Frequency-specific network connectivity increases underlie accurate spatiotemporal memory retrieval

Andrew J Watrous1,2, Nitin Tandon3,4, Chris R Conner3, Thomas Pieters3 & Arne D Ekstrom1,2,5

Successfully recalling an event in our everyday life depends critically on retrieving the context associated with it. A memory, such as what we ate for dinner last night, is more vividly recreated when we can remember contextual details, such as the location of the restaurant1. Neuroimaging and patient lesion studies strongly support the contributions of specific brain regions to episodic memory retrieval, emphasizing selective roles for the medial temporal lobe (MTL)1–7, prefrontal cortex2,3,6,8,9 and parts of parietal cortex2,10–12 in this process. Distributed, coordinated activity across brain regions is also critical to memory retrieval13–18, and synchronized activity in the local field potential (LFP) has been implicated in coordinating this process19. Specifically, low-frequency (3–12 Hz) coordinated activity between hippocampus and prefrontal cortex in rodents is related to learning new rules during a spatial navigation task20 and can bias neocortical neuronal firing21,22. The theoretical perspectives emerging from such work appear to provide conflicting accounts of whether successful memory retrieval is primarily mediated by a specific brain region, best characterized by changes in functional connectivity between multiple brain regions, or some combination of the two (Fig. 1a).

Recalling a prior experience often involves retrieving multiple, disparate2 types of context, for example, not only where we ate dinner, but when it occurred relative to other events. Assuming that specific contextual information is represented by distinct cell assemblies in the same or overlapping brain regions13–16, how do different context representations emerge from within constituents of the same network? Although regional specificity may provide one possible account of this issue17,21, another interesting proposal, the so-called spectral-fingerprint hypothesis, argues that different cognitive operations manifest as distinct, frequency-specific patterns of interregional phase synchronization in large-scale networks23,25. These frequency-specific phase interactions are a strong candidate mechanism for coordinating distributed cell assemblies in parallel27–29, known as frequency multiplexing, and may underlie the rapid retrieval of contextual information specific to a particular experience (Fig. 1b). Although previous findings suggest the importance of low-frequency band power modulations in the MTL using resting magnetoencephalography (between 4–6 Hz)30 and coherence during human free recall tasks using intracranial LFPs (at ~3 and 8 Hz)31,32, the manner in which frequency multiplexing occurs between brain regions involved in retrieval of episodic memory is not known.

We set out to test two fundamental sets of theoretical perspectives on the neural basis of episodic memory retrieval. The first regards whether accurate episodic memory retrieval is characterized by a disproportionate contribution of a specific brain region and/or accomplished by changes in global connectivity across the network (Fig. 1a). The second addresses how different contexts can be retrieved via interactions in the same set of brain regions (Fig. 1b). Specifically, to address the second issue, we tested the above two possibilities regarding regional versus global changes in connectivity along with the spectral fingerprint hypothesis. To directly test these ideas, we employed electrocorticographical (ECoG) recordings in patients undergoing clinical monitoring, focusing on three areas that have been strongly implicated in past studies as being central to episodic memory: parahippocampal gyrus (PHG, which serves as a gateway to the hippocampus5,33), see Online Methods), parietal cortex and lateral prefrontal cortex (Supplementary Fig. 1). We compared low-frequency (1–10 Hz) phase synchronization between these regions, which we term the retrieval network, as patients performed a task requiring both spatial layout and temporal order memory retrieval (Fig. 1c–e, Supplementary Table 1 and Online Methods). By measuring whether retrieval manifested as changes in connectivity
between specific regional hubs, manifested as changes in global connectivity or was best characterized by specific changes in spatio-temporal dynamics, we were able to directly test these different theoretical models regarding the neural basis of episodic memory.

RESULTS
Evaluation of simultaneously recorded ECoG signals revealed prominent low-frequency phase consistency between PHG and specific subregions of parietal and prefrontal cortex (Fig. 2a,b and Supplementary Figs. 2 and 3) when patients accurately retrieved spatiotemporal contextual information. On individual electrode pairs, correct context retrieval was accompanied by increases in PHG-parietal and PHG-prefrontal pairwise phase consistency (PPC) beginning at the onset of retrieval (Fig. 2c,d, Supplementary Fig. 4 and Online Methods). Similar findings were also evident at the population level; we found significantly ($P_{\text{FWE}} < 0.05$) increased low-frequency PPC during correct retrieval across the network, for instance, between PHG-parietal (PHG–inferior parietal lobule (IPL); Fig. 2e) and PHG-prefrontal (PHG–middle frontal gyrus (MFG); Fig. 2f) recordings (Supplementary Fig. 5 and Online Methods). Control analyses examining individual electrode raw traces (Supplementary Figs. 2 and 3) and regional power modulations (Supplementary Fig. 6) revealed that oscillatory power typically increased following cue onset. This regional increase in oscillatory power, however, was not condition specific (Supplementary Fig. 6), suggesting that these PPC changes could not be accounted for by regional power changes alone (Supplementary Figs. 5 and 6).

Network connectivity during correct and incorrect retrieval
To evaluate coherent phase interactions globally across the brain, we adopted a graph theoretic approach\(^\text{34}\). We treated each subregion (for example, MFG, IPL and PHG) as a node in a network that was functionally connected via phase synchronization at a given time and frequency (Fig. 3 and Online Methods). We found the greatest PHG connectivity in the low-frequency (1–10 Hz) band ($\chi^2(3) = 70.48, P < 0.0001$; Fig. 4a and Supplementary Fig. 7), consistent with previous findings that have suggested that MTL networks operate preferentially in the delta-theta band\(^\text{31,35,36}\). Thus, we restricted subsequent analyses to the low-frequency band. We found significantly more interregional pairs (henceforth referred to as network edges) that showed significant task-related low-frequency PPC increases during correct retrieval than during incorrect retrieval at every frequency up to 9 Hz (all $\chi^2(1) > 12.93$, all $P < 0.0008$; Fig. 4b,c). This finding held true when we compared the distribution of connectivity between conditions at each frequency band across subregions (each $\chi^2(6) > 98, P < 0.0001$) and for each subregion across 1–9-Hz frequency bands ($\chi^2(8) > 100, P < 0.0001$). It was also robust to comparisons between nearly all subregions and frequencies.
Figure 2 PHG-parietal and PHG-prefrontal phase synchronization during correct contextual retrieval. (a,c,e) PHG and IPL phase synchronization during correct context retrieval. (b,d,f) PHG and MFG phase synchronization during correct and incorrect retrieval. (a) PHG and IPL raw ECoG traces from patient 3 during a single correct retrieval trial. The x axis corresponds to that shown in (b). PHG and MFG raw ECoG traces recorded from patient 3 during a single correct retrieval trial. Electrode locations for traces shown in a and b are localized in Supplementary Figure 1. (c) PPC difference map for correct versus incorrect trials for the pair shown in a. Warmer colors indicate greater phase synchronization during correct retrieval. (b) Mean PPC difference between correct and incorrect retrieval across all PHG and IPL pairs (n = 39). Dashed black boxes indicate significant differences between conditions (P_{fwe} < 0.05, Online Methods). (f) Mean PPC difference between correct and incorrect retrieval across all PHG and MFG pairs (n = 125, significance testing identical to e). Additional raw trace examples for the pairs shown in a and b are shown in Supplementary Figures 2 and 3.

Figure 3 Memory-related network construction: methods for characterizing frequency and condition specific memory networks. (a) PPC values are pooled along the four dimensions of time, frequency, pair type (that is, MFG and PHG, etc.) and number of electrode pairs (data not shown) for correct and incorrect trials. Comparing PPC during correct versus incorrect retrieval and thresholding the resulting t values (black boxes, P < 0.05, based on bootstrap resampling procedure) provided the time points at which specific interregional pairs showed significant PPC differences for a given frequency and condition. (b) Example connectivity map at 8 Hz for correct retrieval, with black boxes showing significant edges, overlaid on the average correct minus incorrect PPC difference map. IFG, inferior frontal gyrus; PCN, precuneus; SPL, superior parietal lobule. (c) Color bar showing the total number of significant differences between conditions in the 0–2,000-ms interval computed for each pair type. (d) Network topology at three different time windows (orange asterisks in b) for the 8-Hz correct retrieval networks. Green lines indicate a significant difference between conditions. (e) Cumulative edges in three time windows for the 8-Hz correct retrieval network. Color scale identical to that shown in c.

individually (binomial tests, P < 0.05; Fig. 4b,c). Thus, rather than discrete switches in regional specificity in the network during correct versus incorrect retrieval or changes in preferred frequency, our findings suggest instead that network connectivity increases globally during correct versus incorrect retrieval processes across these low frequencies (Fig. 4b,c).

Despite overall increases in connectivity across the retrieval network during correct memory retrieval, specific subregions could act
as hubs; that is, some subregions showed greater levels of connectivity compared with other subregions. To address this, we measured node degree, the total number of connections a node has with all other nodes. Following previous work, we determined whether there were hubs in the network on the basis of the distribution of node degree being different than a uniform network; a hub was then defined to be the node showing the highest degree of connectivity. We found that node degree varied significantly compared with

Figure 4 Correct and incorrect memory networks. (a) Total number of PHG connections in each condition as a function of four equal-sized frequency bins. The black dashed line indicates type I error rate. (b) Total number of connections, expressed as percent connectivity, between nodes for the correct versus incorrect retrieval networks at 3, 5 and 8 Hz. Warmer colors indicate greater connectivity and the radius of each node shows the relative number of connections for that frequency and condition in a specific network; thus, node radius is not directly comparable between networks. (c) Node degree, expressed as percent connectivity, in the correct (top) and incorrect (middle) retrieval networks for each frequency. Total network connectivity for the correct and incorrect networks is shown below.

Figure 5 Frequency-specific synchronization during correct spatial and temporal context retrieval. (a–c) MFG and PHG phase synchronization during correct spatial and temporal retrieval. (a) Raw ECoG traces from patient 2 during a single spatial correct retrieval trial (top) and a single temporal correct retrieval trial (bottom). Electrode locations are shown in Supplementary Figure 1. (b) PPC difference map between correct spatial and temporal trials for this pair. Lighter and darker colors indicate more phase synchronization during correct spatial retrieval and temporal retrieval, respectively. (c) Data are presented as in (e) for the temporal retrieval network. (d–i) Correct and incorrect retrieval networks in the 1–4-Hz and 7–10-Hz frequency bands.

(1–4 Hz) Data are presented as in (e) for the temporal retrieval network. (g–j) Correct spatial and temporal retrieval networks in the 1–4-Hz and 7–10-Hz frequency bands. (k) Average peak frequency for the spatial and temporal networks averaged across all PHG-frontal and PHG-parietal pairs represented separately for each patient using different colors. The black line indicates the mean across subjects. Error bars indicate the s.e.m. across pairs.
network connectivity during spatial and temporal retrieval

Our behavioral task involved retrieving both the location of an item and the spatial layout and its temporal order relative to other items (Online Methods). Thus, we were able to evaluate differences across identical patients, recording zones and visually identical experimental procedures (differing only on remembering spatial versus temporal information) during retrieval of spatial or temporal contexts (Fig. 1c–e). We then evaluated whether this led to changes in inter-regional connectivity, global connectivity or frequency-specific differences in connectivity (Fig. 1a,b). Our findings primarily support the third possibility (Fig. 5). Phase coherent oscillations in the raw trace were visually evident in a lower frequency band during spatial retrieval trials compared with temporal retrieval (Fig. 5a); this difference was also evident in comparisons at the patient (Fig. 5b) and population levels (Fig. 5c; statistical methods identical to those in Fig. 2e,f).

Using our graph theoretic approach, we also found that these behavior-specific and frequency-dependent phase interactions were present across the network. Comparing node connectivity overall in the network, we observed significantly greater connectivity between nodes during spatial retrieval compared with temporal retrieval from 1–4 Hz (all \( \chi^2(1) > 14.61, \) all \( p < 0.0002; \) Fig. 5d,g–j). In contrast, we observed significantly greater connectivity between nodes during temporal compared with spatial retrieval from 7–10 Hz (7–8 Hz, \( \chi^2(1) > 16.5, \) \( p < 0.0001; \) 9–10 Hz, \( \chi^2(1) > 4.1, \) \( p < 0.05 \)). For spatial retrieval, six of seven nodes showed greater functional connectivity in the 1–4 Hz band than in the 7–10 Hz band (\( \chi^2 \) test between bands, all \( \chi^2(1) > 9.13, \) all \( p < 0.003 \); Fig. 5e). In contrast, during temporal retrieval, six of seven nodes showed differential connectivity in the 7–10 Hz band (all \( \chi^2(1) > 11.3, \) all \( p < 0.001 \); Fig. 5f). We confirmed a lower preferred frequency during spatial retrieval both across subjects (\( t_5 = 2.44, \) one-tailed \( p = 0.029; \) Fig. 5k) and across electrode pairs (\( t_{644} = 4.43, \) \( p < 0.000001 \)). These findings indicate that the retrieval network resonates at a lower frequency overall during spatial compared with temporal retrieval.

Despite these differences in the preferred frequency in which connectivity manifested, the PHG node again showed the highest degree of connectivity compared with any other node during both spatial and temporal retrieval (Fig. 5e,f). During spatial retrieval, PHG showed the greatest connectivity in the 1–4 Hz band (Fig. 5g), whereas, during temporal retrieval, PHG showed the greatest connectivity in the 7–10 Hz band (Fig. 5j). During spatial retrieval, we found that the PHG node connections were primarily clustered with superior frontal gyrus (SFG), MFG and precuneus (\( \chi^2(5) = 32.63, \) \( p < 0.00001; \) Fig. 5g), and there was significantly more PHG connectivity with these nodes in the 1–4 Hz band than in the 7–10 Hz band (\( \chi^2(5) = 208.65, \) \( p < 0.00001 \)). In contrast, during temporal order retrieval, PHG connections were preferentially clustered with SFG, MFG and IPL (\( \chi^2(5) = 19.09, \) \( p < 0.002; \) Fig. 5j) and there was significantly more PHG connectivity with these nodes in the 7–10 Hz band than in the 1–4 Hz band (\( \chi^2(5) = 78.58, \) \( p < 0.00001 \)). These differences amounted to a significant condition (spatial versus temporal) by frequency (1–4 Hz versus 7–10 Hz) interaction (\( \chi^2(1) > 14.6, \) \( p < 0.0002 \)).
versus 7–10 Hz) interaction in PHG connectivity (Fisher’s exact test, \( P < 0.00001 \)). Follow-up analyses separately assessing the spatial correct versus spatial incorrect and temporal correct versus temporal incorrect networks revealed similar results as those directly contrasting spatial correct versus temporal correct (Supplementary Fig. 8). These findings suggest that retrieving spatial layout versus temporal order information from an episode is characterized primarily by frequency-specific interactions across the retrieval network. Just as in our earlier analyses, however, PHG had the highest degree of connectivity in the network compared with any other node, indicating that it is central to both spatial and temporal retrieval.

We also evaluated whether spatial and temporal retrieval were characterized by changes in timing of connectivity in their preferred frequencies. For all pairwise combinations of regions in the network, we calculated the connectivity map for the two different conditions based on a matrix of spatial versus temporal PPC difference scores at 2 Hz (Fig. 6a) and 8 Hz (Fig. 6b). During spatial retrieval, significantly more connectivity occurred early (0–1 s), whereas, during temporal retrieval, significantly more connectivity occurred late (1–2 s) (Fisher’s exact test, \( P < 0.0001 \); Fig. 6c,d). Visual inspection of the matrix of network connectivity revealed that spatial and temporal retrieval were also characterized by different clustering of connectivity across regional pairs (Fig. 6a,b and Supplementary Movies 1 and 2). We confirmed this impression by computing the Phi correlation coefficient of binary connections over time (Online Methods), with higher correlation coefficients indicating a more coherent pattern of activity across the entire network and lower correlation coefficients indicating a less coherent pattern of activity across the network. The distribution of correlation coefficients differed between spatial and temporal retrieval (Kolmogorov-Smirnov test, \( P < 0.0001 \); Fig. 6e) and the connectivity in the 2-Hz spatial network was significantly more clustered in time than the 8-Hz temporal network (\( t \text{ test} (189) = 5.77, P < 0.0001 \); Fig. 6f). Critically, however, these two networks did not differ in their total number of connections (\( \chi^2(1) = 0.81, P = 0.37 \); Fig. 5d), we found similar results at adjacent frequencies (Supplementary Fig. 9a), and these findings could not be accounted for by the expected increase in temporal autocorrelation at lower frequencies (Supplementary Fig. 9b). These results confirm that the connectivity during spatial and temporal retrieval, in addition to being characterized by different resonant frequencies, also display differences in the pattern of connectivity over time.

Finally, our results could not be accounted for by poor patient performance or a difference in performance between spatial and temporal retrieval. Patients performed significantly above chance (\( t_5 = 3.58, P = 0.015 \)) and showed similar reaction times in both the spatial and temporal tasks. Neither accuracy (\( t_5 = -0.56, P = 0.59 \)) nor reaction time (\( t_5 = -1.00, P = 0.35 \)) differed between the spatial (71% accuracy, 7.57-s median reaction time) and temporal (76% accuracy, 8.99-s median reaction time) retrieval conditions. Our results were also robust at more stringent statistical thresholds (\( P < 0.001 \); Supplementary Fig. 10).

DISCUSSION

We sought to determine the functional network interactions among brain regions that have been implicated in successful episodic memory retrieval and to determine how multiple contextual representations characterizing an episode were retrieved in this network. We tested three fundamental theoretical models to determine whether one, or a combination thereof, best characterized the neural basis of episodic memory retrieval. These included a model in which a single brain region acted as a hub for mediating episodic memory retrieval, a model in which interactions were distributed equally across nodes, but changed for successful retrieval or retrieval of different contexts, and a model in which changes in spectrotemporal dynamics mediated memory retrieval (Fig. 1). Our first set of analyses compared correct versus incorrect context retrieval, collapsing across spatial and temporal retrieval trials. We found that successful memory retrieval was characterized by increases in network functional connectivity via phase synchronization across the 1–10-Hz low-frequency band. PHG electrodes showed the highest degree of interconnectivity with other electrodes compared with any other subregion in the retrieval network, and this functional connectivity preferentially occurred in the 1–10-Hz band. The macro-electrodes located over the PHG likely captured signals from posterior parahippocampal, perirhinal and entorhinal cortices (Online Methods), all of which provide direct input to the hippocampus5,33,37, suggesting that the hippocampus also participated in these interactions. Overall, although our findings of increased network connectivity during correct versus incorrect context retrieval support the idea of global, rather than regionally specific, changes in connectivity (Fig. 1a), the differentially enhanced PHG connectivity that we observed supports the idea that the MTL acts as a hub in these interactions (Fig. 1a). Thus, our results support a hybrid of the two models shown in Figure 1a, suggesting that successful memory retrieval is best characterized by an overall increase in interactions across key brain regions mediated primarily by the MTL. To the best of our knowledge, this has not been demonstrated previously with invasive human recordings that can pinpoint and disambiguate activity simultaneously across multiple brain regions.

Our results also emphasize the importance of phase-synchronized oscillations between these disparate brain regions as important to memory retrieval. Together with studies examining episodic encoding28 and working memory39,40, our results, which were obtained during retrieval, suggest that phase coding may be a mechanism that is involved in an array of human memory processes. Previous proposals19,25,41 have suggested that synchronized oscillations may facilitate precisely timed depolarizations between neurons in communicating brain regions. This idea is supported by the observation in humans27,28, rats20 and monkeys29 that oscillations coordinate both local and distant neuronal activity. Furthermore, an influential theoretical model of memory retrieval, multiple trace theory (MTT)17, argues that cortical areas represent features bound to experience-specific contextual representation in the hippocampus, whose successful interaction underlies memory retrieval. Thus, our results provide evidence for a possible neural mechanism underlying MTT, namely, coordinated low-frequency oscillations between the medial temporal lobe and cortical areas.

Taken together, our results yield a potentially new perspective on previous findings regarding the importance of MTL, parietal cortex and prefrontal cortex in mediating successful episodic memory retrieval. Several functional magnetic resonance imaging (fMRI) studies have found increased parietal cortex activation during episodic retrieval tasks1–3,10,11, yet lesions to this area in human patients do not consistently impair episodic memory10. Similarly, prefrontal cortex activation is often a hallmark of successful memory retrieval, yet prefrontal cortex lesions produce nuanced impairments in episodic memory retrieval8. For example, prefrontal cortex lesions affect free, but not cued, recall and are thought to affect executive processes, but not retrieval of memory traces, specifically9. In contrast, fMRI studies have consistently shown hippocampal and parahippocampal activation during correct recollection of specific contextual details2,3, and hippocampal lesions in particular markedly impair recollection and episodic memory7,42. Thus, our results suggest that, although
lateral prefrontal and parietal areas communicate with the MTL during spatiotemporal retrieval, the MTL acts as a critical convergence hub during successful context retrieval, broadly consistent with MTT. One possible interpretation of our results is that the MTL serves as the primary locus for indexing particular memory traces, with parietal and lateral prefrontal cortex interacting with the MTL to facilitate and augment memory trace retrieval.

Epilepsy is a disease marked by impaired episodic memory performance and increased synchronized activity of large numbers of neurons, which may manifest as low-frequency phase synchronization. Do these factors confound our results? We believe several considerations weigh against this possibility. First, electrodes showing ictal and interictal discharge were systematically removed from our analysis based on evaluation by our clinical team. All analyzed trials were visually inspected for artifacts related to epilepsy. Second, disease-related low-frequency phase synchronization is likely to impair brain function and may interfere with accurate memory retrieval. Thus, we would expect more low-frequency phase coherence during incorrect compared with correct retrieval if ictal discharge alone accounted for our results, which is inconsistent with our findings. Third, it seems unlikely that epileptic activity would manifest itself as task-related (spatial versus temporal) differences. Finally, we used a metric of phase synchronization that excluded phase differences centered around 0 degrees (Online Methods) to eliminate possible effects of volume conduction and any remaining epileptic synchronization. We note that this also excludes ‘true’ zero-phase lag synchronization (increasing type 2 error), but provides a more conservative estimate of interregional coupling. Although we observed increases in phase synchronization, this does not imply or require direct anatomical connectivity between areas, and is instead taken primarily as a measure of functional connectivity. In summary, we have made every available effort to account for possible confounds while still capitalizing on the increased spatiotemporal resolution afforded by direct human brain recordings. Thus, we believe that our results, which provide insight into the dynamic networks underlying spatiotemporal episodic memory, would generalize to the population if these issues could be studied noninvasively.

Our behavioral task also allowed us to compare retrieval of two different fundamental components of episodic memory, spatial and temporal context. Our results suggest that correct retrieval of the location of an item involves lower frequency interactions compared with correctly retrieving the order in which an item occurred relative to other items. Although we again found that correct retrieval was characterized by higher degrees of connectivity compared with incorrect retrieval for the two processes separately (Supplementary Fig. 8), the overall level of connectivity did not differ between spatial versus temporal retrieval (Fig. 5d). We also found differences in regional connectivity during spatial (PHG-SFG-MFG-precuneus) versus temporal (PHG-SFG-MFG-IPL) retrieval, with the critical difference being the subregions of parietal cortex engaged. Thus, our findings primarily support the spectral fingerprint hypothesis (Fig. 1b), with some regional specificity in parietal cortex (Fig. 1a), but no clear differences in overall connectivity (Fig. 1b). Because PHG acts as a hub for interactions in both cases, our results suggest that spatial versus temporal retrieval involves similar degrees of connectivity with the MTL. In a previous fMRI study using a similar behavioral task, we found similar degrees of hippocampal activation during spatial and temporal retrieval along with greater activation in precuneus during a contrast of spatial versus temporal retrieval, and, in another study, greater functional connectivity between hippocampus and precuneus during spatial retrieval. Other studies have also implicated parts of inferior posterior parietal cortex in temporal processing. Notably, however, many of the same regions in lateral prefrontal, MTL, and parietal cortex remained substantially connected in both networks. Thus, the most salient differences between the networks for retrieval of spatial versus temporal context, in contrast to our findings with correct versus incorrect retrieval, was the sprectotemporal dynamics at which the two networks operated, again consistent primarily with the spectral fingerprint hypothesis (Fig. 1b).

Thus, our results provide a new basis for resolving the question of how multiple contexts underlying an episode can be stored and retrieved in the same network of brain regions. Behaviorally, a spatial layout can be treated as a map, and, thus, a coherent entity overall, and, once well learned, can in principle be loaded and accessed quickly. We found that correct spatial retrieval was characterized by lower frequency interactions overall across the network along with early and prolonged increases in functional connectivity across the network compared with temporal order retrieval. In contrast, remembering temporal order information involves traveling back in time to retrieve different temporal contexts, which would necessitate active comparison of each element in the sequence with the item to be compared. We found that temporal order retrieval was characterized by faster frequency interactions, a more delayed increase in network connectivity and less overall coherence in time across the network compared with spatial retrieval. Although somewhat speculative, these explanations provide possible insight into differences in how the brain is able to process aspects of space and time during memory retrieval. Specifically, our data lend support to the concept of spectro-temporal multiplexing as a means to store and retrieve spatial and temporal context information encoded among neurons in the same regions. Thus, our results provide a possible mechanism by which spatial and temporal context information, which are thought to underlie episodic memory, could be retrieved simultaneously. In our study, however, patients retrieved spatial and temporal context on separate trials, and it is not necessarily the case that the dynamics will be identical, for example, when spatial and temporal context are retrieved simultaneously, an issue future studies will need to address. Notably, a previous study during memory encoding identified frequency-specific differences in spike-field coherence in the low-frequency band that predicted later retrieval, raising the possibility that spectro-temporal multiplexing is a general feature in episodic memory processes.

By employing direct intracranial recordings and a graph theoretic approach, our study provides a new perspective on how the human brain processes episodic memories. Our data provide support for models that emphasize global network interactions and frequency-specific connectivity, rather than regionally mediated activity alone, as being central to how we recover spatial and temporal memories associated with recent experiences. Our results argue for the importance of carefully timed dynamics across multiple brain regions for spatiotemporal memory retrieval.

METHODS

Methods and any associated references are available in the online version of the paper.

Note: Supplementary information is available in the online version of the paper.

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AUTHOR CONTRIBUTIONS
A.D.E., N.T. and A.J.W. designed the experiment. N.T., C.C. and T.P. collected the data. A.J.W. performed the data analysis. A.J.W., A.D.E. and N.T. wrote the manuscript.

COMPETING FINANCIAL INTERESTS
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ONLINE METHODS

Patient electrophysiology. Six adult patients with medically refractory epilepsy underwent ECoG to localize seizures and participated in the study after providing informed consent approved by the University of Texas Medical School at Houston committee for the protection of human subjects. Electrophysiological methods and electrode localization were similar to those described previously48. In brief, subdural circular platinum-iridium electrodes with a top hat design (4.5-mm overall diameter, 3-mm cortical contact, 10-mm interelectrode distance) were implanted and placed solely on the basis of clinical considerations using standard techniques49. Electrode localization was verified by co-registering a post-operative CT image with a pre-operative MRI structural image. Lobar and gyral labels were assigned by an expert in human neuroanatomy (N.T.). Electrodes showing epileptiform activity based on neurologists evaluation were excluded from all analyses.

ECoG signals were sampled at 1,000 Hz using Nihon Kohden NeuroFax software with a recording bandwidth from 0.15 to 300 Hz. Signals were referenced to a common average consisting of all non-ictal electrodes over lateral frontal and lateral temporal areas to minimize the effect of the referencing scheme on synchronization measures50. Recordings were then imported into Matlab (MathWorks) for post-processing.

Behavioral task. Patients played a virtual-taxi game similar to that used previously24 with a few exceptions that were necessary to accommodate the clinical environment. The virtual environment consisted of five stores spaced irregularly and arranged in a circle (Fig. 1d). Patients performed multiple blocks of navigation in which they picked up a passenger in the center of the environment and delivered them to a specific store (Fig. 1c). This involved freely navigating the environment with a fixed order of visits to stores. Both the spatial layout of the environment and the delivery order were independent of each other24 and maintained across blocks to subsequently test spatial layout and temporal order memory.

Following each block of navigation, patients performed interactive training emphasizing the spatial layout as a two-dimensional array and the temporal order of visits to stores as a one-dimensional sequence in time (Fig. 1d). Interim testing was performed to emphasize the different characteristics of the spatial layout and temporal order of deliveries and to ensure that the patient had sufficient knowledge to accurately perform the final retrieval session. Interim testing involved the patient localizing each store onto a grid of the virtual environment viewed from an overview perspective or on a timeline corresponding to the delivery order to stores (Fig. 1d). The patient then viewed the correct answers displayed for 10 s separately for the spatial layout and the temporal sequence. The order of interactive training (spatial or temporal) was randomized following each block of navigation. Patients continued to perform multiple rounds of navigation and interactive training until they achieved either 100% accuracy on both spatial and temporal questions for two consecutive rounds or had completed eight rounds of navigation and interactive training.

During the final retrieval session (Fig. 1e), which forms the basis of these results, patients performed a block of spatial retrieval and a block of temporal retrieval trials, the order of which was counterbalanced across patients. The patient was provided with an image of the cue storefront along with two additional storefronts to choose from. The environment was arranged such that no two stores were ever the same distance apart. This generated 30 different possible unique trials for the spatial condition. During spatial retrieval trials, the patient was instructed to indicate which of the two stores was closer to the cue store in virtual space. For the temporal condition, we designed questions with the constraint that the choice stores either preceded or followed the reference store in time. This generated a total of 40 possible unique trials for the temporal condition. During temporal order retrieval trials, the patient indicated which of the two stores was closer to the cue store in delivery order. The numbers of trials analyzed for each patient in each condition are shown in Supplementary Table 2. One patient was excluded from the correct versus incorrect analysis because they lacked sufficient incorrect responses. Responses for all portions of the task described were subject patched to accommodate patient needs and the clinical testing environment; we therefore analyzed the fixed 2-s interval associated with cue onset during which subjects were instructed to begin retrieving from memory. We did this because we hypothesized that changes in activity related to retrieval would reliably occur immediately after cue onset, consistent with previous studies50. The onset of the each trial was jittered uniformly from 1 to 1.5 s following subject response.

Phase synchronization estimation. All analyses used EEGLab53 and custom-written code in Matlab. Raw EEG signals from the spatial and temporal retrieval session were extracted for both correct and incorrect responses from 1 s before to 2.2 s following cue onset in order to remove edge effects associated with spectro-temporal decomposition. Our primary behavioral contrasts were correct (spatial correct and temporal correct) versus incorrect (spatial incorrect and temporal incorrect) and spatial correct versus temporal correct. Phase synchronization estimates were computed between each pairwise combination of PHG (consisting of parahippocampal, perirhinal and entorhinal cortices), prefrontal (superior and middle frontal gyrus, pars triangularis) and parietal electrodes (superior and inferior parietal lobule, precuneus) for each condition and Table (Supplementary Table 1). Phase estimates were obtained using a Hanning tapered fixed window length fast-Fourier transform at 27 time points using the EEGLab newcross function from 2 to 1,943 ms relative to cue onset and at ten logarithmically spaced frequencies from 0.97 to 9.76 Hz. Frequencies were subsequently rounded to the nearest whole number. For analyses assessing phase synchronization to 200 Hz (Fig. 4a and Supplementary Fig. 7), we sampled a total of 40 logarithmically spaced frequencies such that each of the four frequency bins (1–10 Hz, 11–40 Hz, 40–100 Hz and 100–200 Hz) contained ten sampled frequencies.

We estimated phase synchronization between electrode pairs at the above times and frequencies using the PPC index to address issues associated with differing trial numbers between conditions53. Briefly, the PPC index for an electrode pair was estimated by first computing the relative phase angle difference between signals on each trial. The cosine was then computed between all pairwise (that is, between trials) combinations of relative phases, and the PPC was taken as the mean of these cosine values. PPC values range from −1 to 1, with positive values indicating phase synchronization. We accounted for potential volume conduction confounds, which may artificially inflate phase synchronization estimates, by removing relative phases at 0 degrees ± 5 degrees before calculating the PPC index. We note that using standard phase coherence estimates or PPC estimates that included zero–phase synchronization did not qualitatively change our primary findings.

Network construction and statistical analysis. We used graph theoretic measures54 to determine how functional interactions varied over time, frequency and brain subregion. We considered a functional connection (that is, edge) to exist between two subregions (nodes) if there was a significant (bootstrap corrected P < 0.05, one-tailed paired t-test to test directionality) difference between conditions across all electrode pairs. Specifically, we compared PPC for one condition against a different condition across interregional electrode pairs, pooled across patients, and the degrees of freedom were therefore the total number of electrode pairs in a comparison. To account for issues related to multiple comparisons and to maintain a fixed type 1 error rate of 5%, we estimated the distribution of t values and shuffled the condition labels 1,000 times before recomputing test statistics; observed t values greater than the 95th percentile of this distribution were considered to be significant and were noted as significant connections (edges) in the network. This procedure was repeated separately at each time bin and at each frequency point (Fig. 3). We then computed three basic measures of network connectivity. To assess the connectivity of a single node, we computed the total number of connections between a given node and all other connected nodes over time (0–2,000 ms). We defined this to be node degree. To determine the relative strength of functional interactions between two nodes (Fig. 3c), we computed the total number of connections between those two nodes over time. Finally, we summed all connections in the network at a specific frequency over time, providing a frequency-specific measure of global functional interactions in the network. These measures were used for statistical testing (below) and were then converted to a percent connectivity measure. Percent connectivity was defined as the number of observed edges out of the total number of possible edges (accounting for the number of time, frequency and interregional pairs sampled). Follow-up analyses using a more stringent bootstrap alpha of 0.001 (Supplementary Fig. 10) were consistent with our primary findings.

In a random network, edges are uniformly distributed amongst nodes such that connectivity should not vary across regional pairs or frequencies51. Statistical analyses therefore employed χ² tests to compare the distribution of edges and total number of connections for each node in the actual network against the null hypothesis that edges and number of connections were uniformly distributed.
To assess if edges were more clustered in time in the 2-Hz spatial or 8-Hz temporal networks, for each interregional pair, we extracted a binarized edge map, in which a 1 indicates a connected pair at a given time point and 0 indicates a lack of a connection. Binary vectors for each combination of interregional pairs (20 interregional pairs chosen two at a time, \( n = 190 \) pairs total) were then correlated using the Phi correlation coefficient, resulting in a distribution for each network. Differences between these distributions were assessed using a two-sample Kolmogorov-Smirnov test and additionally using paired \( t \) tests. Follow-up analysis estimated the ‘chance’ correlation by generating 1,000 randomly seeded networks (matched for total number of edges in the 2-Hz and 8-Hz network using Monte Carlo simulations), re-calculating the mean Phi correlation across pairs, and extracting the 95th percentile of this distribution.

Statistical significance in our basic population analyses of task–related differences in PPC (Figs. 2e,f and 5c; numbers of pairs for each comparison are shown in Supplementary Table 1) used family-wise error correction, with \( P_{\text{fwe}} = 0.05 \) (ref. 53). This corresponded to four contiguous time–frequency points, each individually significant with a one-tailed paired \( t \) test at \( P < 0.005 \). We note that the most significant time–frequency points held up to thresholding without cluster correction to at least \( P < 0.00001 \).

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