



Gamma phase-synchrony in autobiographical memory: Evidence from magnetoencephalography and severely deficient autobiographical memory

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ABSTRACT

The subjective sense of recollecting events from one's past is an essential feature of episodic memory, but the neural mechanisms supporting this capacity are poorly understood. We examined the role of large-scale patterns of neural synchrony using whole-head MEG recordings in healthy adults and S.M., who has severely deficient autobiographical memory (SDAM; Palombo et al., 2015), a syndrome in which autobiographical recollection is absent but other functions (including other mnemonic functions), are normal. MEG was conducted while participants listened to prospectively collected recordings documenting unique personal episodes (PE) that normally evoke rich recollection, as well as a condition including general semantic information that is non-specific in place or time (GS; Levine et al., 2004). We predicted that PE (and not GS) would be associated with changes in patterns of large-scale neural synchrony in comparison subjects. We found large-scale neural synchrony, specifically in the gamma frequency ranges (i.e., 27–45 Hz), specific to PE and not GS. These synchrony differences between PE and GS were not apparent in S.M. Our findings provide empirical evidence for the supporting role of large-scale gamma neural synchrony underlying autobiographical recollection.

1. Introduction

In naturalistic contexts, episodic memory involves the recollection of spatial, perceptual, and mental state details associated with specific past events. Such episodic autobiographical memory (AM) evokes a sense of re-experiencing not required for the recovery of factual or semantic knowledge, which can be accomplished in the absence of autobiographical recollection (see Renoult et al., 2012; Tulving, 2002 for reviews). Neuroimaging studies have shown that episodic AM engages a distributed brain network, comprising prefrontal, temporal, and posterior regions, such as precuneus and posterior cingulate cortex (Cabeza and St-Jacques, 2007; Maguire, 2001; Svoboda et al., 2006). These cortical regions dynamically interact with hub medial temporal regions (MTL) including the hippocampus during episodic memory retrieval (Moscovitch et al., 2016; Sheldon and Levine, 2016). These results emphasize the idea that a dense, interconnected, interdependent

network of disparate brain regions facilitates memory recollection. Although the hippocampus is necessary for vivid, rich episodic memory retrieval, its proper functioning in the network is not sufficient, especially in real-life scenarios (e.g. St-Jacques et al., 2008; Levine et al., 2004). Thus, it is reasonable to hypothesize that more global integrative properties of the network may be predictive of the recollective experience of retrieving a personal memory.

Although most healthy adults can recollect their memories in vivid detail, we recently reported for the first time on three cases of healthy individuals with a lifelong, impairment in episodic AM, which we dubbed “severely deficient autobiographical memory” (SDAM; Palombo et al., 2015). SDAM involves a selective impairment in the ability to subjectively re-experience (or “relive”) events from the past in the context of normal cognitive functioning including semantic memory, which likely supports their successful academic, social, and occupational attainment. Their subjective impairment in AM

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recollection was accompanied by an absence of functional magnetic resonance imaging (fMRI) and event-related potential markers associated with naturalistic and laboratory episodic recollection, as well as by behavioral evidence of impaired episodic retrieval, particularly for visual information (Palombo et al., 2015). Due to the selectivity of episodic memory impairment in SDAM, it is considered a useful model to test the global integrative mechanism described above.

In this study we sought to examine global integrative properties of the brain network during the recollection of naturalistic event episodes collected individually in a prospective AM paradigm (Levine et al., 2004; Sheldon and Levine, 2013; Svoboda and Levine, 2009) using whole-head MEG recordings from eight healthy participants and a single-case with SDAM. Prospective collection of autobiographical stimuli provides a high degree of control of autobiographical event selection, providing highly specific retrieval cues, akin to revisiting a particular scene where a unique or important event occurred (Conway et al., 2002). Such cues promote vivid recollection of everyday episodes (Brewer, 1988; Sheldon and Levine, 2013), engaging episodic AM and its accompanying state of autoegetic consciousness (Wheeler et al., 1997), a prominent feature altered in SDAM (Palombo et al., 2015; for a similar approach using autobiographical recordings and fMRI in a case of acquired episodic autobiographical amnesia, see Levine et al., 2009).

Whole-head MEG data recording samples the simultaneous activity of widely distributed brain regions as well as identifying their network interaction at different time scales by means of the representation at distinct frequency ranges. Integration of neural activity within and across brain regions occurs at various spatial and temporal scales. Any mechanism for neural integration must involve interactions between functionally relevant local networks. Among the mechanistic principles of MTL-neocortical interaction supporting mnemonic processing, a prominent role has been given to brain oscillatory activity at the theta (~4–8 Hz) and gamma (> 25 Hz) frequency ranges (Düzel et al., 2010). Indeed, neural oscillations at these frequency ranges have been recorded intracortically in animals and humans at MTL (including the hippocampus, entorhinal and parahippocampal cortex), and at neocortical regions, such as the prefrontal, parietal and temporal lobes, during memory encoding, working memory maintenance and long-term memory retrieval (Colgin et al., 2009; Rutishauser et al., 2010; Tort et al., 2011; Sederberg et al., 2003; Burke et al., 2014; Watrous et al., 2013). Simultaneous recordings in animals from the hippocampus and neocortex showed that hippocampal theta oscillations exerted an effect on local neocortical computation by phase biasing synchrony of local gamma oscillations (Sirota et al., 2005). MTL-neocortical theta entrainment to local neocortical regions would in turn promote their gamma phase synchrony consequently facilitating neural communication (Fries, 2015; Isomura et al., 2006; Sirota et al., 2003; Womelsdorf et al., 2007) and neural plasticity (Fell and Axmacher, 2011). Such MTL-neocortical theta and gamma phase coding schema enables functional integration necessary to link multiple processes and distributed memory representations, promoting recollection of previous experiences (Düzel et al., 2010; Nyhus and Curran, 2010). To examine functional integration in the temporal frame in which the brain completes processes, there is a need to characterize the temporal dynamics of neural networks with millisecond accuracy (Friston, 2000), which is why MEG is a highly effective tool for examining the dynamic interactions of neural networks.

Participants prospectively documented everyday events using an audio recorder from 2 to 7 months before the MEG session (see Methods). During MEG recordings they listened to a random selection of these personal episodic (PE) recordings which had a duration of 30 s and were randomly intermixed with general semantic (GS) trials, composed of readings from a book about local geography recorded by the participants, matched in time to the PE recordings (Levine et al., 2004). In this same sample of participants (not including S.M.), we previously found that the PE condition was specifically associated with MTL-neocortical (midline PFC and precuneus) coordination through

theta phase synchrony, and that this synchrony was in turn related to the vividness of recollection evoked by the PE recordings (Fuentemilla et al., 2014). Thus, our previous findings provided empirical evidence from influential models of memory organization that hold that recollecting personal episodes required the coordination of neocortical areas and the MTL (Marr, 1971; McClelland et al., 1995; Rolls, 2000; Treves and Rolls, 1994). However, whereas our previous analysis was driven by a specific hypothesis concerning MTL-neocortical interactions supported by theta synchrony, in the present study we sought to identify larger scale patterns of neural synchrony in higher frequency ranges, including the gamma band, when contrasting PE and GS across all recording MEG sensors.

2. Material and methods

2.1. Comparison sample

Eight healthy adults (3 males), aged 24–42 (mean age, 30; SD, 5.34; mean education, 18 years; SD, 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 research ethics board at Baycrest Health Sciences. These participants' raw data were also used to derive the measures reported in Fuentemilla et al. (2014).

2.2. S.M.

At the time of this study, S.M. was a 53 year-old married female who volunteered for research to learn more about her memory. She reported a lifelong inability to subjectively re-experience past autobiographical episodes, although other aspects of learning and memory were intact. She was university educated and employed in management. S.M. was healthy, with normal development and no history of psychological or neurological disorders. Her neuropsychological test performance was normal, with the exception of impaired complex figure copy and recall (for details, see Palombo et al., 2015; S.M. is referred to as A.A. in that paper).

2.3. 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 (PE) and general semantic memory (GS). PE recordings comprised a 1–2 min description of a unique autobiographical episode. Very significant emotional events were excluded. Participants were instructed to make PE recordings during or soon after the event occurred and within the same day (mean time elapsed since the event, comparison subjects: 131 min; STD, 91 min; S.M.: 145 min). GS recordings comprised a 1–2 min reading from a book about local neighbourhoods (excluding those evoking a specific autobiographical event), and were yoked in time to the PE recordings (for PE: $M = 159$ d, range: 55–199; for GS: $M = 206$ d, range: 19–226; not significantly different, $t = 0.61$, $p = 0.52$). For practical reasons, S.M.'s mean time elapsed since the event was longer than that of comparison subjects at 305 d for PE (range: 159–403) and 335 d for GS (range: 159–420). This is unlikely to have affected the results as all recordings were in a similar phase of AM vividness with respect to memory age (i.e., approximately one month to one year old). Indeed, we have previously shown that recordings made 1–3 years prior to scanning are capable of evoking vivid recollection (as

measured by ratings and brain activation) in healthy adults (Sheldon and Levine, 2013). Participants included a title in each recording (e.g., “Michael and Erika’s wedding,” “Bloor West Village”). Following PE 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 median number recordings made for the PE and GS conditions was 71 and 41, respectively (for PE: range 58–500; for GS, range 16–206). This oversampling reduced the novelty of the recording activity as well as the predictability of which recordings would be used in the study. S.M. made a total of 45 PE recordings and 37 GS recordings. Although S.M. made fewer PE recordings than did comparison subjects, this would work against the findings of this study in that the oversampling of events in the comparison group made those selected for inclusion in this study less unique (and therefore presumably less memorable) relative to S.M.’s. Moreover, S.M.’s ratings were within the range of the comparison group (see results), confirming that the events selected by S.M. for recording were as personally meaningful and salient as those provided by the comparison group. Although S.M. has severely impoverished autobiographical recollection, she is able to describe recent events with a similar degree of richness to comparison subjects (Palombo et al., 2013). Thus her transcribed PE recordings appeared similar to those of controls; they contained sufficient detail to evoke recollection were they created by someone with normal episodic AM capacity (see examples in Table S1).

2.4. Memory retrieval during MEG recording

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 (PE) or to think about the semantic information (GS). 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 re-activated. Participants also rated the ‘overall’ vividness of recollection. Each scale ranged from 1 to 10, anchored by ‘no recollection’ and ‘vivid recollection’ at either end. The same ratings were collected in response to the GS recordings in order to assess for the presence of intrusive episodic thoughts and to confirm that the PE 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. As reported previously (Fuentemilla et al., 2014), we found significantly greater subjective ratings for PE than GS trials (two-tailed paired t -test: $t(7) = 13.1, p < 0.001$).

2.5. 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., Couquitlam, 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>) as well as using custom-made scripts within MATLAB (The Mathworks Inc., MA, USA). The continuous MEG data from each block were high-passed filtered at 0.2 Hz using a 5th-order Butterworth filter and epoched from 0 s to 30 s relative to the start of the memory retrieval period of each trial.

2.6. Phase synchrony analysis

We adopted a data-driven approach that allowed quantifying the degree of phase synchronization throughout a wide range of the frequency spectrum across the scalp. This approach differed from our previous hypothesis-driven study with MEG data from the comparison participants that examined the specific role of the hippocampus/MTL in coordinating neocortical regions through theta oscillations during the retrieval of PE (see Fuentemilla et al., 2014). For completeness in connection to our prior analysis, we also assessed theta-phase synchrony in S.M. in response to PE and GS (see supplemental materials).

In the present work, phase synchrony was calculated following wavelet time-frequency decomposition of each epoch, using 6-cycle Morlet wavelets, yielding 42 spaced frequencies between 4 and 45 Hz. After wavelet transformation, a phase series was extracted for each time point, frequency bin, and single trial, and the phase differences between scalp sensors calculated (Lachaux et al., 1999). Phase-Locking Value (PLV) ranges from 0 to 1. Values approaching 0 indicate low phase synchrony between the two electrode sites, values approaching 1 indicate high phase synchrony. Phase-Locking values were z -transformed by the use of the arcsine transform (Mormann et al., 2005) before node degree analysis.

2.7. Node degree analysis

In graph theoretical analysis, each channel is defined as a node, and the connectivity strength between two nodes is designated as the edge that connects them. Overall connectedness of the elements (nodes) in the network was calculated as the sum of connections (edges) each single node had with all other nodes in the network (www.brain-connectivity-toolbox.net; Rubinov and Sporns, 2010). In graph theory, this metric is commonly known as node degree (Bullmore and Sporns, 2009). The degree of a node, defined as the total connectivity strength of the corresponding node, is used to describe the importance of that node in the graph. Nodes with high degrees are regarded as hubs and are likely to play an important role in network communications (Bullmore and Sporns, 2009). Derivation of graph-theoretic measures, such as node degree, requires an adjacency matrix (A) for each retrieval condition, in this case consisting of entries with the value 1 for the presence of a connection between two nodes and a 0 for the absence of a connection. A single A matrix was used with each row and each column being a sensor, and each entry in the matrix being the representation of the relationship between 2 sensors. Because brain connectivity is not binary, arbitrary thresholds were applied to generate A .

To obtain a separate adjacency matrix for each experimental condition in the present study (PE: A_{PE} and GS: A_{GS}), a connection between two sensors was considered meaningful if PLV differed between the two retrieval conditions (Paired t -test) with A_{PE} entry 1 if PLV was higher in the PE compared to PLVs in the GS condition while A_{SEM} entry was 1 when PLV was greater in the GS condition. A threshold of $p < 0.005$ was set to determine differences between conditions (see Popov et al., 2013 for similar approach). Node degrees were also calculated using thresholds of $p < 0.01$ and $p < 0.05$. Because the outcomes were virtually identical, only data thresholded at $p < 0.005$ are reported. Node degrees were calculated separately for conditions. Networks were then constructed in sensor space. Here, node degrees were calculated separately for 42 frequencies, ranging from 4 to 45 Hz, thereby allowing assessment of the specificity of connectedness throughout the frequency spectrum.

2.8. Statistical analysis

Differences in node degree across conditions in the comparison group was assessed via Wilcoxon signed-rank tests given the lack of evidence concerning the normal distribution of graph theoretic metrics

(Bullmore and Sporns, 2009). We used a paired sample permutation test (Groppe et al., 2011) to deal with the multiple comparisons problem given the 42 frequencies included in the analysis. This test uses the “ t_{\max} ” method for adjusting the p -values of each variable for multiple comparisons (Blair and Karniski, 1993). Like Bonferroni correction, this method adjusts p -values in a way that controls the family-wise error rate.

To control for multiple comparisons in the node degree scalp distribution analysis, a Monte Carlo estimate of the permutation p -value was calculated by randomly permuting condition labels 5000 times and comparing the clusters statistic (sum of t -values) of each cluster found in real data to that found in surrogate data. The proportion of cluster statistics in surrogate data exceeding that in real data gives the p -value. Clusters were considered significant at $p < 0.05$. Differences in node degree between the comparison group and S.M. were assessed with Crawford and Howell’s (1998) single-case statistics.

3. Results

3.1. Node degree in comparison subjects

Differences in node degree between PE and GS retrieval conditions in the comparison group are displayed in Fig. 1A. These results showed that node degree was similar in the PE and GS conditions for networks of brain activity comprising low frequency ranges (i.e., < 20 Hz). However, clear differences in node degree between conditions appeared at higher frequency ranges. Thus, the PE condition was associated with

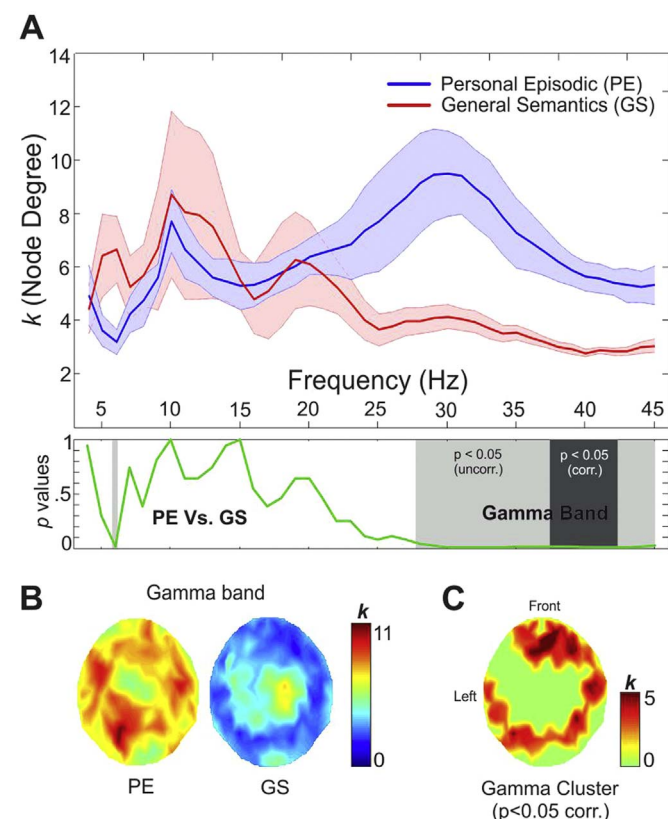


Fig. 1. Functional connectedness by node degree in the comparison group. (A) Participants’ average node degree (k) throughout frequency range (4–45 Hz) during the retrieval of PE and GS information. Colour shades represent SEM. P values resulting from contrasting node degree over frequencies is displayed below. Node degree for frequencies whose contrast resulted significant ($p < 0.05$) and corrected for multiple comparisons are shaded in light and dark grey bars, respectively. (B) Participants’ mean number of node degree (k) averaged over the gamma frequencies that resulted significant ($p < 0.05$ corrected) in (A). (C) Cluster of sensors that were significant when node degrees were compared at sensor level in the gamma range indicated in (A).

an increase in node degree that was absent in the GS condition in a frequency range including the gamma band (i.e., 27–45 Hz; Fig. 1A). To investigate how the gamma effects were distributed over the scalp, we calculated a sensor-by-sensor average node degree for those frequencies where significant differences ($p < 0.05$, uncorrected) were observed in the previous analysis and contrasted these values between the PE and GS conditions. The distributed gamma neural synchrony increase associated with PE included frontal, temporal and parietal MEG sensors (Fig. 1B and C).

3.2. Node degree in SDAM case

As with comparison subjects, we selected events recorded by S.M. on the bases of normal ratings of uniqueness, personal importance and emotional change to select recordings to play back to S.M. during the MEG session. The average of these three ratings was 2.72 and did not differ from those ratings provided by the comparison group ($M = 2.32$, $SD = 0.59$). S.M. also rated the degree of subjective awareness for each PE and GS event. As expected, S.M. showed reduced ability to subjectively re-experience PE memories compared to the comparison group (Comparison group: Thoughts = 7.6, Visual imagery = 7.9, Easily = 7.9 and Overall = 7.9; and S.M.: Thoughts = 2.6, Visual imagery = 2.8, Easily = 4.3 and Overall = 2.6; all comparisons with comparison subjects’ ratings $p < 0.02$ [Crawford-Howell t -test]) but provided similar ratings to GS trials (Comparison group: Thoughts = 2.4, Visual imagery = 2.5, Easily = 2.3 and Overall = 1.7; and S.M.: Thoughts = 1.5, Visual imagery = 2.1, Easily = 1 and Overall = 1.4; all comparisons $p > 0.5$). Although impoverished, S.M.’s ratings for PE recordings were off the floor and generally higher than her GS ratings (Wilcoxon signed rank test: $Z = 2.93$, $p < 0.01$; $Z = 1.29$, $p = 0.14$; $Z = 3.29$, $p < 0.01$; $Z = 4.12$, $p < 0.01$; respectively), suggesting that she differentiated between the two conditions.

We then performed the node degree analysis on the MEG data from S.M. Critically, this analysis revealed greater node degree was in the lower (4–25 Hz) than in higher frequencies (26–45 Hz) for both PE and GS conditions (Fig. 2A). Thus, unlike comparison subjects, S.M. did not show an increase in connectedness for the PE condition at the gamma band. To assess this statistically, we compared k values extracted from the difference between the PE and GS conditions for the comparison subjects and for S.M. (Fig. 2B), thus providing an overall increment/decrement node degree measure throughout the frequency spectrum for PE vs. GS conditions. Unlike comparison subjects, S.M. showed a complete absence of gamma band increment in the PE condition and that such absence was statistically significant at 39–43 Hz, coinciding with the gamma effects found in the comparison group (Fig. 2C).

3.3. Temporal evolution of the gamma band node degree during retrieval

To investigate how node degree evolved during the retrieval of AM we repeated the same analysis reported in previous sections over consecutive windows of 3 s from retrieval onset. The greater node degree in the gamma band for the PE vs GS condition took after ~10–15 s from retrieval onset in the comparison group while no clear relative changes between PE vs GS trials in node degree were observed for S.M. (Fig. 3). To statistically test this observation in the comparison group, the averaged node degree in the gamma band was then submitted to a repeated measures ANOVA, including retrieval condition (PE and GS) time window (10 levels) as within-subject factors. As expected, we observed a significant retrieval condition effect ($F(1,7) = 6.68$; $p = 0.036$) and a trend towards significant interaction between condition and time window ($F(9,63) = 2.49$; $p = 0.062$).

4. Discussion

The recollection of previously experienced events, or “mental time travel” into the past entails binding of information across brain

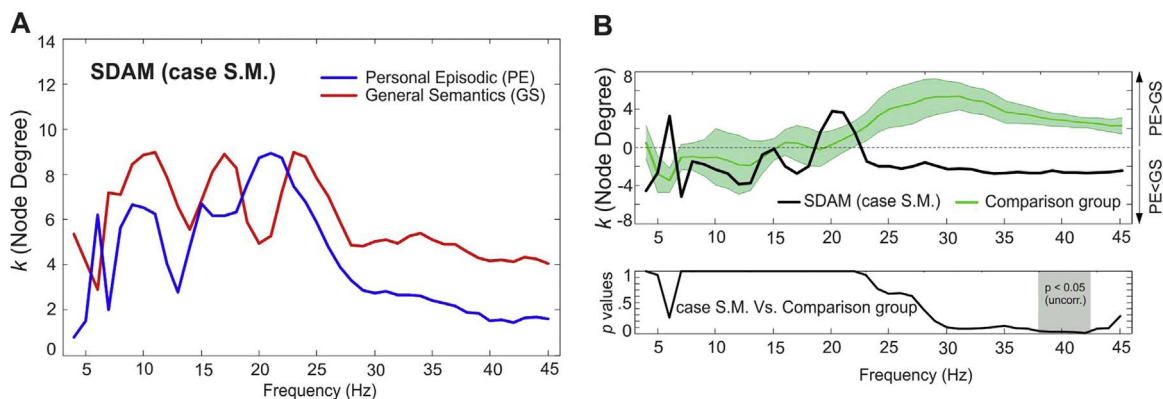


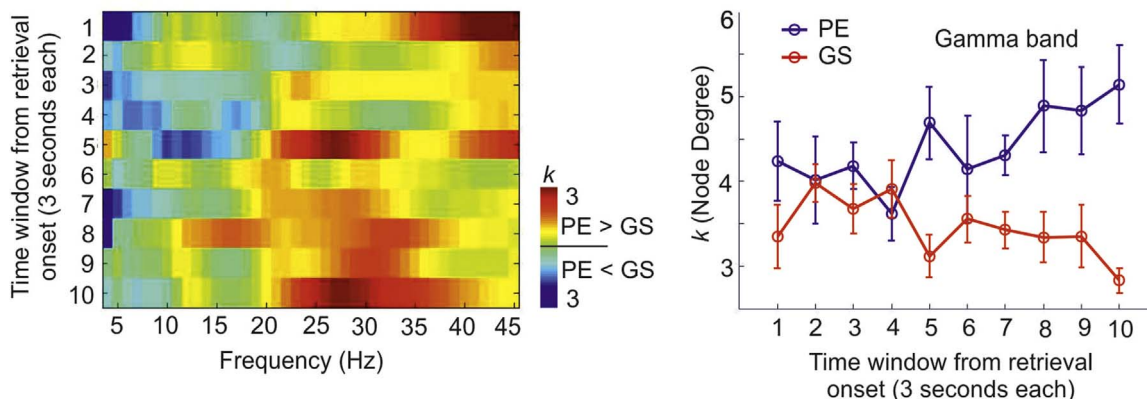
Fig. 2. Functional connectedness by node degree in the SDAM case (S.M.). (A) S.M.'s node degree throughout frequencies. (B) Node degree (k) values extracted from the difference between PE and GS conditions for comparison subjects and S.M. Green shade represent node degree SEM in the comparison group. P values resulting from contrasting node degree over frequencies between comparison subjects and S.M. is displayed below. Significant node degree contrasts ($p < 0.05$) are indicated by a light grey bar.

networks mediating disparate sensory, emotional, and mnemonic processes. In the present study, we drove recollection through the presentation of personal episodic (PE) audio recordings made by the participants in close temporal proximity to the referenced events, evoking a highly vivid mnemonic experience. The recording of brain oscillations at high temporal resolution with MEG in response to hearing these recordings enables the analysis of a potential mechanism mediating AM recollection. The use of a general semantic (GS) control condition

matched in terms of linguistic content and recording features to the PE recordings provided a useful contrast to isolate the brain signals specific to hearing PE recordings.

We showed that high degrees of neural synchrony at the gamma frequency ranges (i.e., 27–45 Hz) were observed in response to PE, but not GS recordings in the comparison group. The distributed gamma neural synchrony increase associated with PE included frontal, temporal and parietal regions. The validity of these observation was

Comparison group



SDAM (case S.M.)

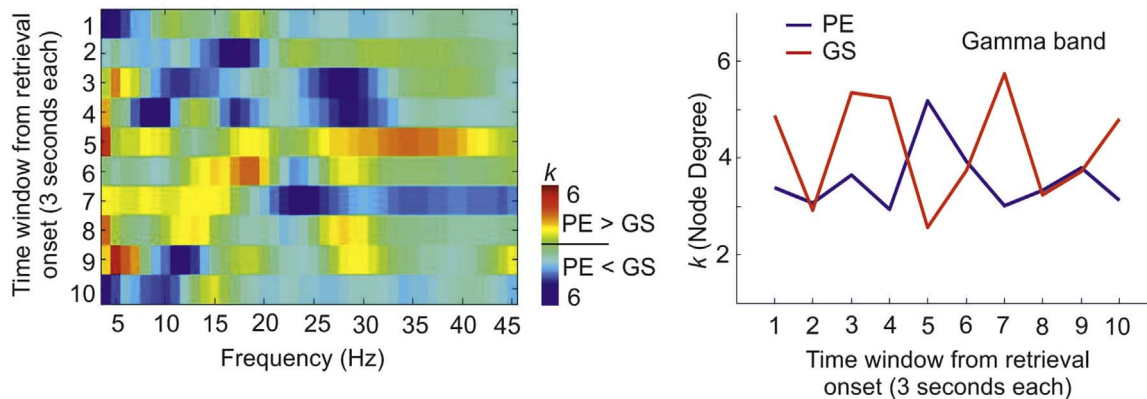


Fig. 3. Gamma band node degree temporal evolution at retrieval of PE and GS trials. Functional connectedness was studied separately for consecutive temporal windows of 3 s during the retrieval period (i.e., 30 s). Charts (left column in the panel) display frequency-to-frequency node degree difference between PE and GS trial conditions. The comparison group showed greater node degree specifically at the gamma band between PE and GS trials starting around 10–15 s from the retrieval onset. No consistent pattern of increase/decrease node degree could be observed in S.M. Circles in the top-left panel depict participants' average node degree (k) throughout frequency range (4–45 Hz) during the retrieval of PE and GS information for each time window. Error bars represent SEM.

supported by the absence of such large-scale neural synchrony increase in response to PE in S.M., who has SDAM, characterized by the inability to recollect previously experiences, with intact sensory, linguistic, and semantic processes (Palombo et al., 2015; for a related finding with fMRI, see Levine et al., 2009).

Less research on this mechanism has been conducted for episodic or AM. Such research has been focused on the MTL as opposed to the cortex, often carried out in rodents or in human neurosurgical patients where highly precise recordings can be made (e.g., Steinworth et al., 2010). Notably, and in line with our findings, the study of Steinworth et al. in humans showed that gamma (30–60 Hz) neural activity was predominant in hippocampally projecting layers during presentation of AM retrieval cues. To our knowledge, however, ours is the first study to examine oscillatory synchrony at the whole-head level in response to autobiographical memory cueing. Our findings highlight the relevance of large-scale integrative properties in the brain during recollection. Previous fMRI findings in humans have shown that successful retrieval of past episodic events resulted in greater overall connectivity combined with greater connectivity to specific hubs, including the hippocampus (Schedlbauer et al., 2014; for a related example using the same recordings paradigm as in this study, see Sheldon and Levine, 2013). These findings underscore the importance of interactions across multiple brain regions rather than the computations of a single primary brain region (such as the hippocampus) in episodic memory, as in our previous MEG study at source space using this same sample of participants (Fuentemilla et al., 2014).

The node degree analysis reflects differences between retrieval conditions at the level of global network. This means that our results are blind as to whether greater node degree was driven by synchronized activity within a small but densely interconnected number of sensors, by a highly distributed set of sensors from the scalp, or by a combination of the two. In fact, the node degree provides a very simple and fundamental metric of network connectedness. While most other measures in graph topology, such as clustering coefficient or path length, are ultimately linked to node degree, this measure represents a rather diffuse picture of the underlying nature of a network. In the past decade, the combination of non-invasive neuroimaging techniques and graph theoretical approaches help delineate human structural and functional connectivity patterns at the macroscopic level (Bullmore and Sporns, 2009), delineating properties of the neural mechanisms that may underlie memory processes in humans (e.g., Schedlbauer et al., 2014). Given the advantage that these measures provide at the mathematical level, their implementation in neuroimaging data provides new perspective on how the human brain processes episodic memories.

Given the node degrees were obtained from contrasting frequency specific phase synchrony patterns at the scalp, the existence of relatively high node degrees in low frequency ranges (i.e., 4–20 Hz) during both the PE and GS suggests that cortical processing common to these two conditions is related to a different brain network from the episodic AM network, such as one mediating semantic and linguistic properties in the absence of recollection. Consistent with the differential network engagement of episodic and semantic components of AM (Svoboda et al., 2006), our findings, lend support to the notion that a prominent differential feature of how large-scale interaction takes place within each of these networks is through the degree of neural synchrony at the gamma range.

Our current results, in combination with previous ones with the same sample of participants (Fuentemilla et al., 2014), fit well with the notion that neural synchrony at the theta and gamma band may index global integrative properties supporting recollection of past episodes. Patterns of neural synchrony at the theta and gamma bands are derived from the integrative properties emerging from a coordinated MTL-neocortical engagement supporting memory processing (Duzel et al., 2010). The widespread interconnections of MTL regions provide support for its role as a convergence zone for such distributed information (e.g. Marr, 1971) and it is shown that theta oscillations may play a key

role in coordinating the long-range interactions with neocortical regions (e.g. Sirota et al., 2008; Jones and Wilson, 2005; Lee et al., 2005) required during recollection. A consequence of such theta-based MTL-neocortical interaction may be the induction of gamma phase synchrony within and/or across the cortical modules (Sirota et al., 2008). More specifically, the timing of individual gamma cycles at certain phases of theta oscillations becomes more precise with increasing memory loading (Fell and Axmacher, 2011). This notion fits well with our findings that gamma phase synchrony increased later during the retrieval period in the PE condition, possibly suggesting greater episodic memory information pertaining to a given memory experience was accumulated at retrieval (see Fig. 3).

The combination of findings provided when studying neural oscillations from scalp MEG recordings in the present work and those obtained when studying them at the source level (see Fig. S1 and Fuentemilla et al., 2014) lend support to the proposal that MTL-neocortical interactions during memory recollection may rely on neural oscillatory activity at the theta and gamma band and that this may be captured through patterns of large-scale phase coupling. Notably, however, our work cannot rule out whether other possible neural mechanisms of how theta and gamma oscillations interact may support memory recollection. Attempts in the future to answer to this question may address it by cross-frequency coupling analysis. Indeed, evidence that theta-gamma cross-frequency interactions are may underlie memory processing have been provided from intracortical recordings in animals and humans during memory encoding (Tort et al., 2009; Heusser et al., 2016) and during short-term memory maintenance (Axmacher et al., 2010; Fuentemilla et al., 2010).

Although it is unknown why people with SDAM lack the ability to recollect previously experienced events, we suspect that the syndrome is developmental in nature. It is not considered to reflect brain pathology (as in developmental amnesia; Cooper et al., 2011; Kwan et al., 2010; Vargha-Khadem et al., 1997, 2003) but rather the extreme along continuum of mnemonic abilities observed in the general population (Palombo et al., 2015). Due to small sample size, the individual difference analyses reported here must be interpreted with caution. Nonetheless, in a larger sample, self-reported episodic AM abilities were found to covary with the degree of medial temporal–posterior cortical connectivity as measured by analysis of low-frequency BOLD signals during rest, attributable to varying degrees of visuo-perceptual information retrieved in association with active autobiographical retrieval (Sheldon et al., 2016). Individuals with SDAM specifically report a lack of visual imagery during AM retrieval (Palombo et al., 2015). The absence of increase neural synchrony in the gamma band during the retrieval of personal AM in S.M. suggests a neurophysiological basis to her inability to subjectively re-experience past autobiographical events.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.neuropsychologia.2017.08.020>.

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