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Hippocampal and Neocortical Oscillatory Contributions to Visuospatial Binding and Comparison

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Over 50 years of research has revealed a critical role for the hippocampus in the formation of long-term declarative memories. More recent evidence has specified the functions of the hippocampus as the binding and comparison of memory representations that may be used under shorter, as well as longer, delays (Olsen, Moses, Riggs, & Ryan, 2012). Hippocampal neural oscillations (e.g., theta rhythm) have been studied extensively in animals; however, the oscillations that underlie binding, comparison, and their relationship to memory performance remain to be fully explored in humans. Here magnetoencephalography was used to examine theta oscillations within the hippocampus and cortex to address this critical gap in the literature. The task consisted of (a) an encoding phase in which participants had to integrate the relative spatial positions among 3 sequentially presented objects, (b) a delay phase, and (c) a test phase in which all study objects were presented simultaneously in novel locations, and participants had to indicate whether the relative positions had changed. Theta power in the hippocampus and medial prefrontal cortex (PFC) increased across encoding and delay periods during which binding and maintenance processes dominate, while comparison of spatial relations at test was associated with greater theta power in right lateral PFC and intraparietal sulcus for manipulated versus intact trials. Critically, relational memory was positively related to hippocampal theta power increases across the encoding period. These findings provide novel evidence for the role of hippocampal theta in the incremental formation and retention of relations across space and time.

Keywords: magnetoencephalography, theta, rhythm, hippocampus, short-term memory

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Although the critical role of the hippocampus in the service of long-term memory has been established for quite some time, the proposal of its involvement in memory over brief delays—on the order of several seconds—has only recently gained momentum. A growing number of neuropsychological and neuroimaging investigations have provided evidence for the involvement of the hippocampus in short-term memory (see Olsen et al., 2012, for a recent review). These findings, taken together with research implicating hippocampal involvement in a number of other cognitive domains outside long-term declarative memory, have motivated a set of more integrative models of hippocampal function (Graham, Barense, & Lee, 2010; Hannula & Greene, 2012; Henke, 2010; Konkel & Cohen, 2009; Olsen et al., 2012; Ranganath, 2010). A common thread among these theories is the role of the hippocampus in relational memory binding—its ability to form lasting representations regarding the relations among distinct elements or items. Motivated by proposals that the hippocampus can detect mismatches between current and previously (recently) studied stimuli (Hasselmo & Wyble, 1997; Lisman & Grace, 2005; Vinogradova, 2001), Olsen et al. (2012) proposed that in addition to

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relational memory binding, the hippocampus performs a comparison process. Comparison refers to the evaluation of the current perceptual input with respect to previously formed representations that are maintained online and are mediated through either short- or long-term memory stores. We proposed that these two processes, binding and comparison, are utilized by the hippocampus to support multiple cognitive processes—including memory—over a variety of delays, even delays as brief as several seconds.

Binding and comparison processes likely occur continuously, and possibly cyclically, throughout cognitive processing. Likewise, binding and comparison contribute to all phases of memory processing, from encoding to retrieval and recognition; however, particular phases or task demands may engage binding and comparison to differing degrees. For example, during the initial encounter with novel information presented separately across space and time (i.e., the study phase), binding processes dominate, in order to form the relational representations that will be required for later memory. By contrast, when the information is subsequently encountered (i.e., the test phase), the current information must be evaluated against the corresponding stored or maintained memory representation in order for recognition to occur, which would rely most heavily on comparison.

The proposal that binding and comparison are continuous, cyclical processes performed by the hippocampus throughout the different phases of memory processing is consistent with the emerging consensus that the hippocampus contributes to memory performance after both short and long delays. Indeed, previous neuropsychological investigations have provided evidence about the critical role of the hippocampus during short-delay memory for temporal and spatial relations (e.g., Konkel, Warren, Duff, Tranel, & Cohen, 2008) and even during matching tasks using complex visual stimuli (Lee et al., 2005; Warren, Duff, Tranel, & Cohen, 2011). However, it is unclear from neuropsychological data alone whether this short-delay memory performance impairment reflects the fact that amnesic participants are unable to incrementally bind the relations among items presented sequentially in time, maintain the relations across the delay period, and/or compare the originally encoded relations with those presented in the test display. Similarly, when amnesic participants are unable to perform perceptual judgment (e.g., matching) tasks on simultaneously presented stimuli, it is possible that this impairment arises due to either an inability to perceive the relations among the study items (i.e., a pure perceptual deficit) or an inability to maintain the relevant visual information for the brief amount of time needed to sample the entire display and perform the matching judgment (i.e., comparison). Thus, neuroimaging is warranted to help further elucidate the mechanistic role of the hippocampus in the formation, maintenance, and comparison of spatial and temporal relations.

Functional magnetic resonance imaging (fMRI) studies have provided insight into the role of the hippocampus in short-delay relational memory; however, due to the relatively low temporal resolution of fMRI, these studies are limited in their ability to draw conclusions about the contributions of the hippocampus to encoding and maintenance, specifically, when the delay period is short (on the order of several seconds). Furthermore, fMRI does not provide a measure of oscillatory activity (e.g., the theta rhythm), which presents limitations in the ability to draw parallels to findings from neural recording in nonhuman animal studies or to electroencephalography (EEG) recordings in humans. Oscillatory activity, which has been studied extensively in nonhuman animals, is generated by synchronous, rhythmic, neural activity and is thought to play a key role in the coding, transmission, and processing of information (Fries, 2005; von der Malsburg & Schneider, 1986). Human intracranial EEG studies have demonstrated neural oscillations within the hippocampus, such as theta (~5 Hz), are associated with binding, integration, and maintenance during memory processing (Axmacher, Cohen, et al., 2010; Axmacher, Henseler, et al., 2010; Kahana, Sekuler, Caplan, Kirschen, & Madsen, 1999; Lega, Jacobs, & Kahana, 2012; Raghavachari et al., 2001) and are closely related to the firing of hippocampal place cells in rodents during spatial navigation (O'Keefe & Recce, 1993). Theta power increases have been associated with the short-delay maintenance of temporal relations using scalp EEG; however, scalp EEG studies are limited in their ability to localize the source of this neural activity (Hsieh, Ekstrom, & Ranganath, 2011; Roberts, Hsieh, & Ranganath, 2013). Thus, as most previous research in humans has either been invasive or nonspecific with respect to localization, the current investigation called for a noninvasive technique with high spatiotemporal resolution, which provided direct measures of neural activity, as well as information about neural synchrony. Using magnetoencephalography (MEG), the current study addressed a critical gap in the literature left open by both neuropsychological studies and neuroimaging (fMRI and EEG)—thus allowing for the investigation of the role of hippocampal theta in the specific memory processes involved during short-delay relational memory performance in a group of healthy young adults.

The goal of the present work was to investigate the role of the hippocampus in the formation of relational memory representations, a process that likely unfolds incrementally across time during real-world cognition. The task was designed such that study objects were presented sequentially, which permitted controlled examination of binding of relations within memory. Additionally, the recognition test probe presented all the objects in new absolute positions, and participants were required to decide whether the relative spatial relations had been maintained. Therefore the test phase required the comparison of relational information that had been maintained over a short delay in memory, and successful performance could not be achieved through item recognition alone or through detection of local luminance changes. The present task is essentially a variant of a visuospatial delayed-match-to-sample task, in which information regarding the relative spatial relations among objects must be bound, maintained across a delay, and subsequently compared to a test probe in order to detect whether a manipulation had occurred.

A previous eye movement monitoring investigation by Ryan and Villate (2009) using this task provided evidence that during the study period participants shift attention overtly among the current and previously presented studied locations. Such findings suggest that during the presentation of each successive object, participants visually resample the now empty locations, possibly as a way to build up a relational memory representation of the three studied locations. That is, knowledge about the relations among the three objects, essential for performance on the task, likely occurs gradually across the study period, in a manner consistent with how real-world spatial information might be integrated across both time and space during navigation of the environment. To this end, the current study utilized the fine spatiotemporal resolution of

MEG to examine the dynamics of hippocampal and cortical function during such integration. Specifically, we employed a time–frequency analysis focused on the hippocampus as well as a whole-brain analysis to investigate sustained, induced changes in oscillatory theta power across the study period.

Previous research has shown that the hippocampus is involved in multiple phases of memory (Lepage, Habib, & Tulving, 1998; Ranganath & D'Esposito, 2001; Schacter & Wagner, 1999), including encoding, maintenance, and recognition; however, the underlying mechanisms of hippocampal and associated cortical activation may differ for each phase (Hasselmo & Wyble, 1997; Norman & O'Reilly, 2003). Given that theta oscillations have been observed in the human hippocampus with intracranial EEG during spatial navigation as well as during verbal working memory encoding (Kahana, Sekuler, Caplan, Kirschen, & Madsen, 1999; Lega et al., 2012; Raghavachari et al., 2001, 2006), we expected to observe theta oscillations in the hippocampus as participants performed visuospatial encoding and maintenance of the study objects. Coactivation of control networks in the prefrontal and parietal cortices was also expected, based on previous scalp EEG studies (Grimault et al., 2009; Holz, Glennon, Prendergast, & Sauseng, 2010; Roberts et al., 2013), intracranial EEG (Sarnthein, Petsche, Rappelsberger, Shaw, & von Stein, 1998), and fMRI investigations of short-delay visuospatial memory (Hannula & Ranganath, 2008). It was expected that similar neural networks would support both the study and delay phases, during which binding and maintenance processes dominate. By contrast, additional brain networks, such as superior prefrontal cortex (PFC) and lateral posterior parietal cortex, were expected to be recruited during the test phase when the comparison process dominates (Spaniol et al., 2009). Thus, the current research uses MEG to examine the timing of theta power changes in the hippocampus and in cortex, and provides a novel and comprehensive investigation into the dynamic neural systems supporting distinct phases of memory: encoding/maintenance and retrieval. The task design uniquely enabled the investigation of the neural mechanisms supporting incremental relational memory binding across time and space. Ultimately, this research provides the first strong link between hippocampal oscillations during the formation and maintenance of relational memories and successful short-delay recognition memory for these recently formed spatial relations.

Method

Participants

The results from two sets of participants were combined for the purposes of this study. Twelve adults (six men, six women; 25.3 years of age, 18.0 years of education) participated in the first experiment, and 12 adults (seven men, five women; 23.4 years of age, 15.6 years of education) participated in the second experiment. There was a small procedural difference between the first and second sets of participants (see Procedure section); however, this difference was for purposes not related to the current investigation, and because the MEG data did not differ appreciably between the groups, the data from the two studies were combined. All participants were recruited from the Toronto community and had normal neurological histories and normal or corrected-to-normal vision. The study was approved by the local ethics committee, and the rights and privacy of the participants were observed. All participants gave informed consent before the experiment and received monetary compensation.

Stimuli and Design

Object stimuli consisted of colored images (1024 × 768 pixels) and novel objects created with Corel Draw (Version 12). Images were grouped into sets that were distinguished by a unique patterned background and three objects. The novel objects were designed to minimize resemblance to real-world objects, and thereby discouraged the use of associated verbal labels to aid in remembering the relative locations (e.g., "the cat is to the left of the boy") and were among the set used in prior work (Ryan, Leung, Turk-Browne, & Hasher, 2007; Ryan & Villate, 2009). The experiment was designed in the same manner as in Ryan and Villate (2009). The study images were each presented sequentially: a single object in a unique spatial location; three study images presented for each set. This ensured that the spatial relations among the studied objects could not merely be derived and processed from the external stimulus; rather, the relations must have been integrated within memory. A single mask image was used during the delay phase for each trial. The test displays consisted of all three studied objects presented simultaneously in new absolute spatial locations, but the relative spatial locations among the objects either remained intact (intact trials) or were altered for one of the objects with respect to the other two (manipulated trials; see Figure 1). Moving each study object in their absolute positions ensured that low-level features such as luminance changes at a given location could not be used to aid performance. Sets were counterbalanced across participants, and alternate study images were created, so that intact test trials for one participant became the manipulated trials for another. In this way, each test image was seen equally often as an intact or manipulated image across participants.

Procedure

The task consisted of 204 experimental trials. For half the participants, MEG was recorded simultaneously with remote eye tracking. For purposes of this work, the eye movement data will not be discussed. Each set of images was preceded by a fixation cross that appeared at the center of the screen for 3,000 ms. Three study images were then presented sequentially for 3,000 ms each, followed by the presentation of a mask image during a delay phase of 2,000 ms, and finally the test image for 4,000 ms (see Figure 1). Half the test displays depicted the objects in the same relative spatial positions (intact), and half depicted the objects with an altered relative spatial configuration (manipulated; i.e., one object was moved relative to the other two objects). Participants were instructed to remember the relative spatial locations among the objects and to indicate whether the relative locations among the objects were maintained from study to test displays. Half the participants made their response during the test phase, whereas the other half withheld their response until after the test phase. Thus, the only difference between the two sets of participants was when their responses were made. This procedural change was for reasons incidental to the purpose of the current investigation. The results reported below have been collapsed across all 24 participants, as the pattern of findings was similar across the two groups.

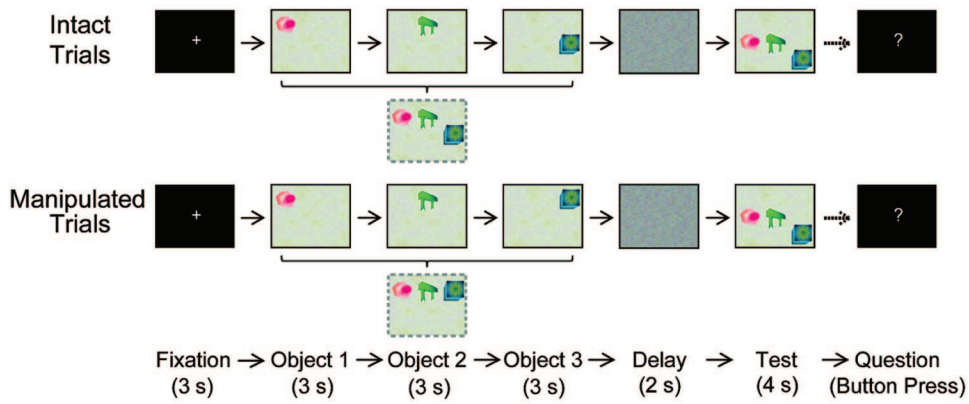

Figure 1. Task design. The task required participants to study the spatial locations of three trial-unique objects (not drawn to scale) that are presented sequentially for 3 s each. A composite image depicting the spatial configuration of the studied objects is also illustrated, surrounded by gray dashed lines, to represent the spatial relationship that must be formed and maintained. The study phase was followed by a 2-s delay phase during which a visual mask was presented. During the test phase, all three study objects were re-presented simultaneously in new absolute locations; however, the relative spatial positions were either identical to those of the study phase (intact condition) or the relative position of a single study object was changed (manipulated condition). For reasons incidental to the present purposes, one set of participants made their response during the 4-s test phase, and the other set of participants made their response immediately following the 4-s test phase when a question mark appeared on the screen.

Data Acquisition

MEG recordings were performed in a magnetically shielded room at the Rotman Research Institute, Baycrest, with a 151-channel whole-head first-order gradiometer system (VSM MedTech Inc.) with detection coils uniformly spaced 31 mm apart on a helmet-shaped array. Participants sat in an upright position and viewed the stimuli on a back projection screen that subtended approximately 31° of visual angle when seated 30 in. (76.2 cm) from the screen. The MEG collection was synchronized with the onset of the stimulus by recording the luminance change of the screen. Participant's head position within the MEG was determined at the start and end of each recording block with indicator coils placed on the nasion and bilateral preauricular points. These three fiducial points established a head-based Cartesian coordinate system for representation of the MEG data.

To specify or constrain the sources of activation as measured by MEG and to coregister the brain activity with the individual anatomy, we also obtained a structural MRI for each participant using standard clinical procedures with a 1.5 T MRI system (Signa EXCITE HD 11.0; GE Healthcare Inc., Waukesha, WI) located at Sunnybrook Health Sciences Centre or with a 3.0 T MRI system (Siemens TIM Trio) located at Baycrest. All participants' anatomical MRIs and MEG source data were spatially normalized with Advanced Neuroimaging Tools (Avants et al., 2011) to allow for group analysis of functional data.

Data Analysis

The MEG data were analyzed in source space via the synthetic aperture magnetometry (SAM) beamformer technique (Sekihara, Nagarajan, Poeppel, Marantz, & Miyashita, 2001; Van Veen, van Drongelen, Yuchtman, & Suzuki, 1997; Vrba & Robinson, 2001) implemented in CTF software (CTF Systems Inc., Port Coquitlam, BC, Canada) to map changes in oscillatory power in the brain associated with encoding, maintenance, and recognition. Oscillatory power was examined in two stages: an initial stage of time–frequency analysis of virtual channels extracted from a priori defined regions and a second stage of whole-brain mapping. The first stage was used to define the time and frequency windows in which oscillatory reactivity occurred in the task. The analysis of beamformer-derived source space signals is preferred over raw MEG sensor data for two reasons: (a) the beamforming procedure attenuates artifacts generated outside the brain, such as eye movements, and (b) analysis in source space compensates for differences across participants in head shape and head position that affect the propagation of magnetic fields from the brain to the sensors.

Virtual channels were placed throughout the brain in MNI space using the macroanatomical cortical parcellation of Tzourio-Mazoyer et al. (2002), consisting of 90 cortical and subcortical regions, excluding the cerebellum. Coordinates at the center of each region were warped from MNI space to the individual brain coregistered to the MEG head position, and beamforming weights for these locations were computed for the entire trial period, at a bandwidth of 1–100 Hz. Single-trial virtual signals for these locations were extracted and submitted to time–frequency analysis in EEGLAB (Delorme & Makeig, 2004), with a short-time Fourier transform (512-point overlapping Hanning windows, 200 windows per trial). Time–frequency transforms were averaged across trials and participants. For the analysis of the study and delay phase, an analysis window of −2,500 ms to 11,000 ms post onset of the first study display was used. For the test phase, an analysis window of −500 ms to 3,900 ms post onset of the test display was used.

The initial stage of virtual channel analysis served to delineate the time and frequency windows in which oscillatory reactivity occurred. To test for statistical significance of power changes

throughout the brain in specified frequency ranges, we generated whole-brain maps using SAM. For each participant, at a regular grid of locations spaced 5 mm apart throughout the brain, a pseudo-*t* statistic, which is a normalized measure of the difference in signal power between two time windows (Vrba & Robinson, 2001), was computed. Due to this "dual-state" analysis approach, multisubject statistical maps were derived from subtractive contrast images computed on the single-subject level, not from individual conditions. Beamformer weights for this analysis were computed from data within the time and frequency windows specified, providing greater spatial resolution than the broadband weights used for the virtual channel analysis (Brookes et al., 2008). Maps of pseudo-*t* values throughout the brain were spatially normalized to MNI space by applying the nonlinear transforms computed by Advanced Neuroimaging Tools (by warping the T1-weighted MRI to an MNI template), enabling random-effects analysis at the group level.

Group statistics on SAM results were computed in a similar fashion as is customary in fMRI studies. For each experimental comparison, the spatially normalized whole-brain map of pseudo-*t* values was submitted to a voxel-wise one-sample *t* test across subjects. Significant voxels reported below reach statistical significance at a threshold of $p < .001$ uncorrected, as well as a false discovery rate (FDR) of $q < 0.05$ corrected for multiple comparisons, unless otherwise stated. MNI coordinates corresponding to the peak statistical value within a given cluster are reported below; additional coordinates are provided to indicate localization of significant areas that span more than one anatomical region.

Results

Behavioral Results

Participants responded more accurately on intact trials ($M = 94\%$) than manipulated trials ($M = 80\%$; $t = 4.667$, $p < .001$).

MEG Results: Study Phase

Changes in hippocampal theta power across the study phase were investigated via a region-of-interest approach, in which virtual channels centered in the left ($x = -22$, $y = -22$, $z = -18$) and right hippocampus ($x = 24$, $y = -20$, $z = -18$) were estimated with the SAM beamformer (see Figure 2A for the localization of the right hippocampal virtual channel). Time–frequency analysis was performed on these virtual channels to investigate potential theta power changes (as compared to a prestimulus baseline period) in the hippocampus. Sustained theta power increases (ranging from 2 to 7 Hz) were observed in the both the left and right hippocampus throughout the study phase, and theta power was especially elevated following the presentation of the third study object (see Figure 2B). These results were specific to the theta band. Alpha power (8–13 Hz) decreased during the study phase, but this decrease did not vary across the three study objects. Together, this suggests that hippocampal theta oscillations contribute in a unique way to the encoding and/or maintenance of the presented information, and presumably to the incremental, online binding of visuospatial associations across time.

To statistically compare changes in theta power throughout the brain over the course of the study phase, we used a dual-state SAM analysis to compute power differences for each subject, across the entire brain. A time window of 750–2,500 ms post onset of the third study image was compared to the same time window following the first study image, in order to focus the analysis on sustained changes in oscillatory power, rather than the initial time-locked evoked response to the visual stimulus (Klimesch, Doppelmayr, Schwaiger, Winkler, & Gruber, 2000). Significantly greater theta power was observed for the period following the third versus the first object in the right and left anterior temporal lobes, including the right and left anterior hippocampus (see Figure 2C, upper panel). Midline cortical areas within the medial frontal gyrus ($x = -2$, $y = 49$, $z = 20$) as well as the posterior cingulate and precuneus ($x = 2$, $y = -56$, $z = 20$) also demonstrated greater theta power following the presentation of the third versus the first object. These findings suggest that theta oscillations in the hippocampus and midline structures are involved in the encoding and maintenance of information over short delays.

MEG Results: Delay Phase

Time–frequency analysis of the delay period (see Figure 2B) revealed sustained theta power increases in both the right and left hippocampal virtual channels. Whole-brain analyses were used to interrogate the network of theta power changes during the presentation of the mask image (i.e., delay phase) during which participants actively maintained a mental representation of the relative spatial configuration of the objects that had just been viewed. Theta power during the delay phase (750–1,500 ms post onset of the mask image) was compared to the pretrial baseline period (750 ms immediately preceding the first study image). Although theta power in the hippocampus did not reach statistical significance at the $p < .001$ uncorrected threshold, a significant difference in theta power was observed in the anterior temporal lobe. After relaxing the threshold to $p < .005$ (uncorrected FDR $q = 0.03$), significant voxels were observed in the hippocampus itself (see Figure 2C, lower panel). Theta power was significantly greater during the delay phase in the medial PFC ($x = -3$, $y = 49$, $z = 25$)—the same region that demonstrated increased theta power during the study phase. A decrease in theta power was observed in the right ($x = 22$, $y = -61$, $z = 55$) and left ($x = -33$, $y = -61$, $z = 50$) parietal cortex and the left inferior frontal gyrus ($x = -53$, $y = 9$, $z = 35$). Time–frequency plots of the left precuneus (see Figure 1 in supplemental materials) and other parietal regions suggests that theta power decreases observed during the delay phase are likely driven by the large alpha power decrease that extended into the theta band.

MEG Results: Test Phase

As in the study and delay phases, theta (2–7 Hz) power changes were observed in the test phase for the left and right hippocampal virtual channels; however, these signals were limited to the first 1,000 ms after test screen onset (see Figure 3A), suggesting that they comprised a rapid response to the test event rather than ongoing, sustained processing. To determine whether these changes in oscillatory power were related to the initial processing of the relations among the test objects and/or retrieval of the

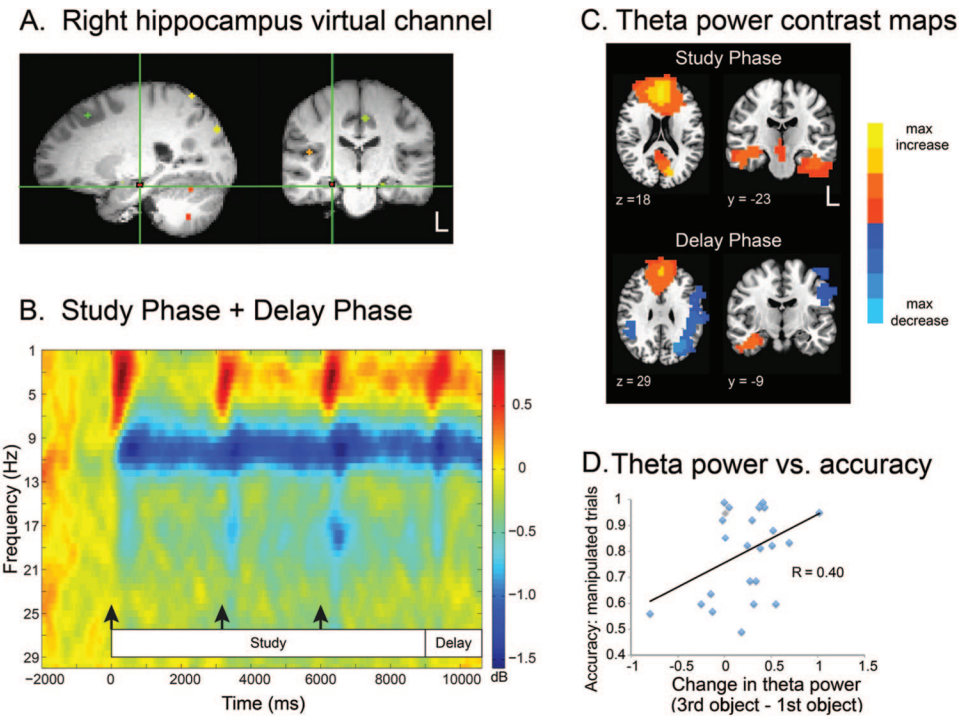

Figure 2. Study and delay phase results. (A) The location of the right hippocampal virtual channel (MNI coordinates: $x = 24$, $y = -20$, $z = -18$) was overlaid on a representative participant's normalized T1 structural image for visualization purposes. (B) Results from the time–frequency analysis from the right hippocampal virtual channel. Data are plotted for 0- to 30-Hz frequency bands and were estimated via a short-time Fourier transform. The onsets of the three sequentially presented study objects are depicted by the black arrows. Note increased sustained theta power (2–7 Hz) during the study phase (which is greater after the presentation of the third study object) and delay phase. (C) Whole-brain synthetic aperture magnetometry (SAM) maps depicting changes in theta power during study (upper) and delay (lower). Statistical maps are overlaid on an MNI template and represent areas of the brain in which theta power was significantly different (based on pseudo-t values derived from the SAM analysis) after the third study object compared to the first study object (upper) or significantly different during the delay phase compared to the prestimulus baseline period (lower). Statistical threshold was set to $p < .001$ uncorrected, false discovery rate (FDR) corrected $q < 0.05$, for the upper panel; and $p < .005$ uncorrected, FDR corrected $q < 0.05$, for the lower panel. (D) Relationship between behavioral performance on manipulated trials and the change in theta power across the study period. Each point represents one participant.

relations presented in the study phase, a whole-brain SAM analysis was performed comparing a 500-ms period following the onset of the test display (250–750 ms post onset) with a time window of the same duration following the onset of the first object during the study phase during which there is visual stimulation, but relational processing and/or retrieval should be relatively minimal. A theta power increase for the test phase was observed in the medial PFC ($x = -3$, $y = 49$, $z = 25$; see Figure 3B, upper panel). Interestingly, the location of this cluster was similar to the region that showed theta increases across the study phase ($x = -2$, $y = 49$, $z = 20$) and was centered in the identical spatial locale as the region that showed theta increases during the delay phase ($x = -3$, $y = 49$, $z = 25$). In addition, a large region in the occipital lobe, encompassing both early and higher level visual areas, exhibited greater theta power in the test phase ($x = -13$, $y = -91$, $z = -5$). This finding must be interpreted with caution, as there was more visual information to be parsed during the test phase (three objects as opposed to one object); nevertheless, this response was robust. Finally, a relative decrease in theta power within the inferior parietal lobule and superior temporal sulcus ($x = -53$, $y = -36$, $z = 25$) was observed.

Although all test trials presumably required some amount of comparison due to the fact that each of the three studied objects moved in its absolute position from the study phase, manipulated trials likely required additional cognitive processing and/or extended engagement of comparison processes to detect and verify a mismatch among the relative object locations. Whole-brain SAM maps were computed to localize significant differences in theta power by comparing a 500-ms time window (250–750 ms post onset display onset) between the two test conditions (see Figure 3B, lower panel). A theta power increase was observed for manipulated compared to intact trials within the right inferior parietal sulcus (IPS; $x = 37$, $y = -46$, $z = 50$) and the right superior frontal gyrus ($x = 27$, $y = 24$, $z = 50$). In summary, theta power increases within the lateral PFC and the posterior parietal cortex (the IPS, specifically) were engaged to support the comparison

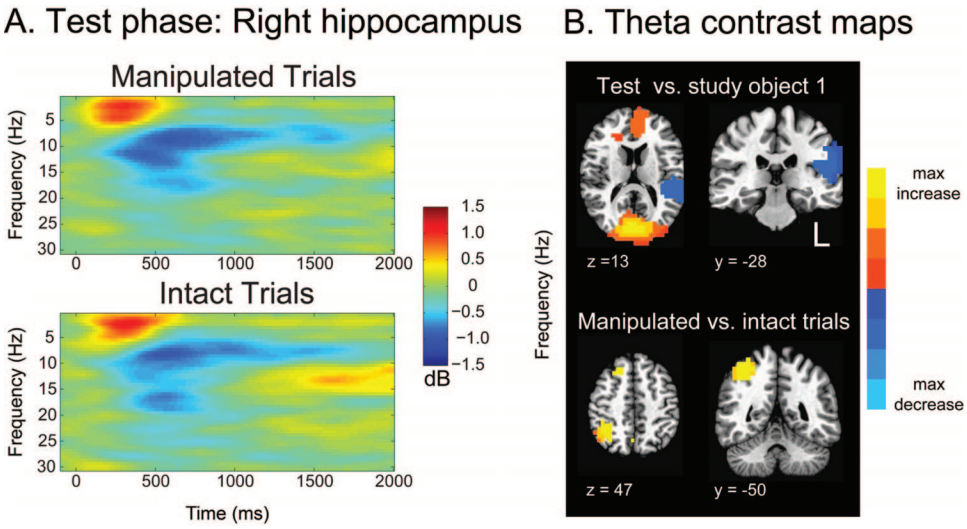

Figure 3. Test phase results. (A) During the test phase, a theta power increase and an alpha power decrease were also observed in the right hippocampus. (B, upper) Areas in which theta power was significantly different between the test phase (250–750 ms post onset) and following the first study object (250–750 ms post onset). (B, lower) Areas in which theta power was significantly different during manipulated trials compared to intact trials during the test phase. The statistical threshold was set to $p < .001$ uncorrected, false discovery rate corrected $q < .05$.

process that occurred during detection of mismatch displays during the test phase.

Relationship Between Theta Power and Task Performance

To determine the extent to which hippocampal theta responses were related to subsequent memory performance, changes in theta power were correlated with accuracy on the manipulated trials. Accuracy on manipulated trials was used as the performance measure, as accuracy on the intact trials was near ceiling (94%). For the study phase, the same time window (750–2500 ms post onset of the first and third study image) was used as in the whole-brain analysis, and the data from both the left and right hippocampal virtual channel were correlated with task performance. Correlations were also computed on the virtual channels corresponding to the left and right medial PFC, right superior frontal gyrus, left and right precuneus, and right IPS, which were the major cortical regions implicated in the study, delay, and test phases; these results are reported in the supplemental materials. There was a significant positive relationship between the study period theta power increase in the right hippocampus and accuracy for manipulated trials ($r = .40$, $p_{\text{one-tailed}} = .026$; see Figure 2D). A similar relationship was observed in the left hippocampus ($r = .37$, $p_{\text{one-tailed}} = .035$). These findings suggest that theta oscillatory activity contributes to the successful binding and maintenance required for subsequent detection of relational changes among studied objects across short delays.

Similarly, a between-subjects correlation was conducted between the theta power response during the delay phase (750–1,500 ms post onset) and accuracy on the manipulated trials. However, unlike the theta response during the study phase, there was no significant relationship between subsequent task performance and theta power in either the right ($r = .29$, $p_{\text{one-tailed}} = .085$) or left hippocampus ($r = -.06$, $p_{\text{one-tailed}} = .382$).

Although the time–frequency analysis of the left and right hippocampus revealed a theta response ~250–750 ms post onset of the test display (see Figure 3A), this rapid theta response did not differ significantly from the response after the first study image, and it was also not significantly greater for manipulated compared to intact trials. Nevertheless, an exploratory analysis was conducted to determine whether differential theta power responses during the test phase (manipulated–intact trials) were correlated with task performance on manipulated trials. No significant relationship was found between task accuracy and the differential theta response in either the left ($r = .31$, $p_{\text{two-tailed}} = .141$) or right hippocampus ($r = .26$, $p_{\text{two-tailed}} = .222$).

Discussion

Using the fine spatiotemporal resolution afforded by MEG, this study characterized the temporal dynamics of hippocampal and cortical neural oscillations that support multiple facets of memory across short delays: binding/maintenance and comparison. Critically, while increased theta power was observed in the hippocampus during the study and delay phases, changes in hippocampal theta power during the study phase were related to task performance. This suggests that the hippocampus plays a major role in the binding of spatial relations and a more limited role in active maintenance of the already formed spatial relations among the presented objects across a brief delay. Posterior parietal cortex (precuneus and posterior cingulate) exhibited greater theta power across the study phase, and increased theta power in medial PFC was observed across all three stages of memory processing, suggesting a role for this region in maintaining the relations bound by the hippocampus for subsequent use during comparison. Addition-

ally, during the test phase, a greater theta power response was observed within the right superior frontal gyrus and right IPS elicited by manipulated trials compared to intact trials. These findings suggest that spatial information was initially processed by the posterior parietal system and bound into relational representations by the hippocampus. Subsequently, these representations were maintained (or to some extent, retrieved) and compared to the test probe through the engagement of the parietal lobe and PFC. By utilizing the fine spatiotemporal resolution of MEG, the present work documents the collaborative involvement of the hippocampus, medial and lateral prefrontal, and medial and lateral posterior parietal neural systems during short-delay visuospatial memory performance.

Hippocampal and Medial PFC Theta Power During Encoding and Maintenance

Hippocampal theta has been measured extensively in rodents, and is closely related to the firing of hippocampal place cells (O'Keefe & Recce, 1993). In humans, increased theta power has been observed during spatial navigation (Ekstrom, Suthana, Millett, Fried, & Bookheimer, 2009; Kahana et al., 1999, 2012). Therefore, the current observation of theta power increases in the hippocampus during visuospatial memory encoding and maintenance is highly complementary to previous research. During the study phase, participants were required to incrementally bind the spatial relations of each presented object with respect to the previously presented object. Theta oscillations could enable binding through the coactivation of location information, and synchrony within the hippocampus could provide a neural "ambience" or framework onto which higher frequency oscillations could then project specific item representations (Fell & Axmacher, 2011; Jensen & Colgin, 2007; Sauseng, Griesmayr, Freunberger, & Klimesch, 2010). Additionally, increased, sustained theta power was observed in the anterior temporal lobe and the medial PFC during encoding and maintenance of the relative spatial relations in the study phase, and these same brain regions showed a sustained theta response during the delay phase.

The present findings converge well with a previous scalp EEG study demonstrating that theta power increases during memory encoding were associated with faster reaction times during cued recall on an associative (word) learning task (Caplan & Glaholt, 2007). However, the present results do not preclude the interpretation that theta oscillations contribute to item encoding or maintenance; indeed, some of the present signal may have reflected information regarding items and their absolute spatial positions. For example, several recent investigations using intracranial EEG have related brain oscillations (including theta) to short-delay maintenance of faces and words (Lega et al., 2012; van Vugt, Schulze-Bonhage, Litt, Brandt, & Kahana, 2010), and other studies that test for items rather than the relations among them have found that delay period theta power increases as a function of memory load (Gevins, Smith, McEvoy, & Yu, 1997; Jensen & Tesche, 2002; Meltzer et al., 2008). Rather, our present findings suggest that, critical for the current task, the observed theta responses carried information regarding the relative spatial positions among objects, which was subsequently used to support performance.

Functional MRI studies have revealed sustained activity in the medial temporal lobe during the delay period of delayed-match-to-sample tasks (e.g., Ranganath & D'Esposito, 2001). Olsen et al. (2009) found sustained activity in the anterior hippocampus that was related to successful short-delay recognition performance; however, the task employed used considerably longer delay periods than those used in the current study. Others have found that although the fMRI response in the medial temporal lobe was not significantly maintained during the delay period, the activity nonetheless was predictive of short-delay task performance (Hannula & Ranganath, 2008). Thus, it is possible that the role of the hippocampus during the maintenance of information over short delays is variable such that it depends on both delay length and the complexity of the information it is required to maintain (Olsen et al., 2012). In the current study, it is possible that the relations among items were relatively simple to maintain once encoded, and that although theta power in the hippocampus was still increased, this sustained delay period processing was not critical for task performance.

Although multiple studies have observed midline theta during the delay phase between study and test (Jensen & Tesche, 2002; Meltzer, Negishi, Mayes, & Constable, 2007), relatively few studies have investigated the role of theta specifically during the encoding phase of short-delay tasks (see Nyhus & Curran, 2010, for review of theta and long-term memory), and even fewer have investigated the contribution of observed theta during encoding as well as maintenance and its subsequent relation to task performance within the same paradigm. Thus, these results provide novel evidence that increased neural synchrony in the hippocampus and medial PFC supports the incremental binding of visuospatial associations in the service of memory performance over short delays. In addition, these findings highlight the role of encoding and maintenance (as opposed to retrieval and comparison) as the specific mechanisms that underlie the observed impairments for short-delay memory of spatial relations in hippocampal amnesics (Konkel et al., 2008).

Theta Power Increases Associated With Comparison

During the presentation of the test display, participants were required to compare current perceptual input with the visuospatial representation formed during the study phase in order to successfully detect a change in the relative spatial locations of the objects. Because the absolute locations of the objects were changed on every trial, the assessment of the relations among the test objects was required on every trial, regardless of whether a change had actually occurred. However, manipulated trials likely engaged extended processing of the spatial relations due to additional encoding and binding of the new spatial relations. In similar paradigms, both mismatch and match enhancement effects have been reported in the hippocampus with fMRI (Duncan, Ketz, Inati, & Davachi, 2012; Hannula & Ranganath, 2008; Kumaran & Maguire, 2006). Mismatch enhancement effects in the hippocampus have been described in the literature as evidence for the detection of associative novelty (Kumaran & Maguire, 2007), which is consistent with its proposed role as a "comparator" of current and previously stored information (Hasselmo & Wyble, 1997; Lisman & Grace, 2005; Vinogradova, 2001). Comparison, however, might rely on multiple stages. First, the current information must be linked to the previously stored relevant information, a process that enables access to the stored representation. Next, the

evaluation process can proceed, and the assessment of the match or mismatched displays is accomplished.

In the current study, no significant differences in the hippocampus were obtained in the theta band when manipulated trials were contrasted against intact trials. One possible interpretation of the current findings is that although the hippocampal theta response is involved in binding and likely provides access to stored memory representations (which would correspond to the initial stage of comparison as outlined above), the evaluation phase of the comparison process (as indexed by the detection of a mismatched display) may involve frequency ranges outside the theta band and/or regions outside the hippocampus.

Alternatively, the binding and maintenance processes occurring during the study and delay phases may have precluded the need for an active retrieval process, which could also explain why the theta response in the hippocampus following the test display was not significantly greater than the response following the first study object. If this interpretation were correct, the stored representation would have been accessed and compared via extrahippocampal cortical regions. Interestingly, an area within the IPS exhibited significantly greater theta power for manipulated compared to intact trials, and this difference in theta power was correlated with accuracy on the task. The role of the IPS in memory has recently become a topic of great interest for researchers and has been implicated in both successful relational binding (Uncapher, Otten, & Rugg, 2006) and the retrieval of previously studied item–context associations (Hutchinson et al., 2012). Indeed, both lateral and medial posterior parietal areas are anatomically connected (Rushworth, Behrens, & Johansen-Berg, 2006; Seltzer & Pandya, 1984) and functionally coupled (Greicius, Krasnow, Reiss, & Menon, 2003; Vincent et al., 2006) with the medial temporal lobe. Thus, further investigation of the relative contributions of the hippocampus, PFC, and posterior parietal cortex to short- and long-term memory retrieval is warranted.

Future Directions

The current investigation revealed a critical role for induced theta oscillations in the hippocampus and associated neocortical networks to the successful binding of spatial relations in the context of a short-term visuospatial memory task. A more limited role for the hippocampus was observed during comparison—suggesting that although the hippocampus may help retrieve the relevant representations, the comparison process itself was performed outside the hippocampus. An important next step in understanding the dynamics of hippocampal–neocortical involvement during distinct phases of memory processing would involve an analysis of functional coupling of disparate neocortical regions (e.g., medial and lateral PFC, medial and lateral posterior parietal cortex) with the hippocampus. This would provide a more definitive understanding of the relative roles of these brain regions in binding and comparison.

The approach employed in the current investigation was particularly well suited for studying cognitive processes that unfold on time scales ranging from less than a second to many seconds and that were not necessarily time locked to an exact moment in time. Although neuropsychological studies have provided important insights into the causal role of the damaged brain regions in cognition, these behavioral impairments are the "output" of many different processes. MEG enabled the investigation of neural synchrony via theta oscillations, which are often observed in nonhuman animals during spatial navigation, and are thought to play a critical role in the coordination and transmission of information, a function critical to binding. Thus, parallel investigations using similar methods in neuropsychological patients, nonhuman animal recording studies, and neuroimaging are necessary for uncovering the functions of specific brain structures and for advancing current cognitive theory. Understanding the dynamics of neural communication through oscillatory changes will enrich our understanding of how memory, and cognition more generally, is manifested in the human brain.

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