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A complementary analytic approach to examining medial temporal lobe sources using magnetoencephalography

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ABSTRACT

Neuropsychological and neuroimaging findings reveal that the hippocampus is important for recognition memory. However, it is unclear when and whether the hippocampus contributes differentially to recognition of previously studied items (old) versus novel items (new), or contributes to a general processing requirement that is necessary for recognition of both types of information. To address this issue, we examined the temporal dynamics and spectral frequency underlying hippocampal activity during recognition of old/new complex scenes using magnetoencephalography (MEG). In order to provide converging evidence to existing literature in support of the potential of MEG to localize the hippocampus, we reconstructed brain source activity using the beamformer method and analyzed three types of processing-related signal changes by applying three different analysis methods: (1) Synthetic aperture magnetometry (SAM) revealed event related and non-event-related spectral power changes; (2) Inter-trial coherence (ITC) revealed time-locked changes in neural synchrony; and (3) Event-related SAM (ER-SAM) revealed averaged event-related responses over time. Hippocampal activity was evident for both old and new information within the theta frequency band and during the first 250 ms following stimulus onset. The early onset of hippocampal responses suggests that general comparison processes related to recognition of new/old information may occur obligatorily.

Introduction

Since Scoville and Milner's (1957) discovery that excision of the hippocampus and surrounding cortex leads to profound and pervasive memory deficits, memory research has focused on the functional significance of this medial temporal lobe region (Eichenbaum and Cohen, 2001; Squire, 1992; Cohen and Eichenbaum, 1993; Cohen et al., 1999). Early neuropsychological studies revealed that damage to the hippocampus leads to severe deficits in memory for facts and events, as typically assessed using recall and recognition tasks in which participants have to either retrieve previously studied items or distinguish previously studied items from novel items, respectively (Corkin, 1968; 1984; Cohen and Squire, 1980; Manns et al., 2003).

With the advent of functional neuroimaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), researchers have studied the contribution of the hippocampus to memory in the healthy brain, often by using recognition memory tasks. Consistent with the neuropsychological data, neuroimaging findings revealed that the hippocampal region is involved during recognition memory tasks compared to control tasks that require simple visual processing/discrimination (e.g. Kapur et al., 1995; Schacter et al., 1995; Squire et al., 1992).

With further advances in technology and analysis, researchers used event-related fMRI to interleave trial types that required different cognitive demands and/or to separate trials based on participants' response (Kensinger et al., 2003; Greenberg et al., 2005; Yonelinas et al., 2005) to determine whether the hippocampus contributes specifically to *successful* retrieval of stored information or whether the hippocampus has a more general role during the retrieval stage. While some studies found that the hippocampus was preferentially recruited during the successful recognition of previously studied (old) information, others found that it was recruited to a

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similar extent (or even more) for novel (new) information (see Henson, 2005, for review). This suggests that the critical role of the hippocampus during memory retrieval may not reflect successful access to a stored representation per se, but instead may reflect a more general processing requirement that is common for both previously studied and novel information (Cohen et al., 1999). However, it is also possible that the hippocampus contributes differentially to the recognition of old/new information in ways that are not reflected in the amount of changes in metabolism as measured using PET and fMRI. Specifically, to the extent that different processes are invoked to support the recognition of old versus new information, the hippocampus may be recruited at a different time and/or in a different manner, as reflected in time course and spectral frequency of electromagnetic brain activity. PET and fMRI techniques do not have the adequate temporal resolution to outline the time course by which the hippocampus may come online during the recognition of different types of information, therefore, we require a neuroimaging method that can localize the hippocampus and outline its precise temporal dynamics.

Precise temporal dynamics underlying neural activity can be observed using electroencephalography (EEG) or event-related potentials (ERPs). For years, ERP studies of recognition memory have described what is thought of as hippocampally-mediated neural activity associated with viewing of previously studied and novel stimuli (for review, see Rugg, 1995). This is known as the late positive component (LPC) of the ERP and is typically observed over medial and posterior sensor sites and begins around 500–600 ms after stimulus onset (e.g. Düzel et al., 2001a,b; Rugg et al., 1996; Smith and Halgren, 1989). This seems to suggest that different types of information recruit hippocampal processing in the same temporal manner. However, it is not known to what extent the late ERP components reflect the contribution from the hippocampus versus other sources. The spatial localization of EEG is compromised by volume conduction and therefore the signals likely reflect multiple underlying neural regions, thereby making it difficult to outline the temporal dynamics of the hippocampus specifically. Moreover, even if the temporal dynamics of hippocampal activity for previously studied versus novel information is similar during later processing (>500 ms), it is not known whether they are similar during earlier stages of recognition memory (<500 ms).

Magnetoencephalography (MEG) is a noninvasive neuroimaging technique that estimates neuronal activity based on recordings of the magnetic flux outside of the head (Hari et al., 2000; Hämäläinen et al., 1993). MEG has the same temporal resolution as EEG, but magnetic fields are less susceptible to attenuation by skull and tissue, therefore, its spatial localization is more precise than EEG. MEG provides recording of neural activity with temporal resolution on the order of milliseconds and spatial resolution comparable to that of fMRI (Miller et al., 2007). These properties make MEG an ideal tool for studying the dynamics of brain function. However, there is some debate of whether MEG can be reliably used to detect signals from deep neural structures such as the hippocampus (Mikuni et al., 1997). First, it has been argued that the specific shape of the hippocampus prevents any signal from being detected by MEG sensors (Mikuni et al., 1997). Specifically, it has been speculated that the "spiral" shaped hippocampal formation may lead to cancellation of all detectable signal from this region (Baumgartner et al., 2000; Mikuni et al., 1997; Stephen et al., 2005). However, complete cancellation would require simultaneous activation of dentate and cornu ammonis (CA) fields with equal signal intensity. Contrary to this, it has been argued that the hippocampus is laminated, thus, signals tend to summate rather than cancel (Nishitani et al., 1999). Moreover, anatomical and electrophysiological asymmetries in hippocampus (Duvernoy, 1988; Yeckel and Berger, 1990) suggest that cancellation will be incomplete and at least some portion of the signal will be visible to MEG (for an in depth discussion, see Stephens et al., 2005).

Second, it has been argued that signals from the hippocampus would be too weak to be detectable by MEG sensors because the magnetic field decreases with the square of distance between neural source and the MEG sensor (Hillebrand and Barnes, 2002; Baumgartner et al., 2000; Hämäläinen et al., 1993). Since the hippocampus is situated deep within the brain, detecting hippocampal activity at the scalp surface is challenging. Under the assumption that deep structures do not contribute to the recorded signal, some source analysis programs constrain the localization of neural activity to the cortex excluding all subcortical structures including the hippocampus (Jerbi et al., 2004; Berg and Scherg, 1994; Gonsalves et al., 2005). However, the development of modern whole-scalp MEG sensor arrays has increased the sensitivity for deep structures (Ahonen et al., 1993) by capturing magnetic flux signals across the entire head. Advanced data analysis methods make use of information obtained by all sensors and support volumetric source analysis, e.g. standardized low resolution brain electromagnetic tomography (sLORETA) (Pascual-Marqui, 2002), L1 minimum-norm current estimate (MCE) (Tesche, 1996; Uutela et al., 1999), synthetic aperture magnetometry (SAM) (Robinson and Vrba, 1999; Fawcett et al., 2004; Gaetz and Cheyne, 2003; Herdman et al., 2003; Herdman et al., 2004; Hirata et al., 2002; Schulz et al., 2004; Luo et al., 2007), and event-related SAM (ER-SAM) (Cheyne et al., 2006; Cheyne et al., 2007; Hämäläinen et al., 1993; Itier et al., 2006; Herdman and Ryan, 2007; Herdman et al., 2007). Our group contributed to these tools with a new source analysis approach using inter-trial coherence (ITC) (Bardouille and Ross, 2008).

Third, there is some question as to whether MEG is sensitive enough to differentiate activity between the hippocampus and parahippocampal gyrus. It has been reported that at the depth of these sources (5–6 cm), spatial resolution ranges from 25 mm to 40 mm, making it difficult to distinguish activity originating in the hippocampus from those originating in the parahippocampal region (Mosher et al., 1993; Cohen et al., 1990). However, in a study that examined the precision of localization using simulated MEG activity presented with real background brain activity, Stephen and colleagues (2005) showed that MEG is able to correctly localize activity to either the hippocampus or the parahippocampal gyrus when activity in these two regions did not overlap in time. When these two regions did overlap in time and were simultaneously active, MEG was unable to differentiate between them and modeled the activity to a single source. However, this is not a problem for localizing the hippocampus per se, rather, this suggests that when both regions are active, activity localized to one region cannot be said to be completely independent of the other, and may reflect simultaneous activity from both regions.

Based on previous literature, it is clear while the localization of deep sources, such as the hippocampus, using MEG remains a challenging task, it is by no means an impossible one. In fact, numerous studies have lent support to the notion that hippocampal activity can be detected by MEG using a variety of experimental paradigms such as sensory oddball tasks (Ioannides et al., 1995; Tesche, 1996; Nishitani et al., 1998; Hamada et al., 2004), conditioning (Kirsch et al., 2003), mental calculation (Tesche, 1997), and motor reaction to an auditory cue (Tesche and Karhu, 1999). Of the MEG studies that examined memory, several have reported observable responses from the hippocampus for tasks of prospective memory (Martin et al., 2007), working memory (Tesche and Karhu, 2000; Campo et al., 2005), and transverse patterning (Hanlon et al., 2003, 2005). However, despite the theoretical and empirical link between the hippocampus and long-term memory, and the prevalent use of recognition memory paradigms in neuropsychological, PET, fMRI, and ERP studies, only very few MEG studies have examined hippocampal activity within this framework (Gonsalves et al., 2005; Tendolkar et al., 2000; Papanicolaou et al., 2002; Breier et al., 1998; 1999; 2000).

The MEG studies that have looked at hippocampal activity during a recognition memory task have been inconclusive. In a recent MEG

study of visual memory by Osipova and colleagues (2006), it was found that correctly recognized old items elicited stronger theta oscillations than correctly rejected new items. The authors suggested that this theta oscillation may derive from hippocampal activity, but were not able to localize the activity to any region in the brain due to insufficient signal-to-noise ratio. In a MEG study of verbal recognition, magnetic evoked activity localized to the right medial temporal region was reported (Tendolkar et al., 2000). However, because the MEG data had not been co-registered with participants' structural MRIs, it is not clear whether the activity originated from the hippocampus or surrounding cortex. In a combined MEG and fMRI study that also examined neural activity during a verbal recognition task, significant left medial temporal lobe (MTL) activity was localized to the perirhinal and parahippocampal cortex predominantly during the 150–450 ms time interval following stimulus onset (Gonsalves et al., 2005). However, since the MEG sources had been constrained to the cortex only, it is unclear whether the hippocampus was also involved. When researchers incorporated co-registration of MEG and structural MRI and did not constrain the MEG localization to cortical sources, activity was localized to the medial temporal lobe, including the hippocampus and parahippocampal gyrus using both visual and verbal recognition tasks (Papanicolaou et al., 2002; Breier et al., 1998; 1999; 2000). However, Papanicolaou and colleagues (2002) only examined the time course of medial temporal lobe activation in general, and while Breier and colleagues (1998, 1999, 2000) localized the activity specifically in the hippocampus and parahippocampal gyrus and found them to be active between 200–800 ms post-stimulus onset, the exact time course of activity in the hippocampus was not outlined. Altogether, all of the MEG studies examining recognition memory of which we are aware reported medial temporal activation when there was sufficient signal-to-noise ratio for brain localization and when source analysis had not been constrained to the cortical surface, (Gonsalves et al., 2005; Tendolkar et al., 2000; Papanicolaou et al., 2002; Breier et al., 1998, 1999, 2000). Furthermore, activity in the hippocampus can be detected when using precise co-registration of MEG and structural MRI (Papanicolaou et al., 2002; Breier et al., 1998, 1999, 2000).

While the above studies have examined hippocampal activity during recognition memory using MEG, questions remain regarding precisely when peak hippocampal activity occurs and whether the manner of activity changes depending on the nature of the stimulus (old/new). For example, hippocampal activity associated with the recognition of previously studied versus novel items may peak at the same/different times and/or oscillate in the same/different frequency range. The purpose of the present study was to provide converging evidence for the earlier work described above, which outlines the potential of using MEG for localizing hippocampal activity, and to expand upon it both methodologically and theoretically. We adapted an experimental paradigm in which participants first studied a series of scenes and scrambled versions of the scenes (Kirchhoff et al., 2000). Immediately following, participants had to distinguish previously studied from novel scenes.

To expand upon prior work methodologically, we provide a comprehensive examination of electromagnetic activity from the hippocampus by analyzing multiple aspects of processing-related signal changes in the observed signals. The three analysis methods used were variations of the beamformer approach (Robinson and Vrba, 1999): Synthetic Aperture Magnetometry (SAM), Inter-Trial Coherence (ITC) of brain source activity, and Event Related SAM (ER-SAM). The beamformer approach to MEG data analysis is a two-step procedure: the first step uses the beamformer as spatial filter for reconstructing source activity, and in the second step, a signal statistic is derived from the source activity and mapped volumetrically. While the three analysis methods in our study use the same beamformer, each method uses different statistics and vary in their degree of specificity for particular aspects of the data such as spectral and temporal information. SAM examines the changes in signal power in a certain frequency band between a specified control and active time window for each volume element. The signal power statistics includes both the phase-locked event-related activity and changes in signal power induced by the stimulus but not strictly phase-locked. ITC is a normalized measure of neural synchrony across multiple trials. ITC reveals the time and frequency range in which high coherence between stimulus and brain activity occurs and provides complementary information to the signal power statistics in SAM. ER-SAM averages waveforms of source activity across all trials and examines event-related, time-locked neural responses. Unlike modeling the MEG data with a small number of equivalent current dipoles (ECD), the beamformer analysis does not require a priori assumptions about the number of active sources. Also, beamformer algorithms take advantage of the high dimensionality of the signal space offered by multi-channel MEG in order to reduce correlations in the data and suppress interactive sources (Cheyne et al., 2006). Specifically, the entire brain volume is covered by a grid, and at each grid node, the beamformer maximizes sensitivity for the signal from that node and suppresses the signal from other nodes (Huang et al., 2004). It should be noted that while the proposed analyses vary in their degree of specificity for particular aspects of the data such as spectral and temporal information, the observed measures may not be completely independent because they are affected by properties of the commonly applied beamformer. Further, the methods of examining the averaged evoked response with ER-SAM and ITC are asymptotically equivalent for a large number of trials. However, two important differences exist between ITC and ER-SAM. First, ITC uses the normalized amplitude of neural activity, which makes the statistics more homogeneous across the whole brain than ER-SAM. This is important for localizing deep sources, which likely have lower signal amplitudes than more superficial sources. Second, ITC provides information about synchrony at a specific frequency, while ER-SAM provides precise timing information. With the three complementary analysis methods we will give an exhaustive description of relevant electromagnetic brain activity as expressed in changes in spectral signal power, time course of event-related activity and changes in signal coherence. To the best of our knowledge, the application of multiple analysis methods to characterize the different aspects of neural activity from hippocampus with the same set of MEG data has not been previously attempted.

To expand upon prior work theoretically, through our multi-method approach, we are able to outline the precise time courses and spectral frequencies of hippocampal activity during recognition of old and new items. This will provide insights into the nature of recognition memory, namely, when does the hippocampus begin to participate in recognition memory of, and does it participate similarly for, old/new information? Such an analysis may speak to questions regarding the functional role of the hippocampus in distinguishing the familiar from the novel.

Method

Participants

Thirteen adults (6 males; 28.1 years of age, 1 left-handed) from the Toronto community with normal neurological histories and normal or corrected-to-normal vision participated in the study. 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

Visual stimuli consisted of 200 pictures of indoor scenes, 200 of outdoor scenes, and 400 scrambled scenes. The resolution of all

pictures was 1024 by 768 pixels. The 400 indoor and outdoor scenes were created from a set of 200 scenes (100 indoor, 100 outdoor) taken from a repository of scenes in CorelDraw. Each scene was divided into two unique non-overlapping images to create a set of target scenes and a set of foil images. In this manner, sets of targets and foils were similar for color, luminance and complexity. Targets were presented during the encoding phase and as 'old' images in the retrieval phase; foils were presented as 'new' images during the retrieval phase. The sets of scenes were counterbalanced such that every scene was presented equally often as a target and foil across participants. The scrambled scenes were random patterns generated from permutations of the indoor and outdoor scenes, such that each scene had a scrambled counterpart, and therefore had similar color and luminance as the original scenes. Scrambled scenes were made using Adobe Photoshop.

Procedure

The experiment consisted of an encoding and retrieval phase, each lasting approximately 20 min. MEG was recorded during both phases; however, only the date from the retrieval phase is presented here. During the encoding phase, participants viewed 200 indoor and outdoor scenes and 200 matched scrambled scenes. Scenes were presented for 1000 ms with an average inter-stimulus interval (ISI) of 2000 ms (range 1750–2250 ms). During the ISI a fixation cross appeared in center of the black screen (Fig. 1). Participants were instructed to distinguish between indoor, outdoor, and scrambled scenes by pressing one of three different buttons with their right hand. Participants were also informed that there would be a subsequent memory test. The retrieval phase immediately followed the encoding phase. During retrieval, participants viewed the 200 previously studied (target) scenes and 200 novel indoor and outdoor scenes (foil images). Participants were instructed to respond whether they were highly confident that the picture had been previously studied ('old'), if they were only somewhat confident that the picture was 'old', or if the picture was 'new'.

Data acquisition

MEG recordings were performed in a magnetically shielded room at the Rotman Research Institute, Baycrest Hospital for Geriatric Care, using a 151-channel whole head first order gradiometer system (VSM-Med Tech Inc.) with detection coils uniformly spaced 31 mm apart on a helmet-shaped array. Participants sat in upright position, and viewed the stimuli on a back projection screen that subtended approximately 31 degrees of visual angle when seated 30 in. 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 using indicator coils placed on nasion and bilateral preauricular points. These three fiducial points established a head-based Cartesian coordinate system for representation of the MEG data.

In order to specify/constrain the sources of activation as measured by MEG and to co-register the brain activity with the individual anatomy, a structural MRI was also obtained 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. All participants' anatomical MRIs and MEG source data were spatially normalized to the Talairach standard brain using AFNI (National Institute of Mental Health, Bethesda, MD, USA) for the SAM and ITC method and using SPM99 (Wellcome Institute of Cognitive Neurology, London, UK) for the ER-SAM method to allow for group analysis of functional data.

Data analysis

Analysis methods were applied to scenes that were later correctly identified as 'new' (correct-new) and 'high confidence old' (correct-old). For all analyses, the beamformer spatial filter as provided by the VSM software package was used to estimate source activity on a grid with regular spacing of 5 mm. Analyses were performed individually for each participant. Resulting individual volumetric maps of functional brain activity were then transformed into the standard Talairach space, using the same transform applied to the anatomical MR image. The resultant functional maps for each time/frequency interval were then averaged across participants. Group statistics were performed to identify which regions of brain activation were significantly different from a pre-specified control window on average across all participants. The type of group statistics applied for each analysis method is consistent with previous work, for example, permutation test for SAM (Chau et al., 2004) and pseudo-z for ER-SAM (Herdman et al., 2007). In order to ensure that significance in the group-averaged results was not driven by outliers, we also examined individual volumetric maps. The purpose of the present paper is to explore hippocampal activity in a visual recognition memory task. As such, we present and discuss only activity restricted to this region.

MEG analysis using SAM

The linearly constrained minimum variance (LCMV) beamformer algorithm (Robinson and Rose, 1992; Van Veen et al., 1997) was used to estimate source activity in a wide frequency band (0–30 Hz) and specifically in the theta (4–8 Hz) frequency band (e.g. Tesche and Karhu, 2000). The control window was defined as the time interval from −500 to −250 ms before stimulus onset, and four active windows of 250 ms duration between 0 and 1000 ms post-stimulus onset. For the two frequency bands, the differences in signal power between all active and the control window were normalized to an estimate of noise power. The resulting expression of stimulus induced relative power changes for each node was termed pseudo t-statistic, which is a normalized measure of the difference between signal power in the active and control window (Robinson and Vrba, 1999). Pseudo-t values at all nodes were compiled to generate a volumetric map of neuronal power changes for each post-stimulus interval and each frequency band. This calculation was performed for both 'correct-new' and

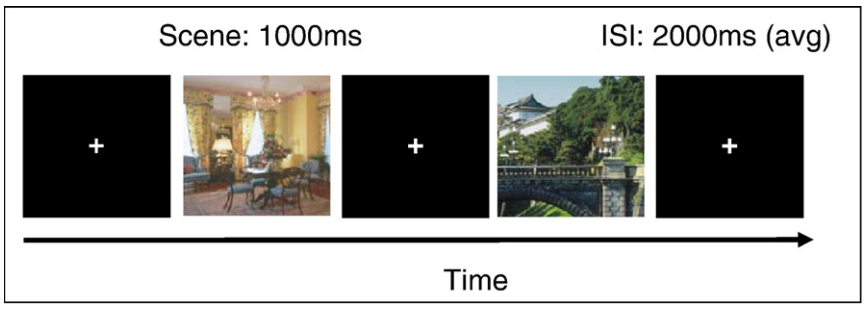

Fig. 1. Example of an indoor and outdoor scene used in the experiment.

'correct-old' scenes. SAM volumetric maps were viewed in AFNI and only spatially distinct regions of activity overlying the hippocampus were considered. Permutation tests were applied separately for the group-averaged volumetric maps corresponding to each time interval, frequency band, and both types of scenes in order to identify the brain regions with significant (α=0.05) signal power changes (Chau et al., 2004).

MEG analysis using ITC

The beamformer algorithm was applied to the 0–100 Hz wide band filtered MEG data in the −1000 to 1000 ms time interval relative to stimulus onset to define a spatial filter. Source waveforms at all volume elements were obtained from spatially filtering the MEG data. Morlet wavelet transform of the source waveforms provided phase information over each 250 ms time interval between −1000 and 1000 ms and seven frequencies centered approximately around 4, 6, 9, 13, 19, 28, and 41 Hz. ITC is a statistic describing the distribution of phase values across repeated trials (Fisher, 1993). ITC is zero in the case of the phase being uniformly distributed between 0 and 2π, which means that the signal does not show any stimulus-related contributions in the specific time and frequency interval. In contrast, ITC is close to 1 if the phase values are concentrated around a mean value indicating that the brain signal is strongly synchronized with the stimulus. A more detailed description of the analysis can be found in Bardouille and Ross (2008).

Volumetric calculation of ITC in time-frequency domain results in a five dimensional data set (three spatial dimensions, time, and frequency). In order to find relevant regions of interest, first the locations of right and left hippocampus were identified on each participant's MRI. ITC values for the closest grid node were compiled to generate time-frequency plots for both 'correct-old' and 'correct-new' scenes. These plots were used as a descriptive guideline to examine more specific spectral and temporal information in whole-head volumetric ITC maps and no statistics were applied. Whole-head volumetric ITC maps were generated for both types of scenes during any specific time/frequency intervals that depicted high inter-trial coherence in the hippocampus. Volumetric ITC maps were spatially normalized and group-averages were calculated as the mean ITC value across corresponding voxels. Individual and group-averaged volumetric ITC maps were visualized in AFNI using each participant's own MRI and the group-averaged MRI, respectively. In order to estimate the distribution of ITC amplitudes under the null hypothesis, we examined ITC values during the baseline period (−500 ms to −750 ms) for each participant and the group average, as outlined in Bardouille and Ross (2008). Only values exceeding the 95% level of this distribution were considered.

MEG data analysis using ER-SAM

The beamformer algorithm was used to define a spatial filter based on the MEG data in the 0–30 Hz frequency and −1000 ms to 1000 ms time interval. The spatial filter was applied to the time domain averaged MEG and normalized to a noise estimate, which resulted in time courses of a pseudo-z statistic corresponding to the amount of event-related brain activity in each volume element across the entire time interval (−1000 to 1000 ms). The pseudo-z is like the t-statistic used in SAM except that it is applied to multiple time points (every 5 ms) rather than normalized over time (i.e. 250 ms intervals), making it more appropriate for evoked and averaged data. Individual volumetric maps of the magnitude of pseudo-z values were transformed onto a normalized brain and averaged across all participants. Individual and group-averaged SAM maps were calculated for 'correct-new' and 'correct-old' scenes and the post-stimulus time interval (0–1000 ms) was examined. A distribution of the pseudo-z values under the null hypothesis was estimated from randomly sampled data in the pre-stimulus interval and thresholds for $\alpha \leq 0.05$ were obtained for all volume elements (Herdman et al., 2007). Threshold values for the group-averaged data were based on the pre-stimulus interval in the group-averaged data and threshold values for individual volumetric maps were based on the pre-stimulus interval for each participant. ER-SAM maps were thresholded accordingly and the locations of activation peaks in the remaining data were identified using a customized MATLAB procedure. This procedure, provided by the CTF software package, marks peaks in the volumetric data by first finding the voxel containing the maximum value within a 3 voxel volume of 15×15×15 mm after the ER-SAM image is thresholded, and then removes all voxels in the surrounding region that are contiguous or lower in magnitude than the maximum. The next peak is found as the maximum value in the remaining volume. This procedure is repeated until the entire volume has been scanned. For individual ER-SAM maps, peaks found in or within less than 1 cm of the hippocampus were considered. Time courses of the magnitudes of event-related neural activities (pseudo-z values) were calculated for the identified locations of peak activity from the grand-averaged ER-SAM maps. In order to examine any differences in hippocampal activity between processing of 'correct-new' and 'correct-old' scenes, we also performed a contrast between the two types of scenes.

Results

Behavioral responses

Three participants were excluded from all analyses due to low numbers of total correct responses (below 25%). Participants were significantly more likely to correctly identify old (hit) scenes with high confidence and novel scenes (correct rejection) than would be expected by chance (old: $t(9) = 2.68$, $p<.05$; novel: $t(9)=3.03$, $p<.05$). The incidence of hits and correct rejections did not differ significantly from each other ($t(9)=1.61$, $p>.10$). A summary of the behavioral recognition results can be found in Table 1. Behavioral results are similar to those obtained in fMRI studies using similar number of stimuli (e.g. Kirchhoff et al., 2000).

Signal power changes in neural responses: SAM

SAM maps for each time interval and frequency band for both 'correct-new' and 'correct-old' scenes were examined. Permutation tests performed on the group averaged activity did not reveal significant differences between the pre-stimulus control and active intervals in the hippocampus for either scene type (α=0.05). The only activity revealed to be significantly different from the control interval was within the visual cortex. However, the permutation test estimates a threshold common for all voxels in the brain and this may be too conservative for deep sources such as the hippocampus. We further explored the data by lowering the threshold limit and found spatially distinct activity in the right hippocampus for 'correct-new' scenes and in the parahippocampal region for 'correct old' scenes during the same time interval and frequency band (Fig. 2).

Coherence in neural responses: ITC

Averaged ITC values in time-frequency domain revealed stimulus-locked activation of the hippocampus during the 0–250 ms and

Table 1
Average accuracy (%) for correctly identifying a scene as 'old' or 'new'

Response	Old scenes % (SEM)	New scenes % (SEM)
High confident old	41.2 (3.06)	18.3 (3.13)
Low confident old	16.8 (3.58)	19.8 (4.29)
New	34.2 (5.57)	53.1 (6.63)

Standard errors of mean (SEM) are noted.

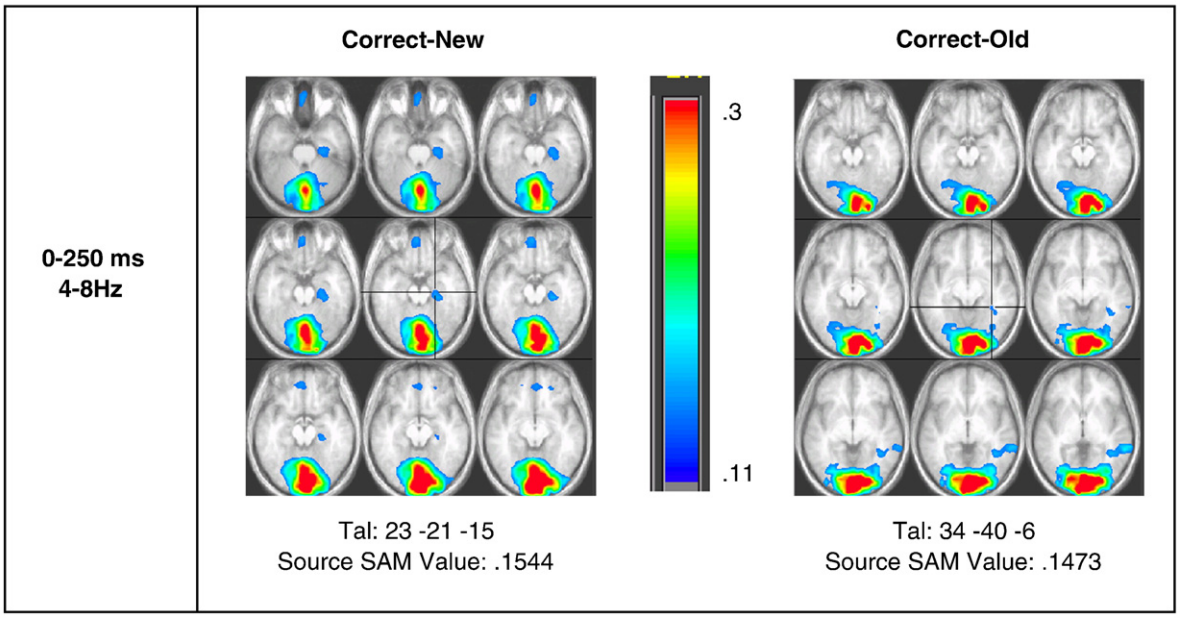

Fig. 2. Group-averaged SAM activation maps are shown for the theta frequency band during 0–250 ms post-stimulus onset. Activity is below the significance level of $p = .05$ for the group statistics (pseudo-t value = .49). However, when the raw data was viewed in AFNI, spatially distinct activity in the hippocampus (pseudo-t value = .15) and parahippocampal region (pseudo-t value = .15) was observed for correct-new and correct-old scenes, respectively. Black cross-hairs indicate the location of the regional peak, also reported in Talairach co-ordinates.

250–500 ms time interval following stimulus onset for the frequency bands up to 12 Hz for both 'correct-new' and 'correct-old' scenes. ITC measures in the hippocampus were specifically expressed in the first two frequency bins, which correspond with the delta (1–4 Hz) and theta frequency range (4–8 Hz), respectively (Fig. 3).

For the group-averaged data, volumetric maps for the theta band and the two time intervals of 0–250 ms and 250–500 ms revealed spatially distinct activity exceeding group baseline threshold values in the right hippocampus for 'correct-new' and 'correct-old' scenes across both time intervals (Fig. 4). Theta band activity in the left

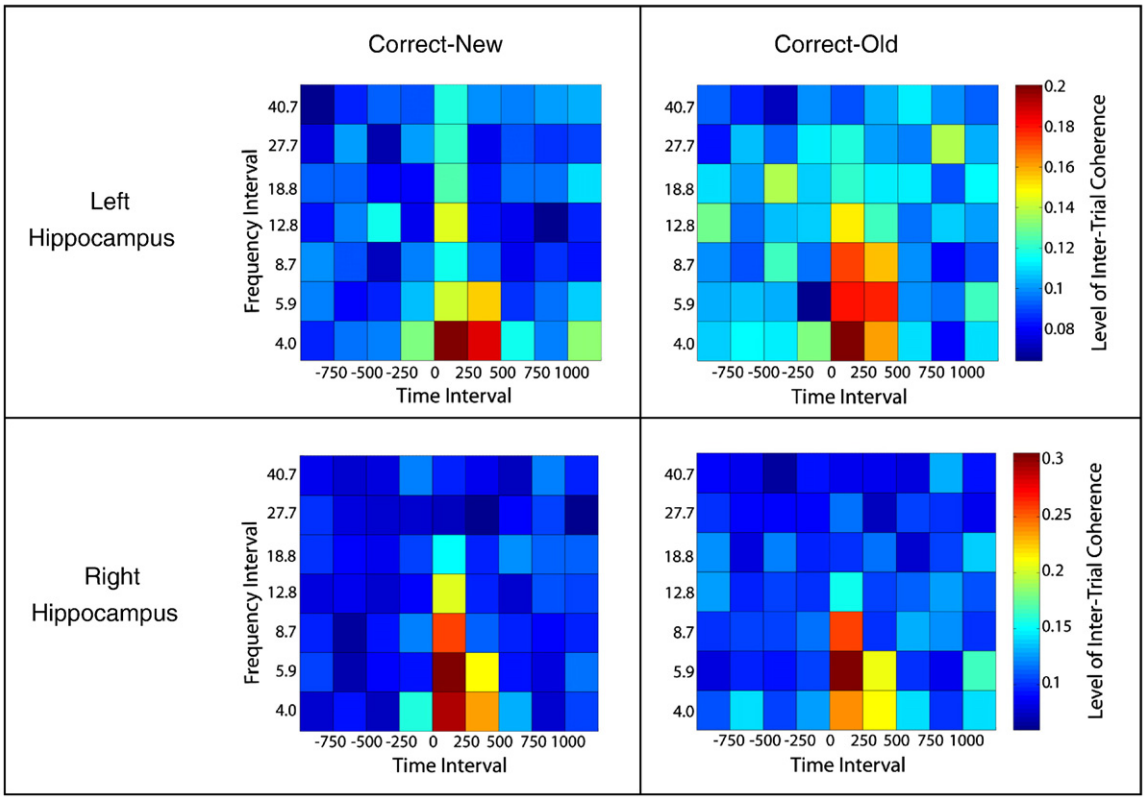

Fig. 3. Time-frequency representations of group-averaged ITC for the left (top) and right (bottom) hippocampus for scenes correctly identifying as 'new' (left) or 'old' (right) with high confidence.

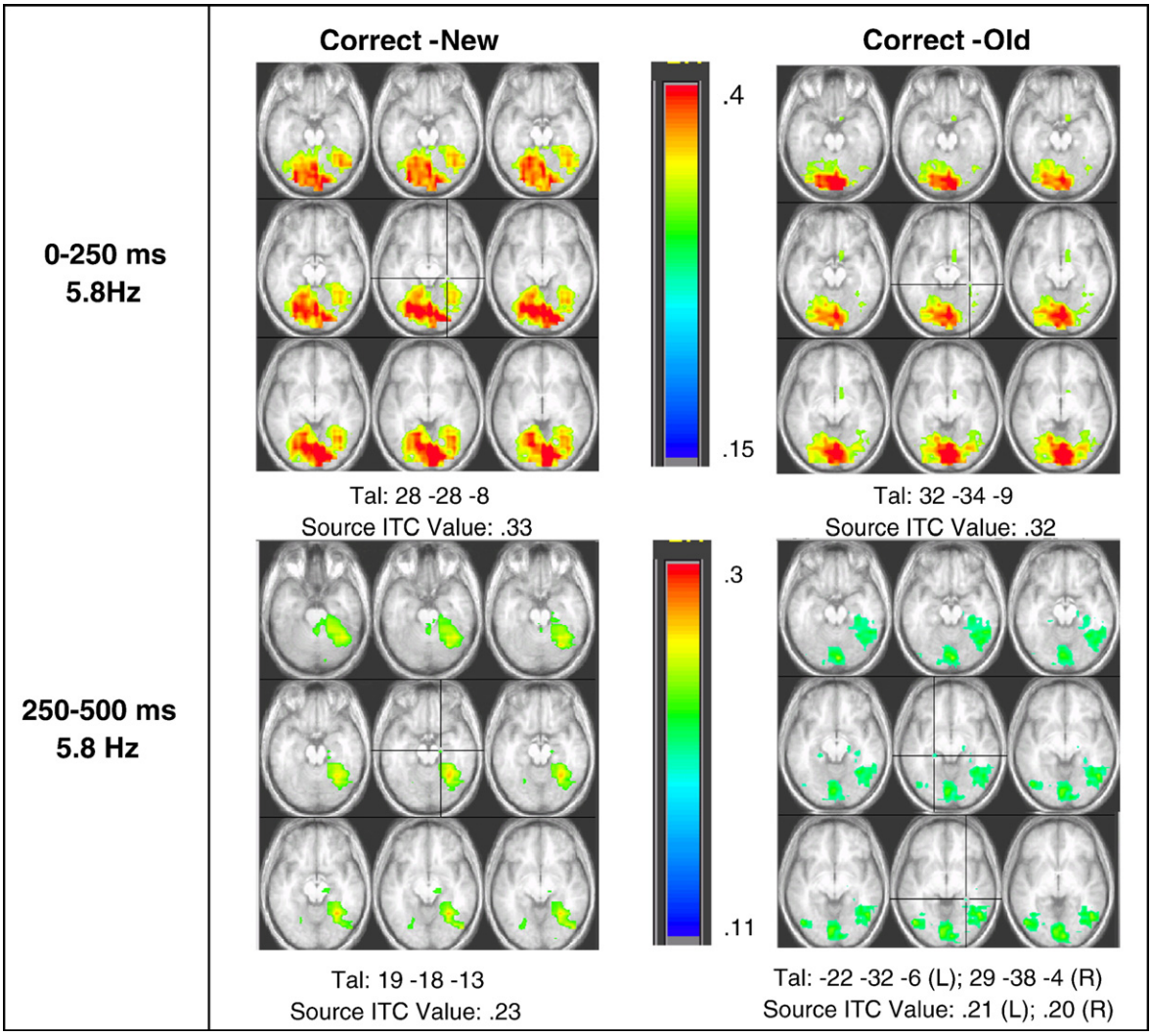

Fig. 4. Group-averaged volumetric maps of inter-trial coherence in approximately the theta frequency band (4–8 Hz, center frequency 6 Hz) during the 0–250 ms (top) and 250–500 ms time intervals (bottom) for scenes correctly identified as 'new' (left) and 'old' (right). Whereas theta band ITC in the right hippocampus was expressed for both time intervals for both 'correct-new' and 'correct-old' scenes, ITC in the left hippocampus was found during the 250–500 ms interval only for 'correct-old' scenes. Black cross-hairs indicate the position of the hippocampal peak, also reported in Talairach co-ordinates. All values exceeding .14 and .17 were considered significant for 'correct-new' and 'correct-old' scenes, respectively, based on threshold levels derived from the baseline period. All activity shown exceeded 95% level of the baseline distribution.

hippocampus was observed as a spatially distinct activation in the hippocampus for 'correct-old' scenes during 250–500 ms.

Individual volumetric maps for ITC in the theta band were examined for each participant. Consistent with group-averaged results, theta band synchrony in or within less than 1 cm of the right hippocampus exceeding the significance threshold occurred in 8 participants during 0–250 ms and 5 participants during 250–500 ms for 'correct-new' scenes, and 6 participants during 0–250 ms and 6 participants during 250–500 ms for 'correct-old' scenes. Group-averaged results also revealed theta band synchrony for 'correct-old' scenes during 250–500 ms in the left hippocampus. Significant activity was found in individual volumetric maps for 2 participants (Table 2). Examples of hippocampal activity found for individual participants is shown in Fig. 5 and the averaged location of peak hippocampal activity based on individual participants' ITC maps are shown in Fig. 6.

Averaged event related neural responses: ER-SAM

Time courses of grand-averaged ER-SAM data revealed peaks of activity in the right and left hippocampus for 'correct-new' scenes, which were significantly different from baseline for the group (α=0.05) (Fig. 7). Activity in the right hippocampus peaked at 225 ms post-stimulus onset. Two smaller peaks were also observed between 300–450 ms. Activity in the left hippocampus peaked initially at 130 ms post-stimulus onset and three smaller peaks were observed between 200–350 ms. For 'correct-old' scenes, significant activity was found for the left parahippocampal gyrus. Peak activity occurred 120 ms post-stimulus onset. Two smaller peaks were also found between 500–600 ms. All reported peaks were above the threshold level of α=0.05.

Consistent with group-averaged results, individual ER-SAM data revealed bilateral activity in the hippocampal region for 'correct-new' scenes with 7 participants showing activity in the left hippocampal region and 6 participants showing activity in the right hippocampal region. For 'correct-old' scenes, we found 4 participants showing activity in the left and 4 in the right hippocampal region. All peaks identified in the individual ER-SAM maps were significantly different from baseline (α=0.01) and occurred predominantly within the first 500 ms post-stimulus onset (Table 3). Examples of peaks found in or within less than 1 cm of the hippocampus for individual participants are shown in Fig. 8 and the averaged location of peak

Table 2
Source ITC values and Talairach co-ordinates for individual ITC maps showing activity above threshold in or within 10 mm of the hippocampus (Hpc) for 'correct-new' (A) and 'correct-old' (B) (L = left hippocampus; R = right hippocampus)

Subject	Max. ITC value for Hpc during Baseline	Max. ITC value during Baseline	Local maxima of Hpc during 0–250 ms (Tal.)	Max. ITC value	Local maxima of Hpc during 250–500 ms (Tal.)	Max ITC value
Table 2A						
Correct-new						
S1	.12	.22	R: 25 −14 −13	.58	R: 25 −30 −7	.33
S2	.12	.18	R: 23 −23 −5	.21	n/a	n/a
S3	.20	.27	L: −21 −39 0	.42	n/a	n/a
S4	.20	.34	n/a	n/a	n/a	n/a
S5	.17	.26	R: 31 −41 2	.73	R: 30 −28 −7	.54
S6	.10	.17	L: −23 −46 5	.51	R: 27 −14 −11	.32
			R: 25 −25 −14	.24		
S7	.23	.29	R: 29 −29 −10	.64	R: 22 −38 4	.42
S8	.24	.31	R: 28 −43 2	.49	L: −27 −32 −5	.35
					R: 26 −44 3	.42
S9	.15	.29	R: 24 −10 −18	.34	L: −24 −37 −5	.33
S10	.19	.23	L: −20 −38 0	.40	L: −18 −11 −12	.25
			R: 15 −39 5	.32		
Average (stdev)	.17 (.05)	.26 (.05)	L: −21 −41 2	.44	L: −23 −27 −7	.31
			(2 4 3)	(.06)	(5 14 4)	(.05)
			R: 25 −28 −6	.44	R: 26 −31 −4	.41
			(5 12 9)	(.20)	(3 16 8)	(.09)
Total			L: 3 participants		L:3 participants	
			R: 8 participants		R: 5 participants	
			Either: 9 participants		Either: 7 participants	
Table 2B						
Correct-old						
S1	.13	.31	R: 25 −19 −12	.41	R: 16 −38 3	.34
S2	.26	.36	n/a	n/a	n/a	n/a
S3	.13	.28	L: −25 −41 −3	.42	n/a	n/a
			R: 30 −11 −20	.38		
S4	.22	.29	L: −30 −24 −15	.32	n/a	n/a
S5	.16	.26	L: −18 −18 −14	.34	L: −34 −35 −6	.30
			R: 34 −39 0	.55	R: 31 −31 −6	.41
S6	.17	.32	L: −24 −41 0	.38	n/a	n/a
S7	.12	.24	L: −23 −36 1	.47	L: −13 −15 −14	.33
			R: 35 −31 −11	.69	R: 30 −31 −8	.43
S8	.18	.33	R: 30 −32 −5	.55	R: 21 −29 −6	.34
S9	.22	.40	n/a	n/a	n/a	n/a
S10	.18	.24	L: −21 −37 0	.38	R: 26 −24 −12	.25
			R: 24 −40 2	.31		
Average (stdev)	.18	.30	L: −24 −33 −5	.37	L: −24 −25 −10	.31
			(4 11 8)	(.06)	(15 14 6)	(.02)
			R: 30 −29 −8	.48	R: 25 −31 −6	.35
			(5 12 8)	(.14)	(6 5 6)	(.07)
Total			L: 6 participants		L: 2 participants	
			R: 6 participants		R: 5 participants	
			Either: 8 participants		Either: 5 participants	

hippocampal activity based on individual participants' ER-SAM maps is shown in Fig. 9. The contrast between 'correct-new' and 'correct-old' scenes revealed no significant differences in the hippocampus.

Discussion

We studied the potential of advanced MEG approaches to localize and outline different aspects of hippocampal activity in a memory recognition task by using three different analyses: SAM for event related changes in spectral power, ITC as a measure of stimulus related coherence in neural responses and ER-SAM as volumetric representation of the averaged event related neural response. We observed hippocampal activity predominantly in the theta frequency band and within the first 200 ms post-stimulus onset for both the successful recognition of novel ('correct-new') and previously studied ('correct-old') scenes. Analyzing multiple features of electromagnetic brain activity in conjunction with previous work, provided converging evidence for the feasibility of localizing activity from the hippocampus with MEG (Ioannides et al., 1995; Tesche, 1996; Nishitani et al., 1998; Hamada et al., 2004; Hanlon et al., 2003, 2005; Kirsch et al., 2003; Tesche, 1997; Tesche and Karhu, 1999; Martin et al., 2007; Tesche and Karhu, 2000; Campo et al., 2005; Breier et al., 1998). Below, we summarize our findings from the different data analyses and discuss its advantages and limitations. In considering the current findings to previous work, we suggest that the functional role of the hippocampus in recognition memory may be related to general processing requirements common to recognizing both novel and previously studied information, such as comparing the externally presented stimuli with internal memory traces. Further, we argue that hippocampally-mediated processes supporting recognition memory occur rapidly following stimulus onset. The observation of early hippocampal activity has implications for theories regarding memory; namely, recognition may be an obligatory process and/or may influence perceptual processing.

Multiple MEG data analyses

In applying three different analysis techniques, we were able to extract unique complementary information pertaining to hippocampal activity during a recognition memory task. Specifically, information regarding the underlying spectral frequencies and temporal dynamics of hippocampal responses were outlined. When we viewed

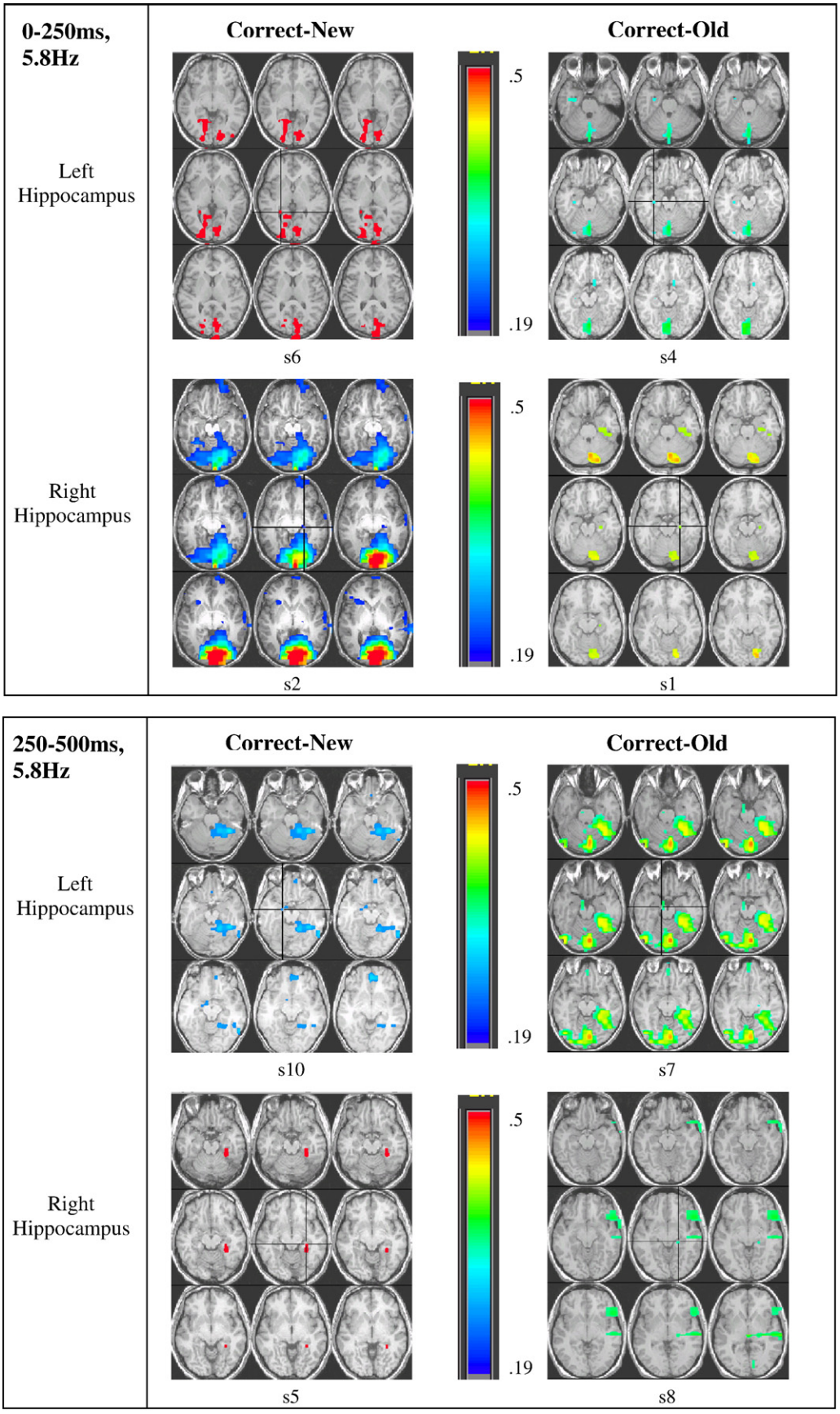

Fig. 5. Representative individual volumetric maps of inter-trial coherence in approximately the theta frequency band (center frequency 6 Hz) during 0-250 ms (top) and 250-500 ms (bottom) time intervals for scenes correctly identified as 'new' (left) and 'old' (right). All activity shown significantly exceeded baseline levels.

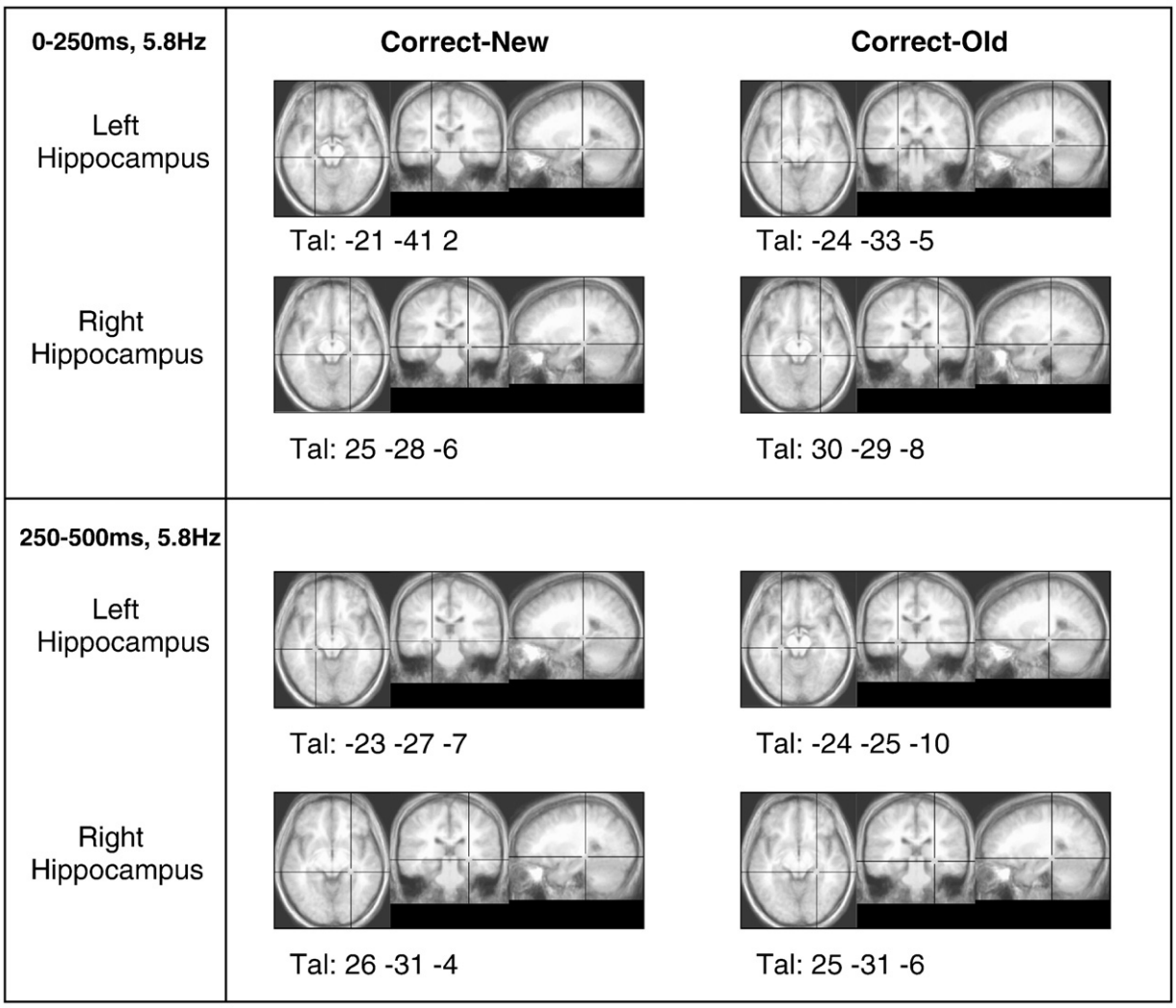

Fig. 6. The averaged location of hippocampal activity based on individual ITC maps.

the group-averaged SAM results, no activity above threshold levels was observed in the hippocampus for either 'correct-new' or 'correct-old' scenes.

SAM analysis is based on the analysis of signal power changes between the pre- and post-stimulus time window and the signal power measure includes both time-locked evoked responses and non-phase-locked or induced activity. It is possible that the signal power changes in hippocampal activity did not reach significance threshold because it occurs predominantly as an evoked response and the inclusion of induced activity reduced its overall statistical power (but see Guderian and Düzel, 2005). It is also possible that the permutation test used was too conservative. The only activity revealed to be significant after the permutation test were superficial sources within the visual cortex, even though multiple regions beyond the visual cortex, such as the parietal and frontal cortex, are thought to be involved in visual recognition (e.g. Buckner et al., 2001; Buckner, 2003; Tulving et al., 1996; Weis et al., 2004). However, when we further examined the data by lowering the threshold, we found spatially distinct activity in the right hippocampus for 'correct-new' scenes and near the right hippocampus or parahippocampal gyrus for 'correct-old' scenes, in the theta frequency band during the 0–250 ms time interval. This suggests that hippocampal activity may include some signal power changes in the theta frequency band that is not strictly phase-locked, but this was not strong enough to reach statistical significance. The permutation test estimates a threshold value common for all voxels in the brain, but the distribution is likely not homogeneous across the brain volume. Further, the level at which neural activity is determined to be significantly different from baseline depends on the number of neurons active, the amplitude of activity, and the amount of synchrony among neural assemblies. While the amount of neural synchrony does not change with distance from the sensors, amplitude of activity becomes weaker farther away from the sensors, making it very difficult for deep source activity to reach threshold levels. Altogether, this suggests that the permutation test may be too conservative for an examination of deep source activity and/or the dominant feature of the hippocampal response in a recognition memory task is not induced.

With ITC analysis we found high levels of bilateral hippocampal coherence in the theta frequency range during the 0–500 ms post-stimulus onset time interval for both 'correct-new' and 'correct-old' scenes. In examining the group-averaged volumetric maps, spatially distinct sources of activity could be seen in the right hippocampus across the entire time interval and for both types of scenes. This was confirmed in the individual participant analysis. However, from the ITC maps, it can be seen that hippocampal theta band activity was most synchronous during the first 250 ms after stimulus-onset (Fig. 3 and Fig. 4), and became less phase-locked to the stimulus over time. Group-averaged results also revealed theta band synchrony in the left hippocampus during 250–500 ms for 'correct-old' scenes. This was confirmed in individual analyses for two participants. Likely, hippocampal synchrony in most participants was below the threshold for individual analyses, but averaging data from all of the participants

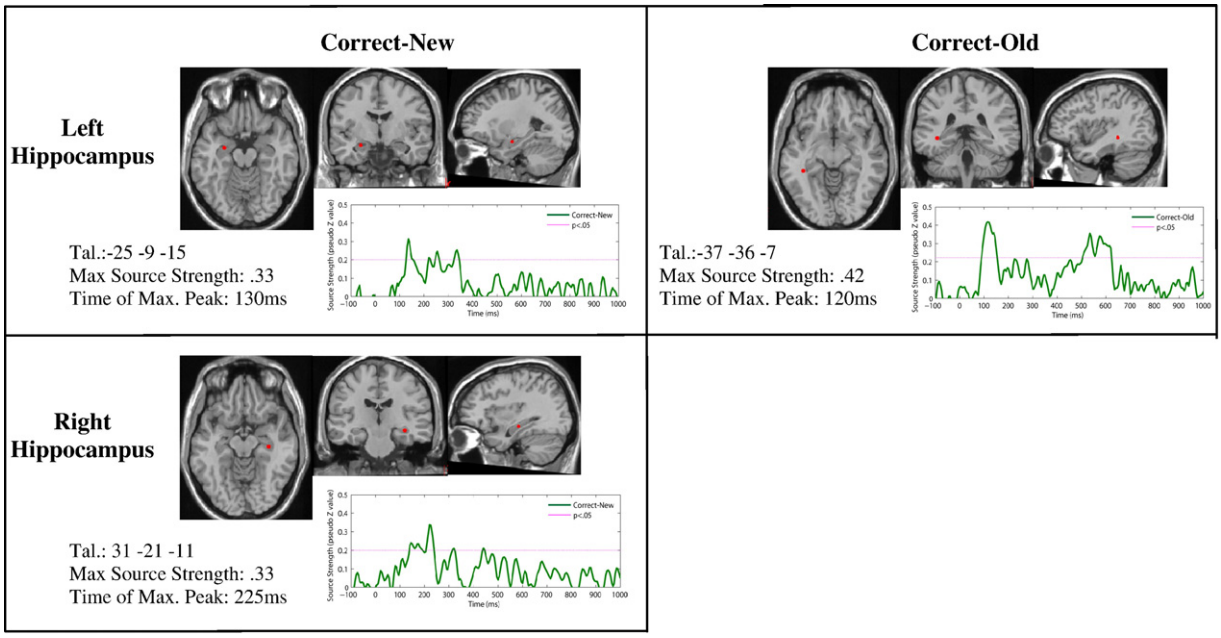

Fig. 7. Group-averaged time-courses of neural activity emanating from the left and right hippocampus as revealed by the ER-SAM analysis. Neural sources are marked with red dots in the MRIs and the location of the hippocampal peak is reported in Talairach co-ordinates. The maximum source strength (pseudo-*z*) and the time of the maximum peak (ms) are also reported.

increased statistical power. The ITC statistic is bound between 0 and 1, thus it is unlikely that single individual data had skewed the group results toward significance. Despite this, it is important to note that theta band synchrony in the right hippocampus was consistently found in both the group-averaged and the individual data.

Using ER-SAM, we found significant bilateral hippocampal activity for 'correct-new' scenes in the group-averaged data. This was confirmed for the majority of participants in the individual analysis. Group-averaged data also revealed significant left parahippocampal activity for 'correct-old' scenes, which was found for 4 participants in the individual analysis. It is important to note that the individual analysis was completed at α=.01 whereas the group-averaged results were viewed at α=.05. This more conservative criterion for the individual analysis may have resulted in smaller than expected number of participants showing activity in the hippocampal region. In the group-averaged data, hippocampal activity was found during the 100–150 ms post-stimulus period for both 'correct-new' and 'correct-old' scenes (Breier et al., 1998; Guderian and Düzel, 2005; Gonsalves et al., 2005).

While SAM is an amplitude-based analysis method, ITC, in contrast, measures the degree of neural synchrony, and thus provides a more homogeneous statistic across the brain volume. Thus, ITC may be a more appropriate analysis method for the examination of deep sources in the presence of activity from other more superficial sources. However, ITC improves the signal-to-noise ratio for the synchrony measure by integrating over relatively long (e.g. 250 ms) time windows (Bardouille and Ross, 2008). ER-SAM, in contrast, can determine the latency of the maximal evoked response with millisecond precision. These two methods can be used in a complementary fashion to understand the temporal and spectral dynamics of evoked responses.

In applying three complementary analysis methods to the same set of data, we were able to consistently localize hippocampal activity in two of the three methods. Below, we explore the similarities and differences in findings from ITC and ER-SAM.

Consistency across the data analyses

Both ITC and ER-SAM revealed time-locked hippocampal activity within the first 250 ms of viewing 'correct-new' and 'correct-old' scenes. Frequency analysis (ITC) also revealed that this hippocampal activity consistently oscillated within the theta frequency band. While the obtained results were consistent in terms of temporal dynamics and frequency of hippocampal activity, there were some differences in the findings that should be discussed.

For 'correct-new' scenes, group-averaged results revealed significant neural synchrony (ITC) in the right hippocampus and significant increases in evoked activity (ER-SAM) in bilateral hippocampi. This is consistent with previous studies showing that whereas verbal information tends to elicit activity in the left hippampus, visual information, such as that used in the present experiment, tends to elicit activity in either the right or bilateral hippocampi (Breier et al., 1998; Gonsalves et al., 2005; Martin et al., 1997; Stern et al., 1996; Kelley et al., 1998; Golby et al., 2001). It is possible that activity in the left hippocampus failed to reach significance in the ITC analysis.

For 'correct-old' scenes, ITC localized activity to the hippocampus and ER-SAM showed that the peak of activity was within the parahippocampal gyrus. It is possible that both the hippocampus and parahippocampal gyrus were activated (Stark and Okado, 2003; Rombouts et al., 2001; Nyberg et al., 1996; Kapur et al., 1995; Gonsalves et al., 2005), but in the ER-SAM analysis, the peak of activity was placed within the parahippocampal gyrus. As mentioned earlier, if the hippocampus and parahippocampus are active simultaneously, MEG tends to place the peak of activity within a single source (Stephen et al., 2005). It is also possible that the signal-to-noise ratio for 'correct-new' scenes was higher than that for 'correct-old' scenes since the average number of trials was greater. A higher signal-to-noise ratio allows for greater power and sensitivity to the localization of functional MEG data, and thus greater ability to localize deeper sources (Hämäläinen et al., 1993).

While both ITC and ER-SAM analyses identify brain activity that is time locked to the stimulus event, ITC is more specific in frequency information, and ER-SAM is more specific in temporal information. However, an evoked response will generate high coherence values at low frequencies (i.e. delta and theta) over sub-second time intervals. Thus, it is difficult to differentiate between an evoked response and synchronous oscillatory activity in this case. Given that ITC and ER-SAM examine different aspects of hippocampal activity, it may not be surprising that differences in laterality and precise localization

Table 3
Source ER-SAM values, Talairach co-ordinates and time of first and maximum peak for participants showing activity above threshold in or within 1 cm of the hippocampus (Hpc) for 'correct-new' (A) and 'correct-old' (B) in individual ER-SAM maps (L = left hippocampus; R = right hippocampus).

Subject	Local Maxima (Tal.)	$P<.01$ Baseline baseline value (pseudo-z)	Time activity reached $p<.01$ (ms)	Value of 1st peak (pseudo-z)	Time of 1st peak (ms)	Value of Max. peak (pseudo-z)	Time of Max. Peak (ms)
Table 3A							
Correct-new							
S1	L: −29 −36 −4	.37	120	.46	125	1.0	635
	R: 35 −25 −21		95	.40	95	1.6	150
S2	R: 27 −32 −7	0.27	105	.35	110	.72	275
S3	L: −21 −32 −7	0.42	110	.67	130	.89	330
S4	L: −33 −40 −4	0.57	150	.57	150	.74	460
S5	L: −29 −28 −8	0.25	90	.45	95	1.01	205
	R: 31 −13 −19		85	.25	85	1.12	220
S6	L: −25 −33 −14	0.26	110	.33	115	.48	215
	R: 27 −17 −14		210	.58	230	.59	445
S7	n/a	n/a	n/a	n/a	n/a	n/a	n/a
S8	L: −29 −13 −19	0.32	90	.32	90	.63	335
	R: 23 −2 −16		60	.38	60	.91	165
S9	n/a	n/a	n/a	n/a	n/a	n/a	n/a
S10	L: −41 −25 −15	0.35	85	.58	90	.76	695
	R: 39 −21 −11		100	.65	105	.65	105
Average (stdev)	L: −30 −30 −10 (6 9 6)	.35 (.11)	139.29 (50.85)	.48 (.13)	113.57 (23.04)	.79 (.19)	410.71 (194.26)
	R: 30 −18 −15 (6 10 5)		109.17 (51.91)	.44 (.15)	119.17 (58.77)	.83 (.21)	307.5 (198.08)
Total	L: 7 participants						
	R: 6 participants						
	Either: 8 participants						
Table 3B							
Correct-Old							
S1	L: −29 −28 −8	.36	110	.64	120	.95	535
S2	L: −21 −13 −15	.36	125	.44	160	.57	230
	R: 27 −24 −8		925	.52	930	.52	930
S3	n/a	n/a	n/a	n/a	n/a	n/a	n/a
S4	L: −33 −25 −11	0.50	230	.51	230	.82	885
S5	L: −29 −17 −18	0.3002	130	.71	135	1.63	230
	R: 19 −6 −19		180	.98	225	.98	225
S6	n/a	n/a	n/a	n/a	n/a	n/a	n/a
S7	R: 23 −29 −11	0.3392	60	.40	65	.54	130
S8	R: 27 −2 −16	0.4387	135	.90	165	.90	165
S9	n/a	n/a	n/a	n/a	n/a	n/a	n/a
S10	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Average (stdev)	L: −28 −21 −13 (5 7 4)	.38 (.07)	148.75 (54.83)	.58 (.12)	161.25 (48.71)	.99 (.45)	470 (311.80)
	R: 24 −15 −14 (4 13 5)		325.00 (403.05)	.70 (.28)	346.25 (394.72)	74 (.24)	362.5 (380.36)
Total:	L: 4 participants						
	R: 4 participants						
	Either: 6 participants						

are observed. This makes clear that claims about hippocampal activity have to consider the specific observed feature of brain activity.

The present study, in conjunction with previous MEG studies, shows that hippocampal activity can be successfully localized using MEG, and that it is characterized by different aspects pertaining to evoked- versus induced-response, frequency, and time. Further, depending on which aspect of the hippocampal activity one is interested in, it is important to select the appropriate analysis method. In the present experiment, we found that hippocampal responses occurred predominantly as a time-locked or evoked response, in the theta frequency band and within 200 ms following stimulus onset during recognition of previously studied and novel stimuli. Critically, we found no significant differences in the hippocampus between 'correct-new' and 'correct-old' scenes using ER-SAM. This suggests that the functional role of the hippocampus may be related to general memory processing requirements common for both the viewing of new and old information (Cohen et al., 1999). Below, we focus on the theoretical implications for the functional role of the hippocampus in light of the present results.

Theoretical implications

A general processing requirement for viewing new and old information in a recognition task is the comparison of the external stimulus that is represented in the sensory cortices with internal memory traces that may be stored within multiple neural assemblies (Ryan et al., 2008). This 'comparison' process (Ryan and Cohen, 2004; James, 1983) is thought to rely not only on the hippocampus (Ryan and Cohen, 2004; Hannula et al., 2006; Rugg et al., 1996), but also sensory cortices where external and internal information is processed and held online (Wheeler et al., 2000; Vaidya et al., 2002; Ryan et al., 2008), and prefrontal regions where search strategies are executed and monitored (Koriat, 2000; Buckner, 2003). During comparison, the functional role of the hippocampus may be to coordinate activity between different neural regions and allow for the exchange of information in a phase-locked manner via theta oscillations (Buzsáki, 2002; Rugg et al., 1996; Düzel et al., 2001a,b; Smith and Halgren, 1989). The current findings revealed that hippocampal oscillations occurred within the theta frequency band, consistent with other work that has observed hippocampal theta oscillations in animal (O'Keefe and Nadel, 1978; Huxter et al., 2003; Wiebe and Stäubli, 2001), human intracranial (Raghavachari et al., 2001; Rizzuto et al., 2003; Sederberg et al., 2003) and imaging studies (Tesche and Karhu, 2000; Guderian and Düzel, 2005; Osipova et al., 2006).

An examination of the temporal dynamics revealed that hippocampal activity was evident as early as 120–130 ms following stimulus onset (Breier et al., 1998; Gonsalves et al., 2005). This time frame is

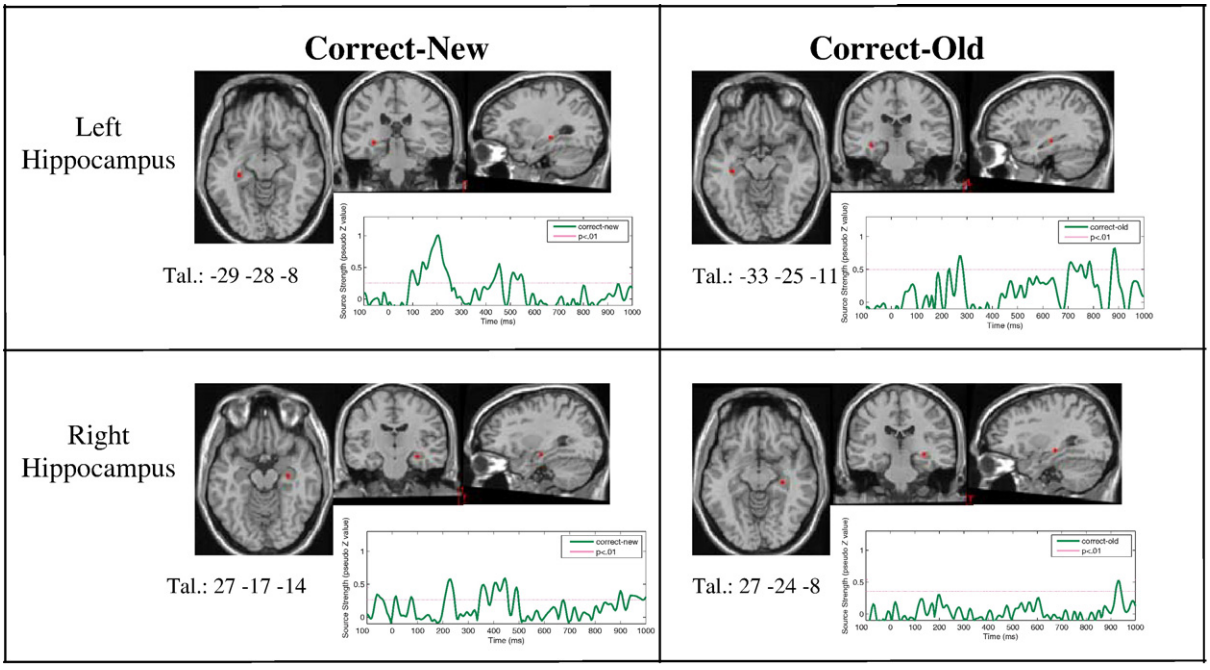

Fig. 8. Representative individual time-courses of neural activity from the left and right hippocampus for 'correct-new' (left) and 'correct-old' (right) scenes as revealed by the ER-SAM analysis. Neural sources are marked with red dots in the MRIs and the Talairach coordinates are provided.

typically associated with perception of externally presented stimuli, independent of the hippocampus (Tsivilis et al., 2001), however, the current findings suggest that the hippocampus may be involved during early perceptual processing of old/new information. The functional role of the hippocampus during this stage may be to aid non-mnemonic visual discrimination of the externally presented stimuli (Lee et al., 2005; Barense et al., 2007), or it may reflect part of a feedforward sweep from visual cortices in order to prime other cortical regions for subsequent processing, such as recognition memory in the present study (Foxe and Simpson, 2002; Herdman et al., 2007). Alternatively, early onset of hippocampal activity may also suggest that processes related to memory recognition occur rapidly and perhaps in an obligatory fashion (Ryan et al., 2008; Ryan et al., 2007). However, since participants were instructed to perform a recognition task and were in a 'retrieval' mental set, the current results cannot address the issue of whether recognition memory is obligatory or not. At the very least, evidence of such an early onset of hippocampal activity suggests that processes related to recognition memory begin rapidly and operate in conjunction with, or parallel to, visual processing. Indeed, conscious identification of a visual stimulus may be aided by rapid access to stored memory representations (Bar, 2004; 2003; Bar et al., 2006; Ryan et al., 2008). Regardless of whether the early onset of hippocampal activity represents a contribution of mnemonic information to the building of perceptual representations (Ryan et al., 2008), perceptual processing in the absence of any memory component (Lee et al., 2005), or a preparatory response for subsequent processing (Herdman et al., 2007), the present findings demonstrate that hippocampal responses are evident at time when perception is thought to occur.

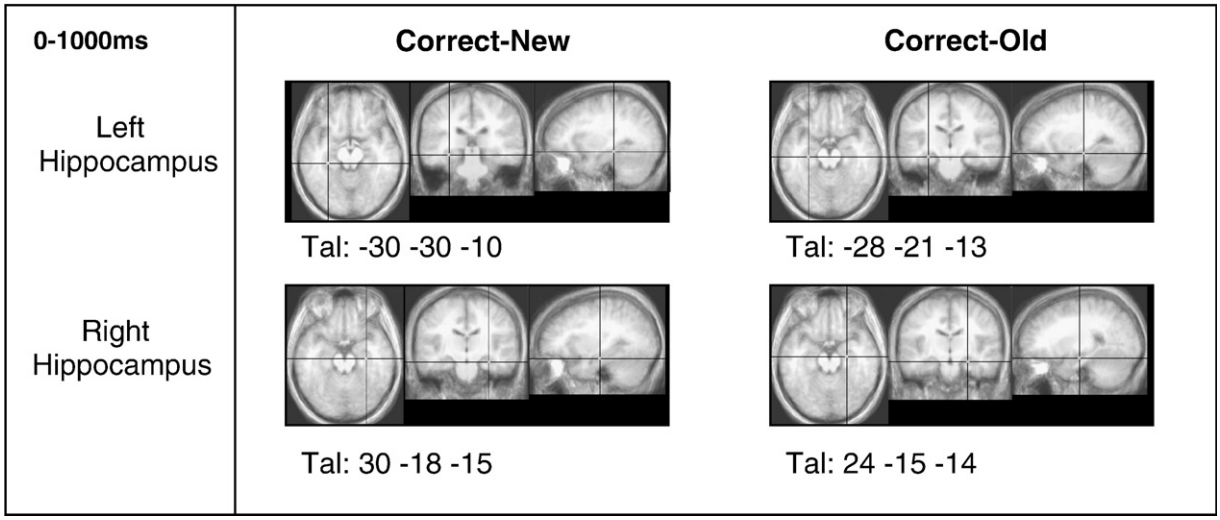

Fig. 9. The averaged location of hippocampal activity based on individual ER-SAM maps. Black cross-hairs indicate the location of the hippocampal peak, also reported in Talairach coordinates.

Concluding remarks and future considerations

The results of this study, together with previous literature, offer converging evidence in support of the feasibility of using MEG to record activity from the hippocampus. Unlike other neuroimaging techniques, MEG can outline the frequency range and temporal dynamics with good spatial resolution. This study highlights the importance of choosing an appropriate analysis method for the localization of deep sources. Specifically, it is critical to use localization algorithms that are not biased toward superficial sources, allow for the imaging of simultaneous sources, and use co-registration of MEG and structural MRI data. We observed that processing of studied versus novel stimuli recruited the hippocampus at similar times and in a similar spectral frequency, suggesting that the hippocampus may be involved in general recognition memory processes. Specifically, the hippocampus may contribute to comparison achieved via theta oscillations (Buzsáki, 2002). Also, onset of hippocampal activity occurred rapidly after stimulus onset, during a time typically associated with visual perception. Future studies are needed in order to distinguish between mnemonic vs. non-mnenomic accounts of early hippocampal responses.

In addition to examining incidences of normal memory functioning, MEG can be applied to the study of memory impairments. It has long been noted that memory impairments are associated with aging and a number of disorders such as Alzheimer's disease, temporal lobe epilepsy, post-traumatic stress disorder, schizophrenia, among others (Eichenbaum and Cohen, 2001). While other neuroimaging techniques such as PET and fMRI show a relationship between decreases in memory performance and reduced hippocampal activity, MEG may reveal patterns of underlying spatiotemporal dynamics that are associated with distinct performance profiles, and are subsequently altered as a function of neurological impairment. Therefore, MEG has the potential to illuminate the nature of hippocampally-mediated memory disorders as well as the nature of normal memory function.

Acknowledgments

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