age throughout childhood (Chou et al., 2006). This suggests that the cortex becomes more lateralized and specialized with development. The neural organization and lateralization patterns of hippocampal-dependent memory in children has not been well characterized.

Recent work has investigated the differences in the organization of hippocampal dependent memory function in children and adults, and how they relate to behavioural performance (Hopf et al., in review). Hopf et al. (in review) discuss previous literature pointing to two different ways in which the relationship between lateralization of hippocampal activation and behaviour may be manifest in children. The first possibility comes from the previously discussed findings of compensatory activation in adults with hippocampal dysfunction (Hanlon et al., 2005). In this work, healthy participants typically showed right hippocampal activation on the nonverbal transverse patterning task, while participants with schizophrenia showed bilateral or left hippocampal activation associated with increases in behavioral performance. Therefore, in adults with hippocampal dysfunction, bilateral hippocampal recruitment may have a compensatory function. Similarly, children may not have a fully developed hippocampal system with unilaterally specialized hemispheres, and, consequently, may recruit the hippocampus bilaterally in order to achieve performance similar to that of adults. Thus, it may be reasonable to predict that, in children, the presence of more bilateral hippocampal activation during the nonverbal transverse patterning task would also lead to improvements in behavioral performance.

However, an alternative prediction is that more right lateralized hippocampal activation during a nonverbal relational memory task (e.g. transverse patterning using visual stimuli) will lead to more accurate performance, as this may be a sign of a more mature and efficient brain. For instance, previous work has shown that children who show more right hemisphere lateralization of activation during navigation show superior performance (Tsujii, Yamamoto, Masuda & Wantabe, 2009). Additionally, language lateralization studies demonstrate that areas of the brain become more specialized with increasing age (Chou et al., 2006; Holland et al., 2001; Ressel et al., 2008; Szaflarski et al., 2006), and that this is associated with superior behavioural performance (Everts et al, 2009; Lebel & Beaulieu, 2009). Therefore, it is also reasonable to predict that children who show a more adult-like pattern of right hippocampal lateralization would show superior performance on a nonverbal relational memory task. These opposing predictions suggest a difference in the manner by which behavioral performance is achieved on a nonverbal transverse patterning

task: bilateral, or stronger left hippocampal responses associated with superior performance in children would reflect compensation, whereas right lateralized responses associated with superior performance would reflect neural maturation.

Hopf et al. (in review) investigated these two competing hypotheses regarding the neural correlates of behavioral performance between adults and children (aged 11-17). The findings of Hopf et al. supported the "maturation" account. Across participants of all ages, the presence of stronger right versus left hippocampal activation was correlated with superior nonverbal transverse patterning accuracy. This relationship was strongest later in the processing stream, particularly around 600 ms, suggesting that the difference was not related to perception but rather higher cognitive processes. This relationship between right lateralization and superior performance was the strongest within the youngest group of children, aged 11-14. That is, the more right lateralized the participant's hippocampal activation, the more accurate their performance; and this was particularly true for the younger children or the least mature participants. Importantly, this positive association between right hippocampal lateralization and accuracy (neural maturation) is opposite to that in adults with hippocampal dysfunction, who show a positive relationship between left hippocampal lateralization and accuracy (compensation) (Hanlon et al., 2005).

Thus, the findings of Hopf et al. (in review) lend support to the notion that typically developing children were not recruiting left hippocampus to compensate for an immature organization of the hippocampal system, or at the very least, this contralateral recruitment was ineffective at boosting performance. Rather, these results suggest that the more the activation pattern of a child's brain resembles that of an adult, the more accurate their behavioural performance will be. In other words, superior performance in typical developing children is associated with a more "mature" brain.

5. Conclusions and future directions

This chapter has shown that MEG can be used to examine memory in healthy adults and in special populations, such as individuals with amnesia, individuals with schizophrenia, and children. MEG investigations with healthy adults have provided insights that invite a re-conceptualization of the construct of memory and how it relates to other cognitive faculties. This work suggests that memory is organized in a distributed manner throughout the brain, and that memory interacts closely with other cognitive operations, such as perception. In particular, memory may influence the way we perceive the world around us. In fact, from a neurological standpoint, the cognitive operations of memory and perception may not even be dissociable, since the effects of both faculties are found in multiple distributed regions throughout the brain and are observed at similar points in the processing stream. MEG investigations with special populations reveal how these distributed networks are altered in the face of neural dysfunction, and at what stage of processing cognitive function differs from the norm.

All together, the MEG studies described throughout this chapter demonstrate the utility of this technique in providing mechanistic detail regarding memory processes, the nature of the impairment in disorders that include hippocampal dysfunction, and the nature of the developmental process. MEG provides comprehensive detail regarding the spatiotemporal dynamics of neural activity that cannot be gleaned from the use of any other neuroimaging technique on its own. As a consequence, MEG is a valuable tool for cognitive neuroscientists to understand the underlying mechanisms of human cognition.

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7. References

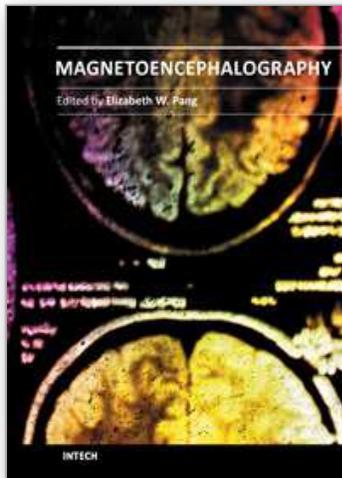
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This is a practical book on MEG that covers a wide range of topics. The book begins with a series of reviews on the use of MEG for clinical applications, the study of cognitive functions in various diseases, and one chapter focusing specifically on studies of memory with MEG. There are sections with chapters that describe source localization issues, the use of beamformers and dipole source methods, as well as phase-based analyses, and a step-by-step guide to using dipoles for epilepsy spike analyses. The book ends with a section describing new innovations in MEG systems, namely an on-line real-time MEG data acquisition system, novel applications for MEG research, and a proposal for a helium re-circulation system. With such breadth of topics, there will be a chapter that is of interest to every MEG researcher or clinician.

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