

Theta oscillations orchestrate medial temporal lobe and neocortex in remembering autobiographical memories

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ABSTRACT

Remembering autobiographical events can be associated with detailed visual imagery. The medial temporal lobe (MTL), precuneus and prefrontal cortex are held to jointly enable such vivid retrieval, but how these regions are orchestrated remains unclear. An influential prediction from animal physiology is that neural oscillations in theta frequency may be important. In this experiment, participants prospectively collected audio recordings describing personal autobiographical episodes or semantic knowledge over 2 to 7 months. These were replayed as memory retrieval cues while recording brain activity with magnetoencephalography (MEG). We identified a peak of theta power within a left MTL region of interest during both autobiographical and General Semantic retrieval. This MTL region was selectively phase-synchronized with theta oscillations in precuneus and medial prefrontal cortex, and this synchrony was higher during autobiographical as compared to General Semantic knowledge retrieval. Higher synchrony also predicted more detailed visual imagery during retrieval. Thus, theta phase-synchrony orchestrates in humans the MTL with a distributed neocortical memory network when vividly remembering autobiographical experiences.

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Introduction

Humans have the ability to vividly recollect previous autobiographical experiences. Neuroimaging studies have shown that a distributed network of brain regions is associated with the retrieval of autobiographical memories (AM), comprising prefrontal, medial (including the hippocampus) temporal lobe (MTL), and posterior regions, such as precuneus and posterior cingulate cortex (Cabeza and St-Jacques, 2007; Maguire, 2001; Svoboda et al., 2006). The sense of recollection brought by the act of recalling unique personal memory episodes is thought to be mediated by the effective coordination of this set of regions (Maguire, 2001). In fact, influential models of memory organization hold that recollecting personal episodes require the coordination of neocortical areas and the

MTL, thereby implementing reinstatement of retrieved information in distributed neocortical assemblies (Marr, 1971; McClelland et al., 1995; Rolls, 2000; Treves and Rolls, 1994). Yet, little is known about the mechanisms governing such neural interactions.

A putative mechanism by which functional neural integration could take place is through brain oscillations. Oscillatory rhythms are thought to coordinate the precise timing of neurons in large-scale neural networks and thereby influence representation and long-term coding of information (Buzsaki and Draguhn, 2004; Huxter et al., 2003; Lisman and Otmakhova, 2001; Steriade, 2000). A special emphasis has been given to theta (4–8 Hz) oscillations in learning and memory tasks in animal (Huxter et al., 2003; O'Keefe and Recce, 1993) and human research (Caplan et al., 2003; Ekstrom et al., 2005; Guderian and Düzel, 2005; Kahana et al., 1999; Osipova et al., 2006; Raghavachari et al., 2001; see for a recent review Düzel et al., 2010). These findings support the view that cortical theta oscillations are crucial to memory-related processes, consistent with computational models of memory postulating that theta mediates a dynamic MTL–neocortical orchestration, allowing a functional implementation of cortical reinstatement during recollection.

Formal assessment of this prediction is hampered by the methodological complexity of testing AM. The typical retrospective sampling of

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AMs for laboratory assessment lacks experimental control over prior rehearsal, personal significance, emotionality, and retrieval effort. Prospective collection of autobiographical stimuli enhances experimental control and can provide highly specific retrieval cues, akin to revisiting a particular scene where a unique or important event occurred (Conway et al., 2002; Heisz et al., *in press*). Such cues promote vivid recollection of everyday episodes (Brewer, 1988; Sheldon and Levine, 2013), engaging episodic memory and its accompanying state of autonoetic consciousness (Wheeler et al., 1997).

Furthermore, despite evidence from animal and human intracranial recordings (e.g., Anderson et al., 2010; Colgin, 2011; Foster et al., 2013; Watrous et al., 2013) and human functional neuroimaging studies (Tambini et al., 2010), investigating the neurophysiological mechanisms sustaining MTL–neocortical interactions in memory has been affected by limited access to simultaneous acquisition of distributed neural activity together with anatomically targeted recordings. However, a number of recent studies (Cornwell et al., 2010; Guitart-Masip et al., 2013; Kaplan et al., 2012; Poch et al., 2011; Riggs et al., 2009) have shown that it is possible to record simultaneously and non-invasively from the MTL and cortex using whole-head magnetoencephalography (MEG), and that such sensitivity might be incremented when using a realistic anatomical and electrophysiological model of deep brain activity (Attal and Schwartz, 2013). In fact, it has been observed that there could be zero-phase lag correlation between hippocampal activity and MEG (Buzsaki et al., 2012). It should be noted that, albeit some initial available empirical evidence that theta emanating from the MTL (specifically from the hippocampus) could be observed in correspondence with MEG activity (Dalal et al., *in press*), it is possible that not all hippocampal activity patterns can be measured from the scalp. One reason for this could be that some circuits within the hippocampus form closed loops (see Nunez and Silberstein (2000) for a theoretical discussion on this topic).

Here, we investigated whether and how MTL–neocortical orchestration takes place during the retrieval of unique episodic elements of AM through the recording of MEG data during stimulation with prospectively collected AM cues. We sought to test the hypothesis that neocortical activity linked to the retrieval of AMs was coordinated by dynamic interactions with the MTL through the phase of the ongoing theta.

Material and methods

Participants

Eight healthy adults (3 males; mean age = 30; STD = 5.34; mean education = 18 years; STD = 2.5 years) participated in the study. None of the participants reported a history of neurological, psychiatric or any other serious medical problems. All participants gave written informed consent for the study, which was approved by the hospital research ethics board.

Collection of autobiographical stimuli

Participants collected stimuli prospectively over 2–7 months using a portable digital recorder (ICD-BP100 V-O-R; Sony) following the methods specified by Levine et al. (2004) and Svoboda and Levine (2009). Extensive training on recording methodology was provided along with a detailed instruction manual and feedback on several practice recordings. A cue-card was attached to each recorder for guidance.

There were two recording conditions, Personal Episodic and General Semantic memory. Personal Episodic recordings comprised a 1–2 min description of a unique autobiographical episode, defined according to theoretical works on this topic (Wheeler et al., 1997), including the story line, location, perceptions, thoughts, and emotional reactions. Very significant emotional events were excluded. Participants were instructed to make Personal Episodic recordings during or soon after

the event occurred and within the same day (mean time elapsed since the event = 131 min; STD = 91 min). General Semantic recordings comprised a 1–2 min reading from a book about neighborhoods in Toronto, Canada (excluding those evoking a specific autobiographical event), and were yoked in time to the Personal Episodic recordings (for PE: M = 159d, range: 55–199; for GS: M = 206d, range: 19–226; not significantly different, $t = 0.61$, $p = 0.52$). Participants included a title in each recording (e.g., “Michael and Erika’s wedding”, “Bloor West Village”). Following Personal Episodic recordings, participants indicated time elapsed since the event and ratings for event uniqueness (1, routine; 4, completely novel), personal importance (1, not important; 4, highly important), and emotional change as a result of the event (1, no change; 4, major change). The average of these three ratings across the eight participants was 2.32 (STD = 0.59), indicating a moderate level of novelty and significance, confirming that, as instructed, participants recorded daily events that were unique, although not of great personal significance. Participants were instructed not to listen to their recordings after dictating them.

The median number of recordings made for the Personal Episodic and General Semantic conditions was 71 and 41, respectively (for PE: range 58–500; for GS, range 16–206). Of these, 10 recordings per condition were randomly selected for this study. This oversampling reduced the novelty of the recording activity as well as the predictability of which recordings would be used in the study. As a result of the high degree of effort and commitment to participate in this study, the sample size was small. This was offset by the high potency of the prospective retrieval cues for the production of a vivid recollection during MEG scanning.

Memory retrieval in the MEG

Recordings were edited to 30 s in length and randomized by condition. The experimental run was preceded by four ‘practice’ memories (two per condition) to allow acclimation to the MEG environment and ensure compliance with instructions. Each recording was preceded by a 30 s fixation (rest, eyes open) condition. At the onset of the recording, participants closed their eyes and heard the title that they had created. While listening to the recording, they were instructed to mentally re-experience the events (Personal Episodic) or to think about the semantic information (General Semantic). After each recording, participants opened their eyes and verbally assigned ratings on four scales: re-experiencing of thoughts, emotions, visual images, and the ease or speed with which the event was reactivated. Participants also rated, from 1 to 10, the ‘overall’ vividness of recollection, anchored by ‘no recollection’ and ‘vivid recollection’ at either end and how easily the episode came to mind, anchored by ‘very difficult’ and ‘very easy’. Thirty seconds were allotted for the ratings. The same ratings were collected in response to the General Semantic recordings in order to assess for the presence of intrusive episodic thoughts and to confirm that the Personal Episodic recordings evoked a higher degree of re-experiencing. Following the 30 s rating period, participants were cued to fixate again for 30 s in advance of the next recording.

MEG data acquisition and preprocessing

MEG recordings were made in a magnetically shielded room by using a 150-channel CTF system with SQUID-based axial gradiometers (VSM MedTech Ltd., Coquitlam, BC, Canada). Neuromagnetic signals were digitized continuously at a sampling rate of 312.5 Hz. Analyses were conducted using SPM8 (<http://www.fil.ion.ucl.ac.uk/spm>) and with custom-made MATLAB scripts. The MEG data from each block were high-pass filtered at 0.2 Hz using a 5th-order Butterworth filter and epoched from –1000 ms to 30,000 ms relative to the start of the memory retrieval period of each trial.

Theta source localization

The linearly constrained minimum variance scalar beamformer spatial filter algorithm (Sekihara et al., 2002) implemented in SPM8 (Litvak et al., 2011) was used to generate maps of source power change on a 10 mm grid. Coregistration to the MNI coordinates was based on three fiducial points: nasion and left and right pre-auricular. The forward model was based on the single-shell model (Nolte, 2003) fit to inner skull surface of the inverse normalized SPM template. The beamformer calculates the weights that map sensors to source locations (constructed based on the data covariance window and the source space lead fields). To obtain a time-series estimate at each source location the raw data is multiplied by these weights. In this case, the time varying estimate of the electromagnetic activity at each of the locations of the brain image was projected through the spatial filter constructed based on the covariance matrix of all trials in the theta range (4–8 Hz). We used a 1000–29,000 ms time window relative to the onset of the retrieval period.

We first created a normalized and smoothed (10 mm FWHM) whole-brain image of theta power over both memory conditions for each participant. To identify the seed location for synchronization analysis, we used a one-sample *t*-test to identify the peak voxel over our region of interest (ROI). This ROI was based on our prior hypothesis of MTL involvement in the retrieval of episodic memories and included the hippocampi bilaterally (identified with the PickAtlas toolbox for SPM8 (Maldjian et al., 2003, 2004) using the AAL atlas (Tzourio-Mazoyer et al., 2002)).

Synchronization analysis

To quantify synchronization we calculated an index of phase lag consistency between a seed voxel identified above and every other voxel in the brain. We used the time-series estimate in theta at each location obtained with the beamformer and used continuous single-trial Hilbert transformation to obtain a phase difference between the seed voxel and all other voxels on each sample within every trial. In order to remove any coupling due to simple linear mixing of MEG channels we used the Phase-Lag Index (PLI) (Hillebrand et al., 2012; Stam et al., 2007). Briefly, this entails assigning each sample a value of +1 or –1 depending on whether the phase difference to the seed voxel is positive or negative. For each trial, the absolute value of the sum of these integers (which will be zero for a random phase difference) divided by the number of samples gives a measure of PLL. This computation yielded a value of phase synchronization ranging from 0 to 1. On each trial, a value of 1 would correspond to perfect phase lag consistency across samples and a value of 0 to random phase variation over time (1000–29000 ms). These trial-by-trial phase lag index values are then averaged within each condition to give a total of 2 (one for the Personal Episodic and one for General Semantic condition) phase lag indexes per voxel. A similar phase lag index method has been recently applied at MEG source level by Guitart-Masip and colleagues (Guitart-Masip et al., 2013).

To test which brain sources showed a significant synchronization with the MTL, we created one normalized image depicting the difference in phase lag index between each of the two memory conditions per participant. The resulting images were then smoothed using a Gaussian kernel at 10 mm FWHM and subjected to a paired *t*-test. As a starting point we used stationary random field theory (as implemented in SPM8) to look for significant Family Wise Error corrected clusters (of extent 20 voxels) in the whole brain that distinguished General Semantic and Personal Episodic conditions. In cases where we found no FWE significant clusters we opted for a more lenient (and arbitrary) threshold of ($p < 0.005$, uncorrected, again extent 20 voxels). We present these data because these active regions, although not in our prior hypotheses, do conform to those one might expect from the literature (Cabeza and St-Jacques, 2007; Maguire, 2001; Svoboda et al., 2006). At the moment we cannot say with great certainty that these regions are involved,

however, future studies might bring these priors to bear and therefore avoid the need for a whole volume correction.

Results

Personal Episodic and General Semantic subjective ratings

Personal Episodic was more effective at evoking vivid recollections than General Semantic condition (Table 1). This effect was confirmed statistically with a repeated measures analysis of variance (ANOVA) with memory type (Personal Episodic and General Semantic) and subjective rating as within factors. The ANOVA showed a significant main effect of condition ($F(1,7) = 169.2$, $MSE = 502.76$, $p < 0.0001$) and a significant interaction memory type \times subjective rating ($F(3,21) = 3.16$, $MSE = 0.82$, $p = 0.048$), indicating that although all ratings differed statistically between conditions (post-hoc paired *t*-tests for each of the rating were all significant, p 's < 0.005), this effect was enhanced for the 'overall' vividness rating (see Table 1).

Theta rhythm and the beamformer-derived MTL source

An ROI analysis revealed that theta band activity in the beamformer-derived left anterior MTL was implicated during the retrieval of Personal Episodic and General Semantic memory events (Family-Wise Error corrected $p < 0.05$) (Fig. 1A). This MTL theta peak was identified at $[-32, -6, -20]$ MNI coordinates and used as a seed for the phase synchrony analysis. The spectral power at this MTL location showed a clear peak at theta range with similar magnitude during both conditions (Figs. 1B and C). However, it should be noted that theta power results are based on a hypothesis-driven ROI analysis within the beamformer-derived MTL (henceforth 'MTL'); significant peaks in other regions cannot be ruled out. Although the spectral peaks in the theta band could be expected because the spatial filters were constructed to maximize theta band activity, this plot shows that power is non-significantly different between Personal Episodic and GS, thus arguing against an alternative hypothesis that any connectivity differences could be driven by differences in power in the MTL.

MTL theta phase synchrony of neocortical activity

MTL–neocortical theta phase lag index analysis revealed that activity in only the mPFC ($p < 0.05$, Family-Wise Error corrected; MNI $[16, 34, -10]$) and precuneus ($p < 0.005$, uncorrected; $[-14, -54, 24]$) was phase synchronized to the theta rhythm of the left anterior MTL in Personal Episodic to a greater extent than in General Semantic trials (Fig. 2A). General Semantic condition showed no brain regions with statistically significant higher theta phase synchronization with hippocampus. We further determined that the increased theta phase synchronization between these brain regions in Personal Episodic was not driven by any outlier in our sample and that the phase lag index effects were robust at individual level (Fig. 2B). The specificity of the MTL–neocortical theta effects was corroborated when a similar analysis (using the same seed) was extended to alpha (9–13 Hz), beta (15–29 Hz) and gamma (30–42 Hz) frequency ranges. We found no statistically significant clusters showing MTL–neocortical phase synchronization (Personal Episodic > General Semantic) for any of these

Table 1

Behavioral ratings. Mean and standard deviation (in parenthesis) of each subjective memory rating (maximum rate = 10).

Memory condition	Thoughts	Visual imagery	Emotions	Overall
Personal events	7.64 (1.07)	7.86 (1.44)	7.91 (1.04)	7.91 (1.04)
General semantics	2.39 (1.77)	2.56 (1.61)	2.27 (1.53)	1.68 (1.47)

frequency bands using previous thresholds ($p < 0.005$, uncorrected). A repeated measures ANOVA including region (mPFC and precuneus), memory condition (Personal Episodic and General Semantic) and frequency (theta, alpha, beta and gamma), using phase-locking index data from the peak, was implemented to further test the specificity of the theta effects. This analysis revealed a significant condition \times frequency interaction ($F(3,21) = 13.34$, $p < 0.001$). A series of post-hoc paired t -tests at each frequency band showed non-significant effects for all bands (all, $p > 0.05$) but theta ($p < 0.05$) in MTL–mPFC and MTL–precuneus, thereby confirming that the MTL–neocortical effects between conditions were specific for the theta band. Furthermore, the specificity of the theta band effect was similar between MTL–mPFC and MTL–precuneus (condition \times frequency \times region interaction, $F(3,21) = 1.43$, $p > 0.05$). Nonetheless, these results do not rule out the possibility that these frequency bands are involved in other connectivity profiles. In addition, the specificity of MTL–neocortical findings was corroborated when synchrony analysis was computed by placing the seed in other deep brain structures such as insula, cingulate and orbital regions. We found that neither precuneus nor the mPFC was phase synchronized to any of those deep structures using the same thresholds as for our MTL phase lag index analysis ($p < 0.005$, uncorrected).

The phase lag index metric is immune to effects of linear signal leakage as it quantifies the asymmetry of the relative phase distribution about zero and so will produce large values only when the relative phase is peaked away from zero. In order to better understand the phase-coupling, we calculated the theta phase-locking value (PLV) (Tallon-Baudry et al., 1996) at a whole-brain level using the same MTL seed as in the phase lag index analysis. PLV, unlike PLI, will be sensitive to zero lag coupling (but also sensitive to linear leakage). With this

analysis, we searched for the existence of significant ($p < 0.05$, 20 voxels extent, uncorrected) increments of theta PLV in the Personal Episodic vs. General Semantic memory conditions within the precuneus and mPFC cluster of voxels identified in the phase lag index results (thresholded at $p < 0.01$, 20 voxels extent, uncorrected). The theta PLV results revealed a number of voxels within the mPFC (peak at [22,50,–10]) and precuneus (peak at [6,–70,40]) that showed greater PLV in the Personal Episodic than in the General Semantic condition (Fig. S1). However, neither of the two clusters survived correction at cluster level (all $p > 0.3$) and only the peak found at the precuneus was significant with a threshold of $p < 0.01$ (uncorrected). These findings might at first seem counterintuitive as the phase lag index is generally regarded as the more conservative metric. One key difference between the two metrics is that that PLV works with phase differences whereas phase lag index works only with the sign of phase differences. In other words, relative to PLV, phase lag index is insensitive to large variability in phase difference as long as the sign of this phase difference remains constant. Thus for certain regimes of coupling it would certainly be possible to have large phase lag index but low PLV. Conversely, when the true phase difference is close to zero phase lag index will be low and PLV will be high. For a more detailed discussion of the fundamental mathematical differences between these two metrics please see Aydore et al. (2013). We should also note that all measures of phase coupling are dependent on some reliable measure of signal above the noise – as the signal disappears phase differences will become random (Muthukumaraswamy and Singh, 2011). There is therefore the possibility that the inherent synchrony (however it is measured) remains constant (but non-zero) between the structures, but the relative signal strength (rather than synchrony) changes between conditions.

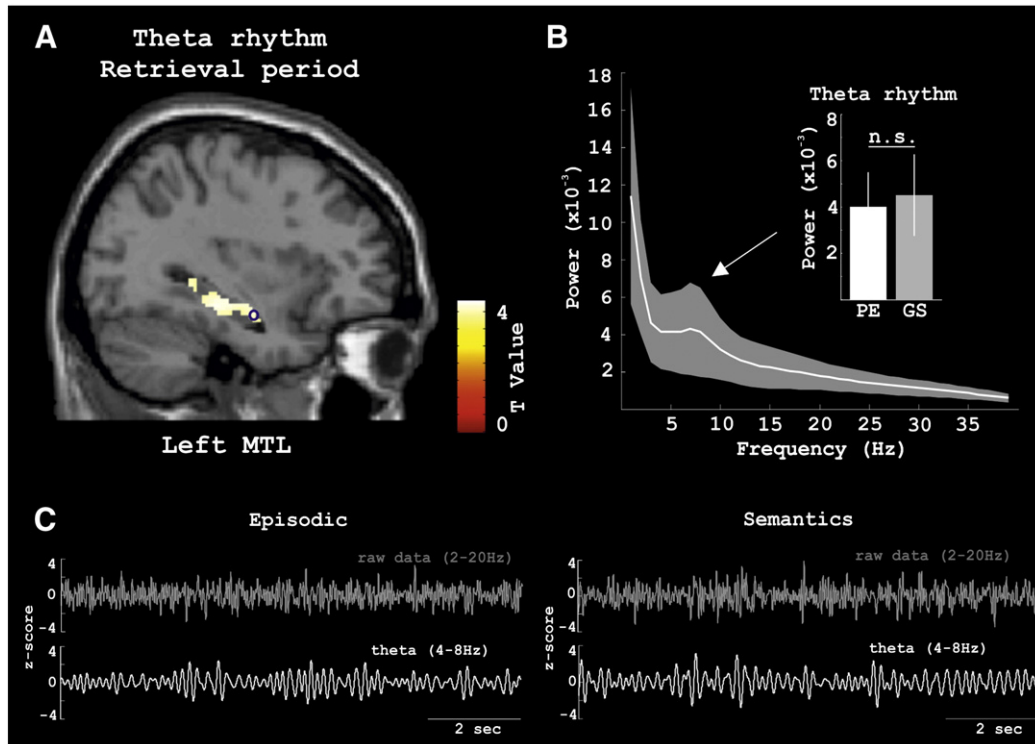


Fig. 1. Theta activity from left MTL during the memory retrieval period. (A) Sources in the left anterior MTL showed the greatest theta power during the retrieval of Personal Episodic and General Semantic information. The plot depicts those voxels that resulted significant (cluster extent threshold 20 voxels, Family-Wise Error corrected $p < 0.05$) in a ROI analysis including bilateral hippocampi regions ($x = -32$). The seed used for phase lag index analysis is indicated with a blue circle. (B) Population grand average Fourier spectrum from the left MTL (arrow, theta power peak at ~ 7 Hz; gray, SEM). Bar plot shows similar (paired t -test, $t(7) = -1.64$; $p > 0.05$ (indicated as n.s.)) theta power at left MTL for Personal Episodic and General Semantic condition averaged across participants (error bars, SEM). Note the source analysis was based on a theta filtered signal. (C) Illustration of MTL theta oscillations during the Personal Episodic and General Semantic condition. Single-trial of spatially (beamformer) 10 s filtered data from the left anterior MTL (bottom, bandpass filtered 4–8 Hz).

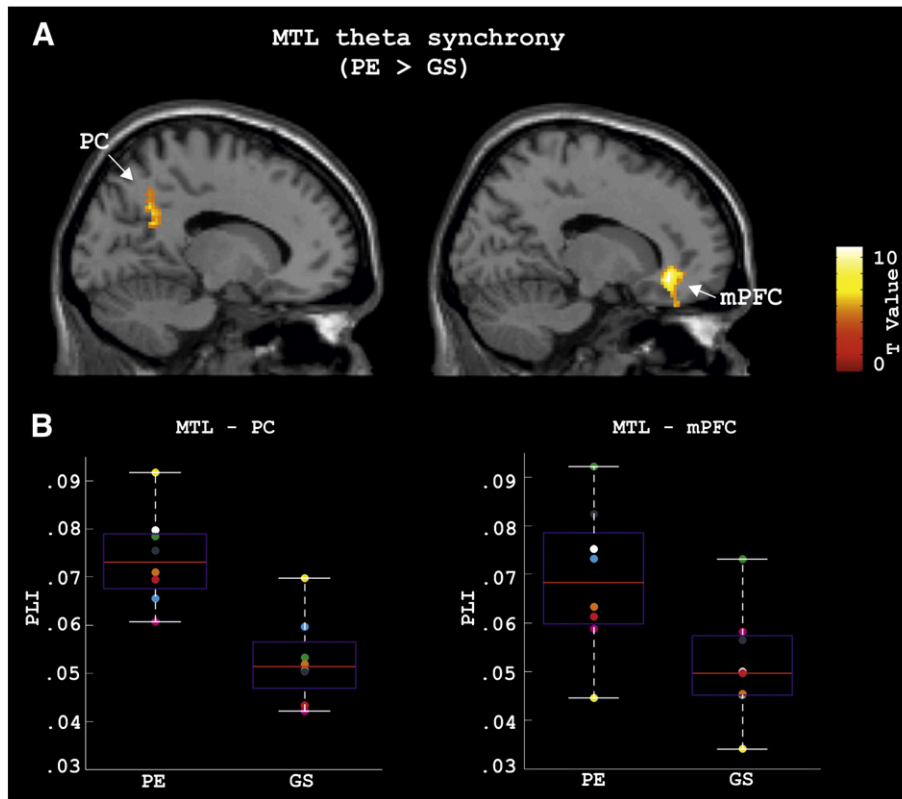


Fig. 2. MTL theta phase synchrony during autobiographical memory retrieval. (A) Precuneus ($x = -12$) and mPFC ($x = 16$) theta activity was coupled to MTL theta oscillations during the 30 s period when participants were required to retrieve Personal Episodic memories. (B) Boxplots illustrate MTL theta phase lag index individual sample distribution for each of the neural regions shown in (A). The top and the bottom of the box represent one STD. The band near the middle of the box represents the median. Phase lag index values from MTL–precuneus connectivity analysis in the left side and MTL–mPFC in the right. Phase lag index values were extracted from the voxel showing maxima within each cluster. Individual theta phase lag index is overlaid for each case and coded with a different color.

We tested whether theta phase lag index results at precuneus and mPFC could be partially attributed to changes in the theta power between conditions. Thus, the theta power was computed for each condition at whole-brain level and differences were calculated by means of a paired t -test. Statistically significant theta power increases (albeit at a low statistical level; $p < 0.05$; 20 voxels extent, uncorrected) were observed for Personal Episodic over GE at parietal and thalamic regions (Figs. 3A and B). Importantly, none of these regions overlapped with regions that showed phase lag index with MTL.

MTL–neocortical theta synchrony predicts the degree of visual imagery of autobiographical memories

We next asked whether MTL–neocortical theta synchrony predicted subjective experiences of vividness derived from the characteristic of richly detailed visuospatial content accompanying the recollection of AM (Greenberg and Rubin, 2003). We correlated the individual average rating of visual imagery with phase lag index obtained at each voxel throughout the brain. Congruent with previous synchronization results, this anatomically unbiased analysis yielded a cluster of voxels within the left precuneus ($[-18, -40, 45]$) and within the mPFC ($[-18, 38, -18]$) and at the insula ($[42, -12, 10]$) that correlated significantly ($p < 0.01$, uncorrected at cluster level; 20 voxels extent) with individual differences in visual imagery ratings (Fig. 4). No significant correlation was found between visual imagery ratings for General Semantic trials and theta phase synchrony.

Discussion

We found that the MTL region was selectively phase synchronized in theta frequency with the precuneus and mPFC during richly detailed

autobiographical recollection evoked by prospectively recorded audio cues from remote everyday events. In a subsequent whole-brain analysis, higher synchrony in similar precuneus and mPFC regions predicted the degree of visual imagery achieved during retrieval, a core property accompanying the recollection of autobiographical memories (Greenberg and Rubin, 2003). Thus, theta phase synchrony might contribute (as one of several possible mechanisms) to orchestrating the MTL with a distributed neocortical memory network when vividly remembering events from one's past.

Part of our MEG source reconstruction rests on our hypothesis of the involvement of the MTL during the memory retrieval stages. However, recent modeling studies have shown the theoretical feasibility of measuring MTL sources (including the HC) with MEG (Attal and Schwartz, 2013; Mills et al., 2012; Quraan et al., 2011). Importantly, also recent MEG studies have been able to spatially identify the MTL using very similar methodology (see for example, Guitart-Masip et al., 2013; Poch et al., 2011).

We chose phase lag index analysis as we know it to be immune to zero-phase leakage between voxels due to MEG source reconstruction. However there are a number of factors, besides a change in mean phase coupling, which could have given rise to the effects observed. For example, a drop in power (which is often accompanied by a drop in signal-to-noise (SNR)) at one or both recording sites in one condition would mean that the noisier signal might exhibit a less reliable phase estimate and hence lower apparent PLI. We tested this by searching for theta power differences between memory conditions over those brain regions that showed a phase lag index effect. The results of this analysis showed no significant theta power differences ($p < 0.005$, 20 voxels extent, uncorrected) either at mPFC or at the precuneus, thereby confirming that our phase lag index results were not affected by the power of the signal. Phase lag index is a measure of phase coupling over a specific time window. However, it should be noted that

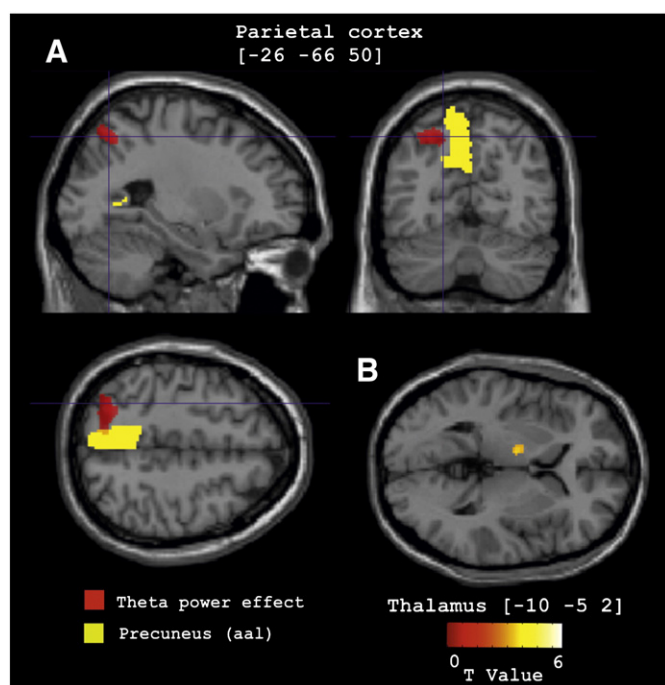


Fig. 3. Theta power during autobiographical memory retrieval. (A) Theta power enhancement during Personal Episodic vs. General Semantic retrieval conditions ($p < 0.05$, 20 voxels extent, uncorrected). A cluster of theta power enhancement at the posterior parietal cortex (MNI $[-26, -66, 50]$) was identified (in red). For comparison, the location of the left precuneus (based on AAL) is highlighted in yellow. (B) Another cluster of theta power enhancement was found in the left thalamus (MNI $[-10, -5, 2]$; $p < 0.05$, 20 voxels extent, uncorrected).

phase lag index does not provide a measure of how coincident the phase angles are in a given time window, as it would be reflected by a phase-locking value. Phase lag index is a measure of whether the imaginary part of phase angle differences has the same sign (positive or negative). Should two areas be coupled, but the direction of these coupling changes within the time window, zero or attenuated phase lag index would be observed. Although we cannot exclude this latter mechanism here, we can say that the phase coupling between the two conditions was significantly different.

It has been suggested that, through theta oscillations, the MTL may drive the reciprocal exchange of information with neocortical areas (Sirota et al., 2008). Accordingly, the MTL may actively control the transfer of neocortical information to the MTL itself via theta-phase biasing of neocortical network dynamics (Sirota et al., 2008), which has been postulated by several computational models of memory (Marr, 1971; McClelland et al., 1995; Rolls, 2000; Treves and Rolls, 1994), and which may also account for recent evidence from human intracortical recordings of MTL–neocortical theta phase-locking during the retrieval of AMs (Foster et al., 2013). Alternatively, and based on the abundant evidence for the possibility that theta is also generated neocortically in humans (Canolty et al., 2006), it could also be that only one of these neocortical regions is entrained by the MTL, whereas the other is entrained through cortico-cortical theta synchrony.

There are several mechanisms through which MTL generated theta could phase bias neocortical activity. Hippocampal activity could entrain other pacemakers such as cholinergic populations in the basal forebrain (Petsche et al., 1962) or the supramammillary nucleus (Kocsis and Vertes, 1994). Alternatively, the hippocampus (subfield CA1) could synchronize with monosynaptic targets in the entorhinal cortex (Colgin and Moser, 2006) and indirectly use their widespread connectivity. These two mechanisms could exploit the intrinsic pacemaker properties of neocortical neuronal subgroups (Blatow et al.,

2003). Finally, there are sparse long-range MTL projections to distant neocortical regions as well as long-range GABAergic interneuron projections (e.g., to the retrosplenial and mPFC) (Jinno et al., 2007) that could directly entrain neocortical populations.

Although fMRI studies have consistently implicated the mPFC and precuneus as belonging to the core neural network participating in the retrieval of AMs (Soderlund et al., 2012; Svoboda et al., 2006) the neural mechanism that entrains them to the MTL has remained unclear. Our results suggest that the two regions may be jointly entrained to the MTL via theta-phase synchrony. It should be noted that although MTL–precuneus theta phase synchrony findings were not as statistically robust as MTL–mPFC theta phase synchrony, the role of precuneus in retrieving AM is well supported by theoretical and experimental evidence (Cabeza and St-Jacques, 2007; Maguire, 2001; Svoboda et al., 2006). Remarkably, mPFC and precuneus were the only regions whose synchrony with the MTL correlated with the vividness of autobiographical retrieval. Hence, our anatomically unbiased analyses revealed that precuneus, mPFC and MTL together form a very specific network for vivid AM. Additional information concerning the distinction between episodic and semantic autobiographical memory may be derived from other neurophysiological signals, such as neural complexity or variability, reflecting distributed non-linear network dynamics. Using the same dataset as in the present study, Heisz et al. (in press) found that multi scale entropy, an information theoretic measure of complexity (Costa et al., 2005), distinguished Personal Episodic from GS, with Personal Episodic recordings eliciting more local entropy and General Semantic recordings eliciting more distributed entropy. Such spectral coherence measures can complement phase synchrony measures as used here by characterizing the distributed networks in which MTL–neocortical communication is embedded.

These results are consistent with the long-held theory that the recollection of personal experiences from AMs is mediated through MTL–neocortical interactions (Marr, 1971; McClelland et al., 1995; Rolls, 2000; Treves and Rolls, 1994). However, one should note that our approach did not consider other wider networks of connectivity that are known to be associated with episodic recollection (Wheeler and Buckner, 2004). A comprehensive investigation of brain networks implicated during the retrieval of Personal Episodic and GE would require the implementation of a data-driven connectivity analysis, as opposed to the hypothesis-driven approach used here. Interestingly, a recent fMRI study using these same recording stimuli found that vividness of recollection was associated with coordinated activation of the left hippocampus and the bilateral frontal (including the mPFC) and parietal regions (including the precuneus; Sheldon and Levine, 2013). Based on previous research, it is feasible to assume that the mPFC relates to self-referential processing and monitoring of retrieved memories (Buckner and Carroll, 2007; Gilboa, 2004; Gusnard et al., 2001; Kelley et al., 2002; Wheeler et al., 1997) whereas the precuneus enables the reinstatement of visuospatial sensory details of personal episodes (Cabeza and St-Jacques, 2007; Maguire, 2001; Svoboda et al., 2006). A naturalistic design allowing individuals prolonged memory retrieval (30 s) as in the current study affords real-world generalizability but may come at the cost of variability (within- and across individuals) as to which memory retrieval operations are used. Yet, a potential issue for future investigation relates to how the recollection of remote autobiographical memories yields to some degree of re-encoding known to boost into subsequent ability to retrieve them vividly (Nader and Hardt, 2009). Thus, the degree of theta entrainment of MTL–neocortical regions could also relate to some sort of reconsolidation that would affect the representational nature of each episodic event.

In sum, we used an anatomically unbiased approach paired with highly specific, evocative retrieval cues to identify a neocortical AM network for vivid autobiographical recollection entrained by the MTL in theta frequency. The spatially unbiased detection of such anatomically wide-spread oscillatory networks is challenging in animal studies as well as using invasive recording in humans. Hence, whole-head

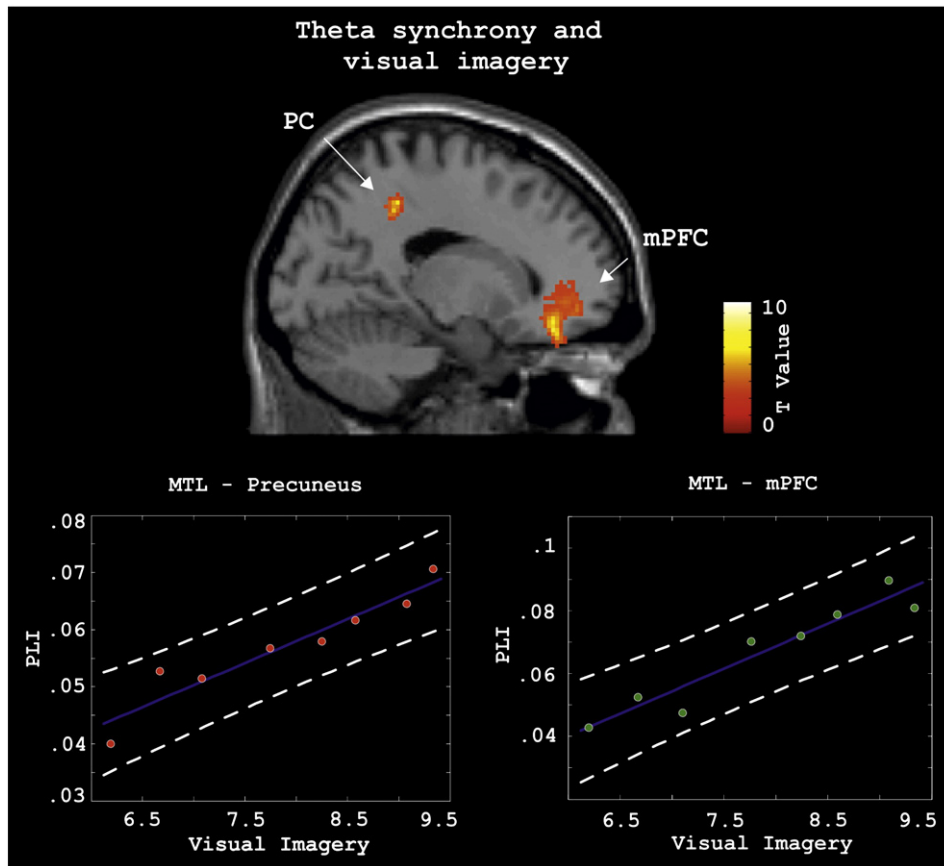


Fig. 4. Individual differences in MTL–neocortical theta phase lag index and degree of visual imagery associated with Personal Episodic memories. Whole-brain correlation analysis between MTL theta phase lag index values and visual imagery ratings ($x = -16$). Illustration of the positive correlation between individuals' subjective ratings of visual imagery of the AMs and MTL–precuneus theta phase lag index from voxel $[-18, -40, 45]$ ($R^2 = 0.90$; $p = 0.0003$) and MTL–mPFC theta PLIs from voxel $[-18, 38, -18]$ ($R^2 = 0.91$; $p = 0.0002$) are plotted below. Solid blue line represents the line of best fit and dashed lines represent 95% confidence intervals.

electromagnetic recordings in conjunction with current advances in source modeling provide a unique opportunity to identify such networks and to study their function and dysfunction.

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.neuroimage.2013.08.029>.

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