Synchronous theta networks characterize successful memory retrieval

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Abstract

Memory retrieval activates regions across the brain, including not only the hippocampus and medial temporal lobe (MTL), but also frontal, parietal, and lateral temporal cortical regions. How these regions communicate to organize retrieval-specific processing, however, remains unclear. Here, we elucidate the role of theta (3–8 Hz) synchronization, broadly implicated in memory function, during the spontaneous retrieval of episodic memories. Analyzing a dataset of 413 neurosurgical patients implanted with intracranial electrodes who completed a free recall task, we find that synchronous networks of theta phase synchrony span the brain in the moments before spontaneous recall, in comparison to periods of deliberation and incorrect recalls. Network hubs, which systematically synchronize with other regions, appear throughout the prefrontal cortex and lateral and medial temporal lobes, as well as other areas. The recall accuracy network, derived from a correct recall–intrusion contrast, includes synchronous hubs concentrated in the temporal lobe and desynchronous hubs in the parietal lobe. Theta synchrony increases appear more prominently for slow (3 Hz) theta than for fast (8 Hz) theta in the recall–deliberation contrast, but not in the encoding or recall–intrusion contrast, and theta power and synchrony positively correlate throughout the theta band. These results implicate diffuse brain-wide synchronization of theta rhythms, especially slow theta, in episodic memory retrieval.

Significance Statement

Analyzing intracranial recordings from 413 subjects who completed an episodic free recall experiment, we analyze the brain-wide theta synchrony effects of memory retrieval. The literature has not previously described the whole-brain regional distribution of these effects nor studied them with respect to intrusions. We show that synchronous medial temporal hubs and desynchronous parietal hubs mark the recall accuracy network, and that theta synchrony in the successful encoding, successful retrieval, and recall accuracy contrasts correlates positively with theta power increases at a region. These findings significantly advance our understanding of the role and localization of theta synchrony effects during human memory retrieval.

Introduction

Complex cognitive processes such as the formation and retrieval of declarative memories depend on the coordination of regions across the brain for information processing and transfer. The need for coordination means that activated brain regions must subsequently recruit other structures to act on the output of their operations (Buzsáki, 2010). Characterizing the patterns of connectivity that distinguish successful cognition from unsuccessful cognitive effort is therefore vital to understanding the neural computations that enable human memory.

The electrical activity of neuronal assemblies generates oscillatory rhythms that, like any oscillatory system, can become phase-locked when coupled (Lachaux et al., 1999). Phase-locking thus lends itself naturally to a measure of functional connectivity of brain signals, and intracranial human recordings permit us to study these transient connections with high temporal and spatial resolution (Fell and Axmacher, 2011). Phase-locking of slow oscillations, called the theta rhythm (3–8 Hz), has proven a robust correlate of successful memory in a variety of experimental paradigms, including recognition memory, spatial memory, and free recall, and in distinct memory functions, such as encoding and retrieval (Buzsáki, 2002; Siapas et al., 2005; Rutishauser et al., 2010; Solomon et al., 2017; Solomon et al., 2019; Roux et al., 2022). Manipulations of theta phase synchrony have been linked to the formation of mnemonic associations (Clouter et al., 2017), and whole-brain networks of theta phase synchronization underlie episodic memory encoding, with regional hubs that reliably capture this effect distributed throughout the brain (Solomon et al., 2017; Solomon et al., 2019). A rich animal literature has likewise associated theta synchrony with memory function, often focusing on the strong rodent hippocampal theta rhythm (Benchenane et al., 2010; Sigurdsson et al., 2010).

Although prior research has thoroughly characterized macroscale theta phase synchrony in episodic memory encoding (Mölle et al., 2002; Fell et al., 2003; Fell et al., 2008; Clouter et al., 2017; Solomon et al., 2017; Solomon et al., 2019), its role in memory retrieval, and the distribution of the functional connections that support these processes, are poorly understood. Studies have implicated widespread low-frequency phase-locking in memory retrieval (Solomon et al., 2017; Solomon et al., 2019; Watrous et al., 2013), and a few have identified specific interregional connections of functional relevance. For example, transient phase-locking between the left medial temporal lobe and left retrosplenial cortex is linked to autobiographical episodic memory retrieval (Foster et al., 2013). Nevertheless, previous studies have not systematically detailed how regions throughout the whole brain participate in the synchronous theta networks of memory retrieval, nor how these networks change between the edges of the 3–8 Hz band in an episodic free recall paradigm, despite evidence that low and high theta frequencies represent distinct functional components of the theta band (Lega et al., 2012; Watrous et al., 2013; Goyal et al., 2020). Other properties of these networks, such as their relationship to theta power changes during successful retrieval or to the theta connectivity that underlies the encoding of the same information, remain largely unexplored. The latter analyses are intriguing in light of findings of reinstatement of encoding spectral patterns during retrieval (Manning et al., 2011), and reliable cross-classification of successful encoding and retrieval (Kragel et al., 2017).

Here, we construct the functional networks of successful memory in a free recall paradigm that probes encoding and retrieval of episodic memories. We aim to answer four key questions about the synchronous theta activity supporting successful and accurate memory retrieval. First, which brain regions serve as hubs of the memory retrieval network, and which specific regional connections do these hubs target during successful recollection? Second, how do theta synchrony correlates of memory retrieval differ across the frequencies of theta band? Third, how does the memory retrieval network compare with the memory encoding network derived from the same

patients performing the same memory task? Fourth, what is the relation between spectral power and phase synchrony effects during successful retrieval?

Analyzing hundreds of subjects' intracranial electrophysiological recordings, we detail the distributed whole-brain synchronous theta networks that are associated with successful retrieval, both in comparison to baseline periods of silence and to incorrect recalls. We also discover that slow theta synchrony particularly supports memory retrieval and that theta power increases at a region correlate with global increases in theta synchrony. These findings advance our understanding of the role of theta phase synchrony in human memory and the functional connectivity and spectral correlates of memory retrieval.

Experimental Procedures

Participants

413 patients with pharmacoresistant epilepsy completed a delayed free recall memory task while implanted with intracranial electrodes for seizure monitoring. A number of hospitals contributed data to the project as part of a multi-site collaboration: the Hospital of the University of Pennsylvania, Thomas Jefferson University Hospitals, Freiburg University Hospital, University of Texas Southwestern Medical Center, University of Texas Health Science Center at San Antonio, the National Institute of Neurological Disorders and Stroke, Dartmouth-Hitchcock Medical Center, the Mayo Clinic, UCHealth University of Colorado Hospital, and Emory University Hospital. The electrode configurations — depth, strip, or grid — and electrode contact locations were selected according to clinical considerations alone. All patients provided informed consent to the study, and each hospital's institutional review board approved the research protocol before study activities began.

Free recall memory task

Patients performed a delayed free recall memory task on a laptop computer, while EEG data were recorded from their implanted electrodes at a sampling rate between 200 and 2000 Hz, depending on the settings of the clinical system in place. The patient's behavior in the memory task was synchronized with the EEG recording either with synchronization pulses or with network packets transmitted online between the computer that recorded the EEG signal and the computer on which the participant performed the memory task.

A full session of the memory task consisted of 12 or 25 trials identical in structure. Each trial consisted of three phases: encoding, a distractor task, and retrieval. During the encoding phase, words randomly drawn from one of two wordpools of common English nouns appeared one at a time for 1600 ms on the screen, with a 750–1000 ms randomly jittered interstimulus interval, or in a variant of the experiment, 800–1200 ms. Each trial presented 12 words, or in the variant, 15. Participants then completed an arithmetic distractor task, answering problems of the form A + B + C = ??, where A, B, and C were random integers between 1 and 9. This phase lasted for at least 20 s, or 25 s in the variant, allowing participants to finish any problem that appeared on the screen during that time. Finally, participants attempted to recall words aloud for 30 s, or 45 s in the variant, from the list of words just presented during the same trial's encoding phase. The audio recordings of the retrieval phase were then manually annotated to evaluate the content and accuracy of the vocalized responses.

Behavioral event selection

Events in the encoding and retrieval phases were classified as successful or unsuccessful. In encoding, a word presentation event was considered successful if the word was subsequently recalled during the retrieval phase of the same trial, and unsuccessful if the participant failed to recall the item. The post-presentation interval of 250–1250 ms was analyzed, in order to center the 400–1100 ms window during which prior work identified the peak of the encoding-evoked theta synchrony effect (Solomon et al., 2017; Adamovich-Zeitlin et al., 2021), and to avoid spectral leakage from the preceding or following items' presentation intervals through convolution buffers. Encoding items presented at intermediate serial positions tend to be recalled with lower probability than items presented at the beginning or end of the list. Therefore, to control for systematic differences in serial position between subsequently recalled items and not-recalled items, we matched subsequently recalled items with not-recalled items that differed in serial position by no more than 1 and analyzed only the items in these matched pairs.

In retrieval, items correctly recalled from the same trial's encoding phase represented successful memory. Subjects subsequently recalled 30.4% ± 12.0% (mean ± SD across subjects) of presented items. We did not analyze each trial's first recall or nonverbal vocalizations. To analyze the neural activity specific to retrieval processes, we compared the pre-vocalization periods of correct recalls to periods of failed memory search. We matched the 1000 ms pre-vocalization analysis window of each correct recall by its vocalization onset time in the recall window to a 1000 ms period of silence in a nearby list, with preference to closer lists in view of contextual drift. We matched recalls to a period of silence within 0.5 s if available or within 5 s otherwise. These periods of silence, drawn from after the first recall and before the last recall in the trial, were considered periods of unsuccessful memory search. To prevent the inclusion of vocalization artifact or neural signal associated with successful retrieval in the analyzed signal, matched periods of silence that began less than 2000 ms after a vocalization onset or ended less than 1000 ms before a vocalization onset were not considered. Likewise, correct recall windows that began less than 1000 ms after a vocalization onset were not analyzed to avoid vocalization artifact. We did not analyze sessions with fewer than 10 recalls that met these criteria. After applying these inclusion criteria, 36.5% ± 11.9% (mean ± SD across subjects) of subjects' correct recalls remained in the analysis.

In the recall accuracy analysis, we analyzed correct recalls and intrusions that met the same relative timing criteria as in the retrieval analysis to avoid vocalization contamination, and matched them by vocalization onset time in the same way. Again, we did not analyze sessions with fewer than 10 pairs of correct recalls and intrusions that met these criteria. After applying these inclusion criteria, 25.7% ± 11.0% (mean ± SD across subjects) of subjects' correct recalls remained in the analysis.

We verified that our procedure for matching events by serial position in the encoding analysis and by vocalization onset time in the retrieval and recall accuracy analyses was effective. The difference in the average serial position between successful and unsuccessful memory events was –0.14 ± 0.24 (mean ± SD across subjects), the difference in the average vocalization onset time in the retrieval analysis was 0.45 s ± 0.71 s (mean ± SD across subjects), and the difference in the average vocalization onset time in the recall accuracy analysis was -0.75 s ± 1.47 s (mean ± SD across subjects).

Anatomical localization of electrodes

After a pre-operative structural T1-weighted MRI scan was parcellated and segmented (Fischl et al., 2004), a post-operative CT scan was coregistered to it by means of Advanced Normalization

Tools (ANTS) to provide coordinates for all locations in the CT scan (Avants et al., 2008). Medial temporal lobe subregions were also automatically labelled in a pre-operative T2-weighted MRI scan (Yushkevich et al., 2015). Implanted electrode contacts were manually identified and annotated according to these coordinates. An automated pipeline then mapped these coordinates to brain region labels (Dykstra et al., 2012). Two clinical neuroradiologists reviewed a subset of these labels for accuracy.

80 ROIs, evenly divided between the hemispheres, constituted the nodes for network analyses. All brain plots represent region locations in Montreal Neurological Institute (MNI) space.

EEG processing

Bipolar re-referencing was applied to all channel recordings before analysis; bipolar differencing was carried out between neighboring electrodes and bipolar pairs between contacts more than 20 mm apart were not analyzed. All EEG recordings were resampled to 250 Hz, with 1000 ms buffers to avoid edge artifacts. For encoding events, the buffers consisted of the EEG signal adjacent to the analysis window. For recall events, 1000 ms mirrored buffers were appended to either side of each analysis window to preclude the introduction of vocalization or motion artifact into the analyzed signal, and clipped after time-frequency decomposition. A 4th-order Butterworth bandstop filter at 58–62 Hz (United States) or 48–52 Hz (Germany) removed line noise. Morlet wavelet convolution (wave number = 5) then extracted instantaneous phase and power from the EEG recordings during the selected event windows at each integer-valued frequency in the 3–8 Hz theta band.

Phase synchrony analysis and functional network construction

Phase synchrony refers to the consistency across behavioral trials — periods of item encoding or memory search — of the phase lag between signals across time. To analyze phase synchrony, we computed the difference in instantaneous phase for each pair of contacts. Then, we circularly averaged the phase lag across the analysis window into five 200 ms bins, or epochs. For each pair of contacts, each frequency, and each epoch, we computed the pairwise phase consistency (PPC) (Vinck et al., 2010) for successful memory events and unsuccessful memory events separately. Finally, we aggregated phase synchrony values across contacts located in the same region. The difference in pairwise phase consistency between successful and unsuccessful memory events corresponded to the network connectivity specific to improved memory function.

Network analyses and statistical procedures

The average ΔPPC for an ROI pair gave the connectivity value in subject-level connectivity matrices. Paired-samples t-tests across the 413 subjects were used to test hypotheses about differences in theta synchrony related to successful memory in contrast with unsuccessful memory.

A region that reliably exhibits high mean synchronization to other regions in the brain is a hub. To assess the "hubness" of a region, we averaged both successful memory and unsuccessful memory PPC values over all theta frequencies and epochs of the analysis window, and all other regions to which the test region had connections to compute a within-subject "hubness score." Then, we applied a one-sample t-test against population mean zero to the distribution of the region's hubness scores across those subjects for whom recordings from that region were available. We did not test hubness among ROIs for which less than 7 subjects' worth of data was available.

To perform hypothesis testing in a multiple comparisons setting, we controlled the false discovery rate at $Q_{\text{FDR}} = 0.05$ by deriving a plug-in cutpoint estimate from a bootstrap procedure (Efron, 1979; Hastie et al., 2001; Sederberg et al., 2003; Sederberg et al., 2006; Serruya et al., 2014; Long et al., 2014). We applied this nonparametric approach to achieve greater power over the commonly used sequential Benjamini-Hochberg method for FDR control, which is excessively conservative when the simultaneous tests are correlated and many of the underlying null hypotheses are false. We permuted the "successful" and "unsuccessful" class labels of the PPC values 10000 times, and recomputed the each test's t-statistic as described above for each permutation. Then, we aggregated the null distributions from all tests to estimate the distribution of t-statistics that would arise under the set of all the underlying null hypotheses. Given m tests, we estimated the rate p_0 of true underlying null hypotheses by $2T/M$, where T is the number of test statistics among all M tests that fall between the 25th and 75th percentiles of this aggregated null distribution, and obtained an FDR-corrected p-value from $p_0 \cdot \#\{t_0 \in \text{ aggregated null distribution} : |t_0| \geq |t|\}/(\#\{\text{aggregated null distribution}\} + 1)$ (Hastie et al., 2001). Any test statistic that yielded a p-value less than $Q_{\text{FDR}} = 0.05$ was deemed statistically significant.

The Holm-Bonferroni method was applied to control the family-wise error rate at $\alpha = 0.05$ where specified.

For correlation analyses between encoding- and retrieval-evoked theta synchrony, we performed a one-sample t-test against population mean zero on Pearson correlation coefficients computed within subject. We computed the correlation between synchronous theta encoding and retrieval networks by correlating contact-level hubness scores — i.e., average synchronization to all other contacts — across contacts. To take into account the intrinsic neural variability between behavioral events that limits the maximal theoretical correlation between encoding- and retrieval-evoked activity, we sought a benchmark correlation value by conducting a split-half correlation analysis on retrieval events. For each analyzed session, successful–unsuccessful retrieval event pairs were randomly divided into two halves, synchrony values and hubness scores were calculated as aforementioned separately for each half, and hubness scores were correlated across contacts. We applied the Spearman-Brown correction to the within-subject split-half correlation values before computing sample statistics.

To analyze the relationship between spectral power and phase synchrony during successful memory in both encoding and retrieval, we quantified the size of the difference in mean power between successful and unsuccessful memory events for each contact with the Cohen's d measure. We correlated Cohen's d values with each contact's hubness score across contacts within subject, and performed a one-sample t-test against population mean zero on the Pearson correlation coefficients for hypothesis testing.

Data availability

All analyzed datasets are available for public use (`http://memory.psych.upenn.edu/Electrophysiological_Data`).

Results

Synchronous theta networks during memory encoding and retrieval

Analyzing data from 413 patients performing a delayed verbal free recall task, we computed intertrial phase synchrony at 3–8 Hz during the encoding of items (250–1250 ms after word

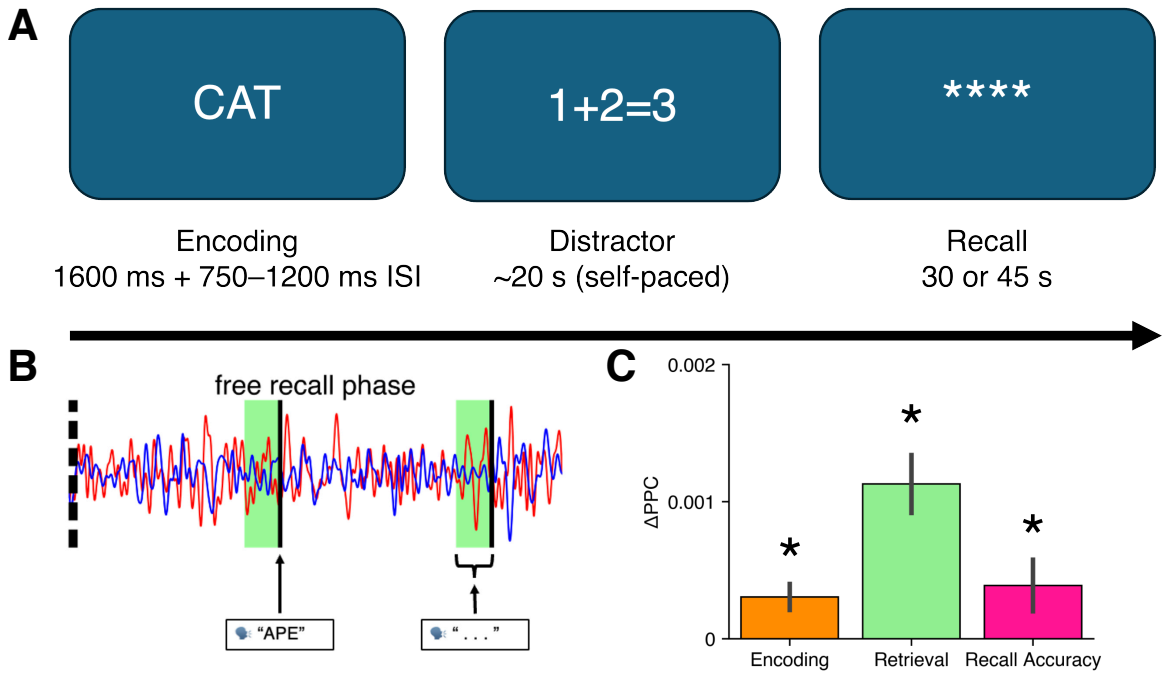

Figure 1: (A) Structure of free recall task. (B) Correct and incorrect recalls and periods of silence were analyzed during the recall phase. (C) Whole-brain theta synchrony effects for encoding, retrieval, and recall accuracy behavioral contrasts.

onset) and during the periods immediately preceding spontaneous recall (–1000–0 ms before vocalization). To identify theta synchrony effects specific to improved memory function, we contrasted subsequently recalled items with not-recalled items presented during the encoding phase, and correctly recalled words with matched deliberation periods (Methods) during the retrieval phase. Replicating previous results in the literature (Solomon et al., 2017; Solomon et al., 2019), we observed increased theta synchrony throughout the whole brain both for successful encoding ($p = 0.0014$) and for successful retrieval ($p = 1.5 \times 10^{-7}$). Comparing correct recalls and incorrect recalls, or intrusions, in a subset of 194 subjects for whom at least 10 matched pairs of correct recalls and intrusions (see "Methods") were available also revealed an effect of theta phase synchrony ($p = 0.040$). Theta synchrony therefore distinguishes successfully encoded items from more poorly encoded items, memory retrieval from failure to retrieve any memory, and correct recalls from false memories (Figure 1).

Global theta synchronization during successful memory function might arise from a distributed increase in synchrony among a diffuse set of connections across many brain regions, or from the action of particular regions, or hubs, that strongly synchronize with the rest of the brain. As previous studies have reported network hubs for successful memory encoding, we now sought to determine the hubs of the synchronous theta activity that precedes spontaneous recall. Following the notion of a hub as a node central to a network's global topology, maintaining widespread connections (Sporns, 2014), we considered a region a hub if its mean synchronization value with all other regions in the brain was reliably positive across subjects. We evaluated 80 ROIs throughout the brain for hubness, controlling the false discovery rate at $Q_{\mathrm{FDR}} = 0.05$ in our hypothesis testing (see "Methods").

We found 18 hubs of positive synchronous activity and zero hubs of negative synchronous

activity in the encoding network, and 43 synchronous hubs and zero desynchronous hubs in the retrieval network. Figure 2 illustrates these hubs and the connections that exhibit the strongest effects (Xia et al., 2013). As both networks comprise synchronous hubs throughout the brain whose connections span considerable distances across the brain, and few regions reliably desynchronize from other brain regions, widespread and distributed synchronous theta networks characterize successful memory, during both encoding and retrieval.

We also identified seven hubs of the recall accuracy network given by the connections that distinguish correct recalls from intrusions: five synchronous hubs and two desynchronous hubs. Four of the five synchronous hubs, which included left and right hippocampus, left middle temporal gyrus, right parahippocampal gyrus, and right orbitofrontal cortex, lay in the bilateral medial temporal lobe, while the two desynchronous hubs, the left postcentral gyrus and the left precuneus, lay in the parietal lobe. One possibility is that the synchronous theta activity that distinguishes the retrieval of true and false memories is more localized to specific regions, in contrast to the diffuse networks that we have demonstrated to characterize the encoding and retrieval processes in general. Another is that the smaller dataset available for intrusions, a consequence of the rarity of intrusions and of intrusions uncontaminated by vocalization in particular, limits our statistical power to detect modulations of theta synchrony at the level of particular regions.

Stronger memory-related increases in slow theta synchrony than fast theta synchrony

The previous analyses describe retrieval-related theta synchrony in diverse brain regions by averaging effects across the canonical 3–8 Hz theta band. However, research on human verbal and spatial memory has associated distinct low and high theta components with different aspects of memory (Lega et al., 2012; Jacobs, 2014; Goyal et al., 2020; Rudoler et al., 2023). Because of the heterogeneity of spectral correlates of memory across the theta band, we asked whether global theta synchrony effects differed between low and high theta frequencies (Figure 3A). In light of the frequency domain leakage arising from Morlet wavelet convolution, we took 3 Hz and 8 Hz to represent low and high theta, respectively. Regions throughout the brain tended to synchronize during successful retrieval both at 3 Hz ($p = 1.3 \times 10^{-8}$) and at 8 Hz ($p = 0.0029$), but reliably more so at 3 Hz ($p = 4.1 \times 10^{-6}$). On the other hand, in encoding, there was a statistically significant effect at 8 Hz ($p = 0.0039$) but not at 3 Hz alone ($t_{412} = 1.8, p = 0.0699$), and in the recall accuracy contrast, at neither frequency alone (3 Hz: $t_{193} = 0.59, p = 0.56$, 8 Hz: $t_{193} = 1.7, p = 0.083$). Neither the encoding network nor the recall accuracy network exhibited a difference between slow and fast theta (encoding: $t_{412} = -0.47, p = 0.64$, recall accuracy: $t_{193} = -0.44, p = 0.66$).

Figure 3B visualizes the time courses of the theta synchrony effects at each theta frequency. In contrast to the recall–matched deliberation comparison, marked by uniform increases in synchrony at all epochs and theta frequencies, the recall–intrusion comparison reveals a desynchronization trend early in the 1000 ms retrieval period, including a statistically significant effect at 6 Hz between 1000 and 800 ms before vocalization onset ($p = 0.023$). The theta synchrony patterns that underlie retrieval and recall accuracy thus seem to differ in their temporal dynamics, with the theta synchronization effect of the recall accuracy contrast appearing later in the retrieval period. The whole-brain theta synchrony effect recall accuracy also includes a tendency toward desynchronization, consistent with the earlier finding of desynchronous hubs in the recall accuracy network but not the encoding or retrieval networks.

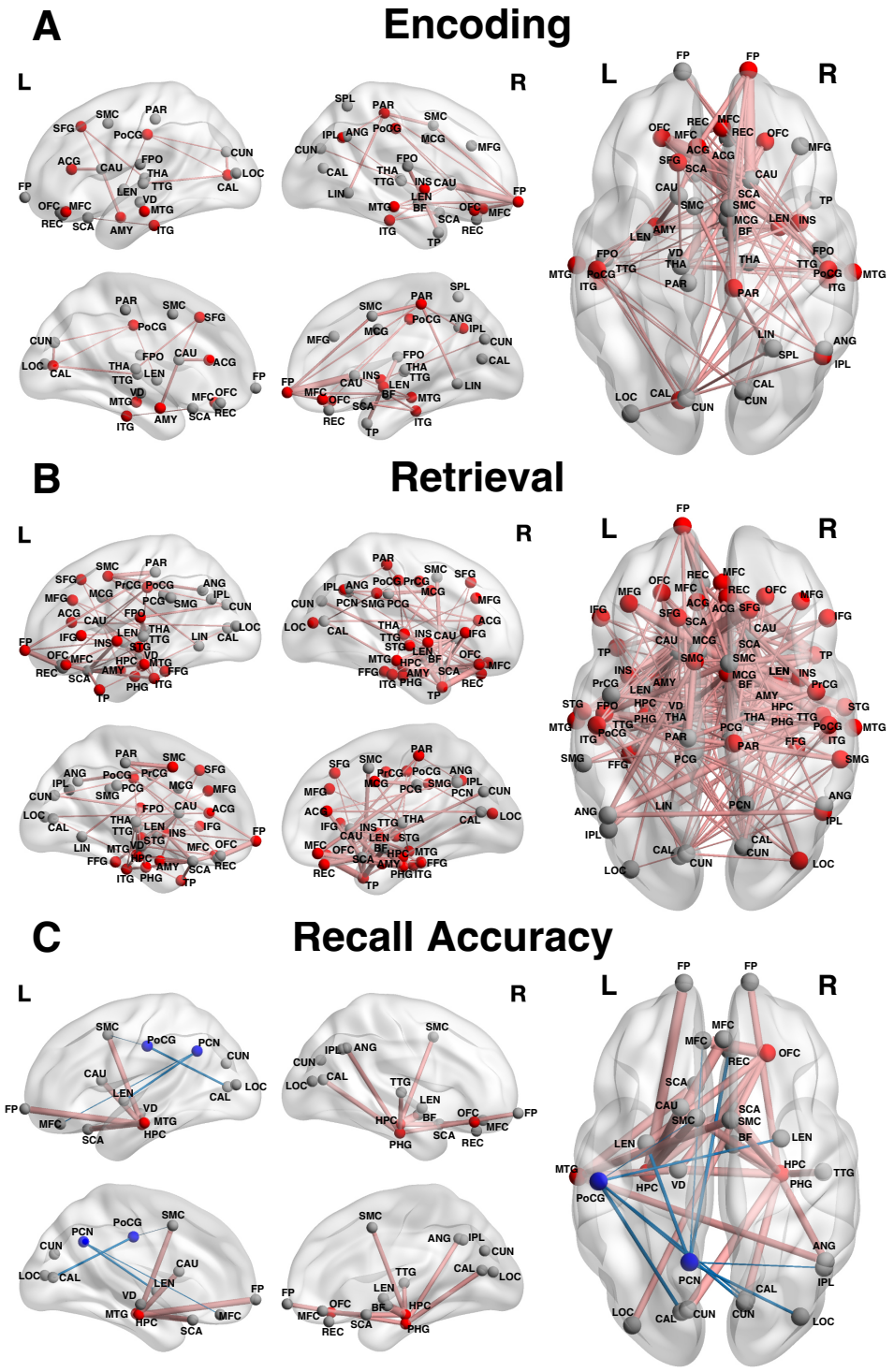

Figure 2: Theta synchrony networks specific to encoding, retrieval, and recall accuracy behavioral contrasts. These networks were generated for visualization by plotting the network hubs determined by the hub analysis and for each hub, the five connections with the highest subject-average ΔPPC values, after removing all connections with less than 7 subjects' worth of data. Positive hubs are colored in red, negative hubs are colored in blue, and regions that are not hubs are colored in gray. Width of connections corresponds to strength (|ΔPPC|). Positive connections are colored in red and negative connections are colored in blue.

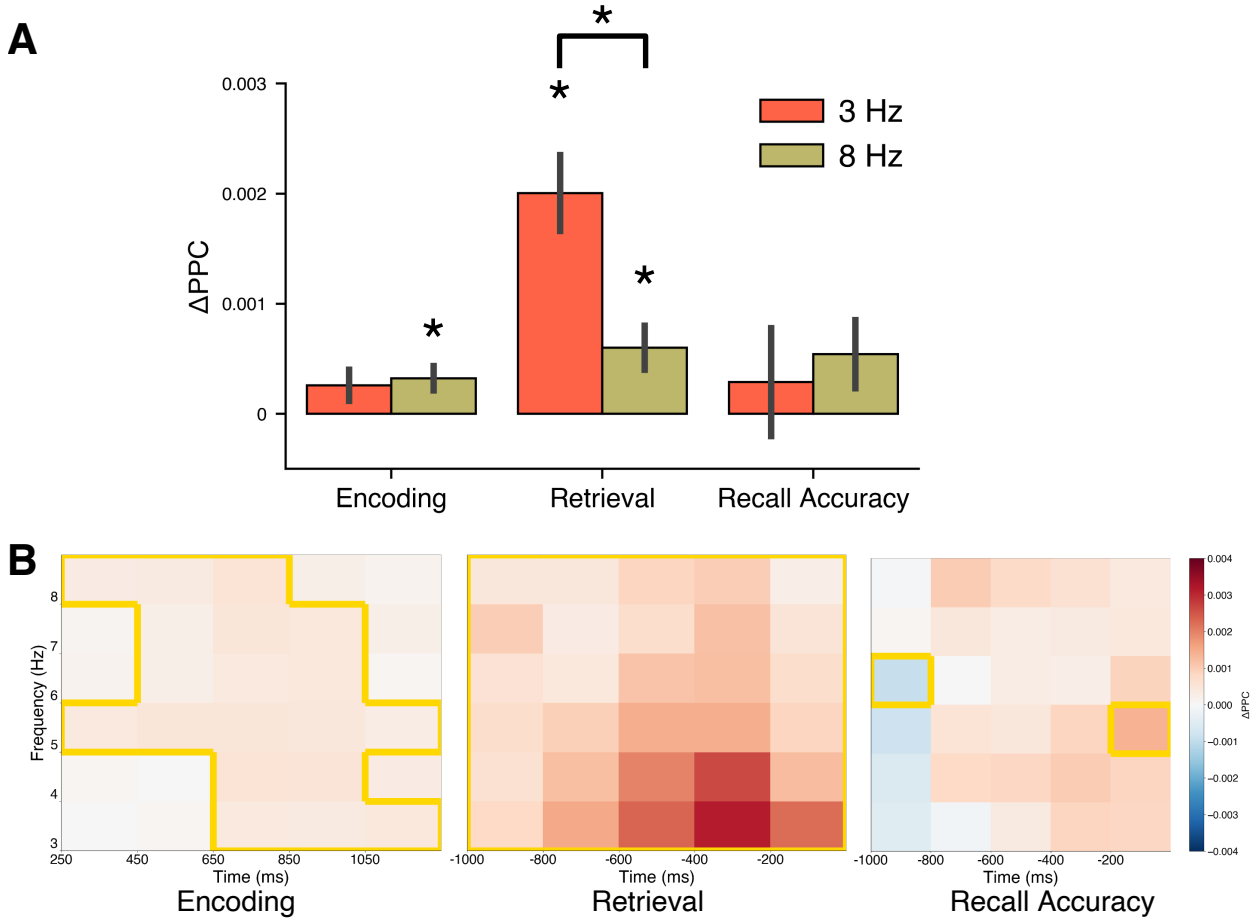

Figure 3: (A) Mean whole-brain connectivity at 3 Hz and 8 Hz for encoding, retrieval, and recall accuracy networks (mean ± SEM across subjects). (B) Time-frequency plots for encoding, retrieval, and recall accuracy whole-brain theta synchrony effects. Clusters of time-frequency pixels with statistically significant effects are outlined with a yellow border. Hypothesis testing was carried out with the same FDR control procedure as for the hub analysis to account for the tests' spatiotemporal correlations ("Methods").

Role of MTL and hippocampus in synchronous theta networks

Having established that brain-wide increases in theta synchrony mark the imminent recall of previously studied items and that this effect is stronger for slow theta oscillations, we next asked whether the medial temporal lobe (MTL) is a stronger hub than other brain regions implicated in memory: in particular, the lateral temporal cortex (LTC), prefrontal cortex (PFC), and parietal lobe. Although studies of memory have long signaled the special importance of the medial temporal lobe to episodic memory (Staresina et al., 2012; Solomon et al., 2019), prior investigations of the electrophysiology of memory retrieval have identified some of the strongest neural correlates in the lateral temporal and frontal cortices (Burke et al., 2015; Kragel et al., 2017). We hypothesized that the MTL was a stronger hub of the synchronous theta network of memory than the LTC, PFC, or parietal lobe. In comparing the MTL to these lobe-level ROIs, we analyzed the MTL's mean connectivity to all regions but the subregions of the lobe with which it was compared, and the compared lobe's mean connectivity to all regions but the subregions of the MTL. The encoding network exhibited no such differential effects (LTC: $t_{324} = -1.3, p_{\text{FWE}} = 0.55$, PFC: $t_{291} = 1.1, p_{\text{FWE}} = 0.55$, parietal: $t_{264} = 1.0, p_{\text{FWE}} = 0.55$), nor did the recall accuracy network (LTC: $t_{150} = 0.86, p_{\text{FWE}} = 0.39$, PFC: $t_{133} = 1.97, p_{\text{FWE}} = 0.15$, parietal: $t_{118} = 1.8, p_{\text{FWE}} = 0.15$). In the retrieval network, the MTL did exhibit stronger global synchrony than the parietal lobe ($t_{264} = 4.0, p = 2.3 \times 10^{-4}$) but we did not find such an effect for the LTC ($t_{324} = 0.15, p_{\text{FWE}} = 0.88$) or for the PFC ($t_{291} = 1.6, p_{\text{FWE}} = 0.23$).

Next, we looked within the MTL to the hippocampus, which may maintain interregional connections crucial to memory-related neural activity. Hippocampus–PFC connections are of considerable interest in the functional connectivity literature (Eichenbaum, 2017), and specifically cited for a role in exerting strategic control over memory function, such as selecting the context-appropriate memory during memory search. We examined hippocampal connections both to the dorsolateral PFC (Edin et al., 2009; Anderson et al., 2016; Oehrn et al., 2018), located in the middle frontal gyrus, and to the medial frontal cortex, including the MFC proper and the anterior cingulate gyrus (Euston et al., 2012; Preston and Eichenbaum, 2013; Morici et al., 2022). Controlling the family-wise error rate across these two regions, we did not find an effect of memory-evoked theta synchrony between the hippocampus and dlPFC in the encoding ($t_{212} = -0.01, p_{\text{FWE}} = 0.99$), retrieval ($t_{212} = 1.29, p_{\text{FWE}} = 0.20$), or recall accuracy ($t_{92} = 1.3, p_{\text{FWE}} = 0.31$) networks. We found evidence for theta synchronization between the hippocampus and mPFC in the retrieval network ($t_{100} = 2.5, p_{\text{FWE}} = 0.028$) but not in the encoding ($t_{100} = 1.97, p_{\text{FWE}} = 0.10$) or recall accuracy ($t_{39} = 1.5, p_{\text{FWE}} = 0.31$) networks.

Comparison of encoding and retrieval networks

Having identified the regional distribution of the memory retrieval network, we asked whether it coincided with the synchronous theta network that underlies the encoding of subsequently recalled items. Although prior work has described a common core of cortical regions that are activated during memory encoding and retrieval (Kragel et al., 2017), and shown that spectral patterns during item recall reinstate those present during the same item's encoding (Manning et al., 2011), studies have also reported differing patterns of theta synchronization during successful encoding and retrieval within the MTL (Solomon et al., 2019). Hence, it is unclear whether widespread theta connectivity of a region during encoding corresponds to similar activation during retrieval.

Correlating hubness between the encoding and retrieval networks across all electrode contacts within subjects revealed a small correlation of $r = 0.054 \pm 0.010$ ($p = 1.3 \times 10^{-7}$). Because neural variability between behavioral events at different times attenuates the maximal observable correlation, we contextualized this finding with a split-half correlation analysis on the retrieval events

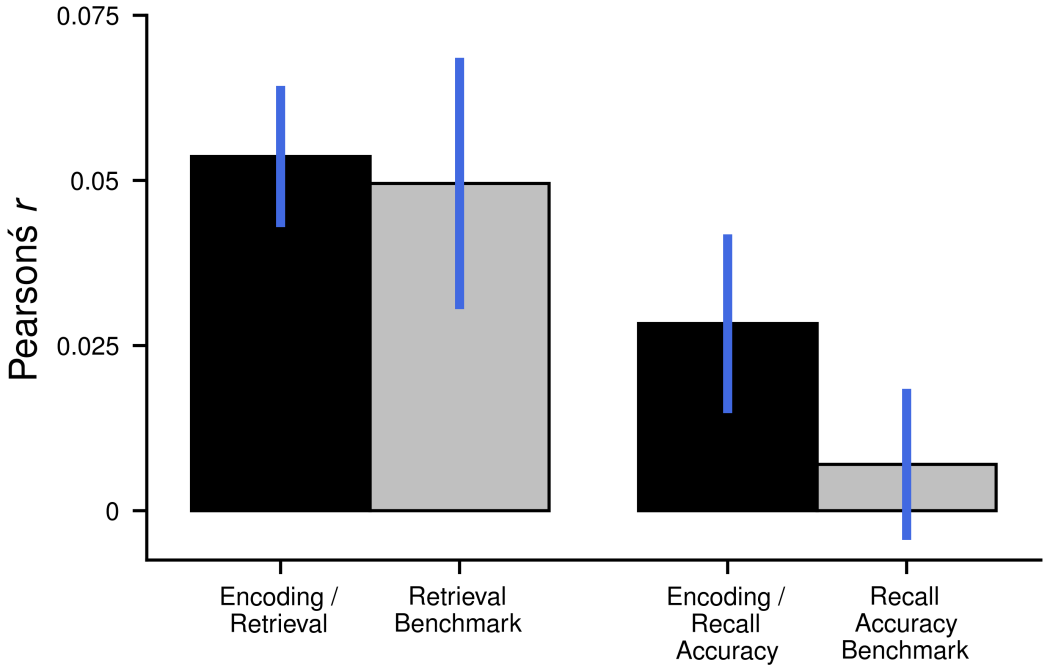

Figure 4: Pearson's product moment correlation (mean ± SEM across subjects) between encoding hubness and retrieval or recall accuracy hubness, and split-half correlation benchmark.

("Methods"), obtaining a benchmark correlation value of $r = 0.050 \pm 0.018$. We considered a similar comparison between the encoding and recall accuracy networks and found a small hubness correlation of $r = 0.028 \pm 0.013$ ($p = 0.029$) and a benchmark correlation value of $r = 0.007 \pm 0.011$, suggesting a limited ability to detect correlations at the level of contacts between the neural activity associated with different sets of events (Figure 4). There was no statistically significant difference between the encoding–retrieval or encoding–recall accuracy correlation values and the associated benchmark values. Despite the low observed correlation values, perhaps due to the limited quantity of analyzable within-subject recall events, the similarity of the empirical correlation values to the benchmark values established by the split-half correlation analyses suggests that the correlation between the encoding network and the retrieval or recall accuracy network may achieve the noise-imposed upper bound, rather than a lack of relationship between underlying patterns of functional connectivity during encoding and retrieval.

Power–synchrony relationship

Having detailed the whole-brain networks of theta synchrony that distinguish successful retrieval from unsuccessful memory search, we sought to establish their relation to other spectral correlates of memory function. Modulation of theta power also underlies memory retrieval (Burke et al., 2014; Kragel et al., 2017; Rudoler et al., 2023), with broadband low-frequency power decreases and narrowband low theta increases accompanying periods of successful spontaneous recall in comparison to periods of unsuccessful memory search. In addition, theta coherence positively mediates stimulation-evoked theta power (Solomon et al., 2018). We therefore examined how memory-related changes in theta power and theta synchrony covary throughout the brain (Figure

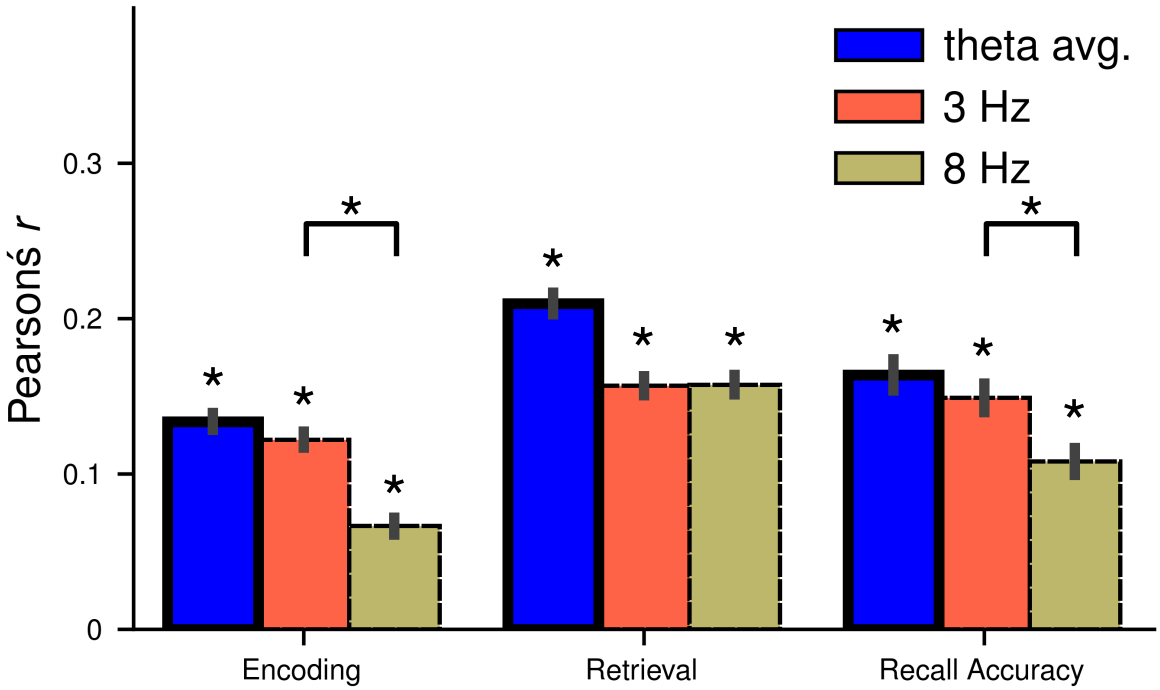

Figure 5: Correlation between spectral power and region-averaged phase synchrony ("hubness") effects across electrode contacts (mean ± SEM across subjects) of the encoding, retrieval, and recall accuracy networks, with effects analyzed averaged across the theta band, at 3 Hz only, or at 8 Hz only.

5). Correlating a given region's change in theta power during improved memory retrieval with its hubness value, or mean brain-wide theta synchrony effect, across contacts revealed a positive correlation between theta synchrony and power effects in the encoding ($r = 0.13, p = 2.2 \times 10^{-82}$), retrieval ($r = 0.21, p = 4.8 \times 10^{-107}$), and recall accuracy ($r = 0.16, p = 1.1 \times 10^{-37}$) behavioral contrasts. Moreover, in encoding, the correlation at 3 Hz, $r = 0.12$, is stronger than at 8 Hz, $r = 0.066$ ($p = 2.7 \times 10^{-15}$), as in the recall accuracy contrast ($p = 7.7 \times 10^{-4}$), with a correlation of $r = 0.15$ at 3 Hz and 0.11 at 8 Hz. There was no such effect in the retrieval analysis ($p = 0.94$): the correlation both at 3 Hz and 8 Hz was $r = 0.16$. Alongside the earlier findings of stronger memory-evoked synchrony at 3 Hz than at 8 Hz in the retrieval network, but not the encoding or recall accuracy networks, these results suggest important differences among the spectral correlates of these behavioral contrasts across the theta band. In light of findings in the literature of memory-related coupling between theta phase and gamma amplitude (Belluscio et al., 2012; Lega et al., 2015), we also examined the relationship between memory-evoked theta synchrony with memory-evoked gamma power. We found no statistically significant correlation across contacts between gamma power and theta synchrony hubness in the encoding ($p = 0.26$), retrieval ($p = 0.51$), or recall accuracy ($p = 0.90$) networks.

Discussion

We aimed to characterize the whole-brain synchronous theta networks of successful memory retrieval, leveraging our study's large dataset comprising recordings from 47,905 intraparenchymal and depth electrodes across $N = 413$ subjects. We found a marked pattern of whole-brain theta synchrony accompanying both successful memory encoding and retrieval, and distinguishing the imminent recall of correct items from that of intrusion errors. The synchronous theta networks identified during encoding and retrieval spanned widespread brain regions, centering on the prefrontal cortex and lateral and medial temporal lobes. Whereas prior studies have reported dissociations between slow (3 Hz) and fast (8 Hz) theta, we did not find any reliable differences between slow and fast theta for the encoding or recall accuracy comparisons; we did, however, find greater retrieval-evoked theta synchrony when comparing correct recalls to deliberation periods. Having demonstrated widespread theta synchrony during both successful memory encoding and retrieval, we asked whether similar networks underlie both effects. We found reliable but modest correlations between encoding and retrieval networks, but these correlations did not differ from a split-half correlation benchmark. Thus, our analyses are consistent with the hypothesis of encoding–retrieval neural similarity. Finally, we link increases in theta synchrony during successful memory at sites in the brain to higher theta power for both slow and fast theta. While studies of theta phase synchrony in cognition often center on the connectivity of a handful of regions, such as the hippocampus, these results highlight the role of distributed, brain-wide theta synchrony in memory function. They also raise the possibility that phase synchrony modulates the spectral power changes that are of widespread interest in the cognitive electrophysiology literature.

We found that retrieval and recall accuracy are marked by brain-wide theta phase synchrony, with network hubs throughout the brain. In the recall accuracy contrast, the effects of theta synchrony are more mixed than for encoding or retrieval, involving desynchronous hubs in the parietal lobe and a desynchronization tendency early in the analysis window. Solomon et al. (2017) demonstrated that widespread theta synchronization marked memory encoding, and also reported a whole-brain theta synchrony effect of retrieval. However, the specific regional hubs and connections that constituted the functional networks behind memory retrieval remained unknown, and the patterns of theta synchrony associated with correct recalls in comparison to intrusions were not investigated. Like encoding, successful retrieval and accurate recall rest on extensive and diffuse connections. Indeed, despite the theoretical importance of MTL to human memory, and its observed prominence among the hubs in the recall accuracy network, we were unable to detect differences in network hubness between the medial temporal lobe and the prefrontal or lateral temporal cortices.

We also observed stronger retrieval-related whole-brain synchrony in slow theta than in fast theta, in agreement with a growing recognition of distinct low and high theta bands in the human electrophysiology literature (Lega et al., 2012; Watrous et al., 2013; Jacobs, 2014; Goyal et al., 2020; Rudoler et al., 2023), which has concentrated on functional dissociations between slow and fast theta. For example, Watrous et al. (2013) showed that slow and fast theta were differentially associated with spatial recall and temporal recall, respectively, in a forced-choice spatial and temporal retrieval paradigm. Here, we show that in a retrieval–deliberation contrast in episodic free recall, slow theta appears to drive the synchrony effects associated with improved function, as it displays considerably stronger effects than fast theta. Functional differences across the theta band may therefore be a hallmark of memory retrieval in general.

After describing retrieval-related synchrony effects, we considered the extent to which the neural activity associated with memory retrieval recapitulates the activity associated with memory encoding. Although phase synchrony remains a widely studied neural correlate of cognition, few

studies have compared phase synchrony effects across memory encoding and retrieval. However, because similarity of retrieval-related neural activity to encoding-related activity supports the important theoretical notion that memory retrieval rests on the reinstatement of the context present during encoding, this line of investigation is crucial. Hubness across recording sites displayed a relatively low correlation between the encoding and retrieval networks. Earlier studies on theta power changes during encoding and retrieval, which have suggested that theta power increases associated with successful encoding and retrieval are uncorrelated across sites in the brain (Lega et al., 2012), and have found that improved encoding and retrieval overlap in low-frequency power effects, especially in the temporal lobe, while also uniquely activating many other regions, with much more widespread activation in retrieval (Kragel et al., 2017). Moreover, Kragel et al. (2017) proposed that encoding and retrieval processes activate a common core of regions while differing in patterns of interregional connectivity. More recently, a study of hippocampal connectivity observed that theta synchrony patterns specific to memory function appeared to differ between encoding and retrieval (Choi et al., 2020). While our results are not inconsistent with these earlier studies that have compared correct recalls to matched deliberations, our benchmark analysis indicates a low capacity to detect correlations between functional connectivity effects from distinct sets of behavioral events from our limited data. These results are an instructive first step in encoding–retrieval similarity analyses, a topic of key interest in cognitive neuroscience and important for future studies of the neural correlates of memory, including spectral phase synchrony.

We also report a positive correlation between a region's changes in brain-wide theta synchrony and theta power associated with successful retrieval and accurate recall. Encoding also exhibits a similar correlation. Little is known about whether phase coupling mediates changes in power, and if so, how. A previous study related low-frequency coherence to theta power evoked by direct electrical stimulation, alluding to the existence of a relationship between baseline phase synchrony and transient power changes (Solomon et al., 2018). Other research on low-frequency power and phase synchrony correlates of memory formation in a paired-associates learning task found increased 2–4 Hz phase synchrony among regions that exhibited 2–4 Hz power increases during successful memory formation (Haque et al., 2015), but did not systematically investigate the correlation between memory-related changes in global phase synchrony and power across all recorded regions within subjects. Our results significantly extend these suggestions by demonstrating a positive relationship between power and phase synchrony in the time-locked context of cognitive function. This positive relationship held in both slow and fast theta. Since broadband low-frequency activity decreases during successful encoding and retrieval, one possibility is that regions associated with power changes associated with successful memory tend to be distinct from those that exhibit stronger phase synchrony during retrieval. Another is that narrowband power effects form the basis for the power–synchrony correlation. During successful encoding and retrieval, narrowband slow theta power increases, and narrowband fast theta power decreases (Rudoler et al., 2023). In this case, regions that exhibit increases in slow theta phase synchrony also exhibit the increases in slow theta power associated with successful memory. Meanwhile, regions that exhibit the fast theta phase synchrony effects of successful memory are less likely to exhibit memory-related narrowband fast theta power decreases. In part, this proposal echoes the hypothesis of Herweg et al. (2020), which aimed to reconcile LFA decreases with theta synchrony increases during successful memory, but that review of the literature on memory-related theta effects did not consider the important distinction between slow and fast theta rhythms and their opposing narrowband power effects.

Our findings indicate that diffuse, global theta synchrony, particularly in slow theta, characterizes successful memory, including encoding, retrieval, and recall accuracy. Understanding the functional connectivity correlates of human memory may improve accounts of the interactive roles

of brain regions in memory, lead to subtler descriptions of diseases that impair memory, and even serve as a guide to targeted therapeutic interventions for memory — for example, with electrical stimulation (Ezzyat et al., 2023). In future work, a richer picture of the functional networks of human memory will benefit from relating patterns of theta synchrony across experimental behavioral paradigms and to functional connectivity results in other modalities and settings.

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