Directional coupling of slow and fast hippocampal gamma with neocortical alpha/beta oscillations in human episodic memory

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Episodic memories hinge upon our ability to process a wide range of multisensory information and bind this information into a coherent, memorable representation. On a neural level, these 2 processes are thought to be supported by neocortical alpha/beta desynchronization and hippocampal theta/gamma synchronization, respectively. Intuitively, these 2 processes should couple to successfully create and retrieve episodic memories, yet this hypothesis has not been tested empirically. We address this by analyzing human intracranial electroencephalogram data recorded during 2 associative memory tasks. We find that neocortical alpha/beta (8 to 20 Hz) power decreases reliably precede and predict hippocampal “fast” gamma (60 to 80 Hz) power increases during episodic memory formation; during episodic memory retrieval, however, hippocampal “slow” gamma (40 to 50 Hz) power increases reliably precede and predict later neocortical alpha/beta power decreases. We speculate that this coupling reflects the flow of information from the neocortex to the hippocampus during memory formation, and hippocampal pattern completion inducing information reinstatement in the neocortex during memory retrieval.

Significance

Episodic memories detail our personally experienced past. The formation and retrieval of these memories have long been thought to be supported by a division of labor between the neocortex and the hippocampus, where the former processes event-related information and the latter binds this information together. However, it remains unclear how the 2 regions interact. We uncover directional coupling between these regions, with power decreases in the neocortex that precede and predict power increases in the hippocampus during memory formation. Fascinatingly, this process reverses during memory retrieval, with hippocampal power increases preceding and predicting neocortical power decreases. These results suggest a bidirectional flow of information between the neocortex and hippocampus that is fundamental to the formation and retrieval of episodic memories.


The authors declare no competing interest.

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object, a face, and a scene. During retrieval, participants are presented with a life-like dynamic stimulus (either a video or sound) and a subsequent verbal stimulus. During retrieval, participants are presented with verbal stimuli and are asked to retrieve the associated face and scene. Electrophysiological analysis was conducted during the presentation of the verbal stimulus at encoding and retrieval (blue outline). (E) Plot of each electrode location (Left; red represents hippocampal electrode; blue represents the ATL). Bar plot (Right) depicts the number of electrodes for each participant.
processing (37)]. Foreshadowing the results below, we show that ATL alpha/beta power decreases precede hippocampal fast gamma power increases during successful memory formation, and that hippocampal slow gamma power increases precede ATL alpha/beta power decreases during successful memory retrieval.

**Results**

**Behavioral Results.** Participants, on average, recalled 47.9% of all pairs in the first task, a percentage much greater than what would be expected by chance (25%). When breaking trials down by modality, participants recalled 52.7% of video-word pairs and 45.9% of sound-word pairs. An independent-samples t test (only a subset of participants completed both variants of the task) revealed no significant difference in memory performance for video-word and sound-word pairs (\( P > 0.5, d = 0.275 \)). As there was no apparent difference in memory performance between the 2 trial types and electrode contacts were not located in anatomical regions that should respond uniquely to one of these sensory modalities, trials involving video-word and sound-word pairs were combined for all further analyses. In the second task, participants recalled both associated items on 66.2% of trials—a percentage much greater than what would be expected by chance (16.7%; where the probability of selecting the first item correctly is 50% and the probability of selecting the second item correctly is 33%, making the joint probability 50% × 33% ≈ 16.6%).

**Distinct Oscillatory Signatures Exist in the Neocortex and Hippocampus.** We first sought to empirically define the peak frequencies in our 3 ROIs. Broadband spectral power (1 to 100 Hz) was computed using 5-cycle wavelets across a 1,500-ms window starting at the onset of the verbal stimulus (at encoding and retrieval). The data were then z-transformed across trials to facilitate comparison across participants, and the 1/f component was subtracted from the data (38–40) to attenuate broadband noise (see Methods for details). Subsequently, the resulting power spectra were collapsed over time and trials, and split into hippocampal and neocortical ROIs. Across participants, a slow-theta peak could be observed in the hippocampus at ~2.5 Hz and an alpha/beta peak could be observed in the 2 neocortical regions between 8 and 20 Hz (Fig. 2A). We defined the peak frequency of each ROI for each participant individually and conducted all subsequent analyses on these peak frequencies (see SI Appendix, Table S1 for individual peak frequencies).

**Distinct Hippocampal Gamma-Band Frequencies Underlie Encoding and Retrieval Processes.** We then investigated whether distinct gamma-frequency bands support encoding and retrieval processes (7, 31). To test this, the broadband hippocampal gamma power (30 to 100 Hz) for successfully remembered pairs at encoding and retrieval was calculated and contrasted in a group-level, nonparametric permutation test. Fast hippocampal gamma frequencies (60 to 80 Hz) exhibited significantly greater power during encoding, relative to retrieval, trials (60 to 70 Hz, \( P_{\text{fdr}} = 0.001, d = 1.308; 70 to 80 Hz, P_{\text{fdr}} = 0.020, d = 0.947; \text{Fig. 2B–E} \)). In contrast, slow hippocampal gamma frequencies (40 to 50 Hz) exhibited greater power during retrieval, relative to encoding trials (\( P_{\text{fdr}} = 0.023, d = 0.754 \)). No significant difference between encoding and retrieval could be observed during the epochs of forgotten stimuli (SI Appendix, Fig. S1). Peak fast and slow gamma frequencies for each participant were derived from the “encoding vs. retrieval” contrast and used in all subsequent analyses (see Methods for details; see SI Appendix, Table S1 for individual peak frequencies). These findings suggest that 2 functionally relevant gamma-band oscillations relate to episodic memory formation and retrieval in humans.

To rule out the possibility that the difference in fast/slow gamma was driven by the 1/f slope and/or its removal, the beta weights describing the 1/f slope at encoding and retrieval were extracted and averaged across time, electrodes, and trials. These weights were then contrasted between encoding and retrieval in a group-level, nonparametric permutation test. This test revealed no significant difference in the beta weights for remembered items (\( P = 0.198 \)) or for forgotten items (\( P = 0.246 \)), suggesting the distinction in gamma rhythms between encoding and retrieval was not driven by differences in the 1/f slope.

**Hippocampal Gamma Power Increases Track the Successful Formation and Retrieval of Episodic Memories.** To examine how memory-related fluctuations in fast and slow gamma power differentially contribute to episodic memory encoding and retrieval, we conducted a group-level, nonparametric, permutation-based, 2 × 2 repeated-measures ANOVA that investigated the influence of the factors “gamma frequency” (fast vs. slow) and “memory operation” (encoding vs. retrieval) on memory-related power (remembered > forgotten) collapsed across time. We anticipated an interaction whereby fast gamma selectively supports successful memory formation and slow gamma selectively supports successful memory retrieval. Group analysis revealed a significant interaction (\( P = 0.003, \text{partial } \eta^2 = 0.294; \text{Fig. 2G} \)), indicating that fast and slow gamma exhibited dissimilar memory-related power fluctuations during encoding and retrieval. These results demonstrate that 2 functionally distinct gamma-band oscillations support the successful formation and retrieval of episodic memories in humans.

Analysis of the power time series showed that the opposing effects of fast and slow gamma were particularly prominent during retrieval. When successfully recalling a stimulus, a rapid decrease in fast gamma power was observed (200 to 400 ms, \( P_{\text{fdr}} = 0.025, d = 0.862; \text{Fig. 2F} \)), followed by an increase in slow gamma power (800 to 1,000 ms, \( P_{\text{fdr}} = 0.007, d = 1.177; \text{Fig. 2F} \)), relative to stimuli that were not recalled. Perplexingly, a similar effect was not observed during encoding, even though the time series of the 2 gamma band trends in the correct directions (i.e., an increase in fast gamma and a decrease in slow gamma; Fig. 2F). As will be revealed later, this absence may be driven by the fact that gamma power changes are not time-locked to stimulus onset during encoding but rather the neocortical power decreases that precede hippocampal activity.

**Neocortical Alpha/Beta Power Decreases Track the Successful Formation and Retrieval of Episodic Memories.** We then investigated whether neocortical alpha/beta power decreases accompany the successful encoding and retrieval of episodic memories. Peak alpha/beta power was computed across a 1,500-ms window commencing at stimulus onset. As above, the 1/f characteristic was subtracted, attenuating broadband noise (41, 42). The alpha/beta power was z-transformed across the entire session for each electrode–frequency pair separately, smoothed to attenuate trial-by-trial variability in temporal/spectral responses (Methods), and split into “hits” and “misses” for contrasting. A group-level, nonparametric permutation test revealed a significant decrease in ATL alpha/beta power during encoding (\( P_{\text{fdr}} = 0.035, d = 0.858; 400 to 600 ms after stimulus onset; \text{Fig. 3} \)) for remembered stimuli relative to forgotten stimuli. During retrieval, a group-level permutation test revealed a significant decrease in ATL alpha/beta power (800 to 1,000 ms, \( P_{\text{fdr}} = 0.042, d = 0.777; 1,000 to 1,200 ms, \( P_{\text{fdr}} = 0.039, d = 0.849; \text{Fig. 3} \)) for remembered stimuli relative to forgotten stimuli. These results reproduce earlier findings of neocortical alpha/beta power decreases during the encoding (10–18) and retrieval (19–24) of human episodic memories.

**Hippocampal Gamma Power Increases and Neocortical Alpha/Beta Power Decreases Cooperate during the Encoding and Retrieval of Human Episodic Memories.** So far, we have demonstrated that both neocortical alpha/beta power decreases and hippocampal fast and slow gamma power increases arise during episodic memory processes. Critically, however, the synchronization/desynchronization framework (3) would predict that these 2 markers correlate in
such way that neocortical power decreases precede hippocampal power increases during encoding while hippocampal power increases precede neocortical power decreases during retrieval. Such a hypothesis can be tested through the use of cross-correlation, where the time series of neocortical alpha/beta power is offset relative to the time series of hippocampal gamma power in an attempt to identify at what time lag the 2 time series most strongly correlate. A negative lag indicates that early neocortical signals correlate with late hippocampal signals, while a positive lag indicates that early hippocampal signals correlate with late neocortical signals. Like traditional correlations, a negative correlation (from here on termed “anticorrelation”) indicates an increase in one metric is accompanied by a decrease in the other.

At encoding, we hypothesized that the degree of neocortical power decreases can predict the degree of hippocampal gamma power increases (i.e., a negative lag anticorrelation). On a cognitive level, this would signify information processing within the neocortex preceding representational binding in the hippocampus. The cross-correlation was computed for every trial, and the memory-related difference was calculated by subtracting the mean cross-correlation across remembered trials. By calculating the memory-related difference, any correlation between the 2 time series that is driven by shared noise (originating from a shared reference) is removed, as this reference-related correlation is consistent across remembered and forgotten trials (additional analysis in SI Appendix confirms that shared reference activity does not account for the observed effects reported here). Furthermore, the memory-related difference highlights memory-specific dynamics in neocortical–hippocampal links, rather than general, memory-unspecific connectivity.

In line with our hypothesis, later remembered items showed a significant anticorrelation at a negative lag between ATL alpha/beta power and hippocampal fast gamma power relative to later forgotten items ($P_{fdr} = 0.006, d = 0.961$; see Fig. 4A for a difference line plot). This cross-correlation suggests that alpha/beta power decreases precede fast gamma power increases by ∼100 to 200 ms. No correlation was observed between ATL alpha/beta power and hippocampal slow gamma power at any lag. These results indicate that a unique connection exists between the ATL and the hippocampus during episodic memory formation, where ATL power decreases precede hippocampal fast gamma power increases.

It is worth noting that while the absolute magnitude of the Fisher $z$-transformed correlation coefficients is small, one should exercise caution in interpreting such a value. As we focus on the difference in the ATL–hippocampus cross-correlation for remembered and forgotten items, we only probe the fraction of the total cross-correlation that can be explained by cognition and not that which can be accounted for by numerous undefinable variables (e.g., measurement noise, placing of electrodes, choice of reference, resting connectivity). As such, it is better to consider the variance in cross-correlation across participants. Here, the variance is minimal and hence returns a small $P$ value ($P_{fdr} = 0.906$) and a large effect size ($d = 0.961$), indicating that ATL alpha/beta power decreases precede hippocampal fast gamma power increases reliably across participants.

We then investigated whether this relationship reverses during episodic memory retrieval (i.e., hippocampal power increases precede neocortical power decreases). On a cognitive level, this would represent pattern reinstatement in the hippocampus preceding information reinstatement in the neocortex. To test this, we repeated the cross-correlation analysis in the same manner as above...
for epochs covering the presentation of the retrieval cue and then calculated the memory-related difference by subtracting the mean cross-correlation across forgotten items from the mean cross-correlation across remembered trials. Relative to forgotten items, remembered items showed a significant anticorrelation at a positive lag between ATL alpha/beta power and hippocampal slow gamma power ($P_{\text{unc}} = 0.037$, $d = 0.751$; Fig. 4B), where an increase in hippocampal gamma power preceded a decrease in ATL alpha/ beta power by 200 to 300 ms. No correlation was observed between ATL alpha/beta power and hippocampal fast gamma power at any lags. These results indicate that hippocampal slow gamma power increases precede ATL alpha/beta power decreases during the retrieval of episodic memories—a reversal of the dynamic observed during episodic memory formation.

We then examined how the neocortical–hippocampal dynamics differed between encoding and retrieval. To this end, the subsequent memory effect (SME; remembered minus forgotten cross-correlation at encoding) for ATL alpha/beta power and hippocampal fast gamma power was contrasted with the retrieval success effect (RSE; remembered minus forgotten cross-correlation at retrieval) for ATL alpha/beta power and hippocampal slow gamma power in a group-level, nonparametric, permutation test. This revealed an interaction whereby ATL power decreases preceded hippocampal power increases during encoding ($P_{\text{unc}} = 0.005$, $d = 1.151$; 100 to 200 ms) but hippocampal power increases preceded ATL power decreases during retrieval ($P_{\text{unc}} = 0.025$, $d = 0.855$; 200 to 300 ms) (Fig. 4C). These results support those reported in the previous 3 paragraphs: 1) ATL alpha/beta power decreases precede hippocampal fast gamma power increases during episodic memory formation, and 2) hippocampal slow gamma power increases precede ATL alpha/beta power decreases during episodic memory retrieval.

Lastly, we examined whether the fast gamma effect was specific to encoding and the slow gamma effect was specific to retrieval. To this end, we conducted a nonparametric, permutation-based, 2 × 2 repeated-measures ANOVA (memory operation × gamma frequency), taking encoding-related activity from the −200- to −100-ms time bin and retrieval-related activity from the 200- to 300-ms time bin. Analysis revealed a significant interaction between the 2 factors ($P = 0.001$; partial $\eta^2 = 0.172$). The interaction (as pictured in Fig. 4D) suggests that the hippocampal fast gamma power negatively cross-correlated with ATL alpha/beta power to a greater degree than hippocampal slow gamma power during encoding, while the hippocampal slow gamma power negatively cross-correlated with ATL alpha/beta power to a greater degree than hippocampal fast gamma power during retrieval.

Notably, these effects cannot be explained by any epileptic activity such as IEDs (interepileptical discharges) traveling between the cortex and hippocampus. IEDs are broadband, so one may expect that IEDs that are temporally correlated across regions may give rise to spurious coupling between frequency bands. While certainly true, this cannot explain the effects observed here for 2 reasons. 1) Our findings are bidirectional—there would need to be pathological activity generated in both the ATL and the hippocampus to produce such bidirectional hippocampal–cortical interactions, where IEDs generated in the ATL travel to the hippocampus to produce the encoding effect, and IEDs generated in the hippocampus travel to the ATL to produce the retrieval effect. None of the patients who took part in the experiment had pathological tissue in both the ATL and the hippocampus, so the IED confound explanation cannot explain the directionality of our effect. 2) IEDs are broadband, yet our effects are narrowband. During encoding, we observe the cross-correlation between neocortical alpha/beta and hippocampal fast gamma, but importantly not neocortical alpha/beta and hippocampal slow gamma. Any IED-induced broadband artifact would inherently yield cross-correlations with alpha/beta power and both gamma bands, and not within 1 singular band. Complementary quantitative analysis to support this conclusion can be found in SI Appendix.

Discussion
To successfully encode and recall episodic memories, we must be capable of 1) representing detailed multisensory information, and 2) binding this information into a coherent episode. Numerous studies have suggested that these 2 processes are accomplished by neocortical desynchronization (as measured by decreases in oscillatory power) and hippocampal synchronization (as measured by increases in fast and slow oscillatory gamma power), respectively (Fig. 7.26). Here, we show that these 2 processes coexist and interact. During successful episodic memory formation, alpha/beta power decreases in the anterior temporal lobe reliably precede fast hippocampal gamma power increases (60 to 80 Hz) by 100 to 200 ms. In contrast, slow hippocampal gamma power increases (40 to 50 Hz) precede alpha/beta power decreases by 200 to 300 ms during successful episodic memory retrieval. These findings demonstrate that the interaction between neocortical alpha/beta power decreases and hippocampal power increases in distinct, functionally relevant gamma rhythms underpins the formation and retrieval of episodic memories.

Our central finding demonstrates that ATL alpha/beta power decreases and hippocampal fast and slow gamma power increases interact during the formation and retrieval of episodic memories, respectively. This result draws together a multitude of conflicting studies, some of which indicate that synchronization benefits memory (e.g., refs. 43–45) and others which indicate that desynchronization benefits memory (e.g., refs. 13, 24, and 46), and provides a possible empirical resolution to the so-called synchronization–desynchronization conundrum (3). These findings are in line with previous observations demonstrating that hippocampal gamma power increases precede hippocampal alpha power decreases during associative memory retrieval (47). However, we also show that this sequence reverses during encoding, and that these 2 mechanisms interact across brain regions (via simultaneous hippocampal–neocortical recordings unavailable to ref. 47). We speculate that the delay in hippocampal response relative to ATL
During encoding, a reduction in ATL alpha/beta activity precedes an increase in hippocampal fast gamma power. During retrieval, an increase in hippocampal slow gamma power precedes a decrease in ATL alpha/beta activity.
interact with alpha/beta power decreases in the visual cortex to facilitate the encoding and retrieval of visual memories (20). Speculating further, hippocampal gamma power increases may be the metaphorical spark that lights the fuse of memory replay, coded in desynchronized neocortical alpha-phase patterns (19).

Second, does the observed fast/slow gamma distinction reflect 2 true narrowband oscillations? While we have uncovered a distinction between fast and slow gamma frequencies during encoding and retrieval, we cannot say with certainty whether these differences are driven by 2 distinct oscillators, as proposed by others (31, 36, 52). Indeed, one could argue that the observed differences are driven by fluctuations in the frequency of a single oscillator. While we are unaware of such a phenomenon in hippocampal gamma, such an effect has been reported in neocortical alpha (53). Notably, however, the reported alpha-band fluctuations were very subtle (<0.5 Hz), so it would be highly questionable to interpret the much larger 25–Hz shift between fast and slow hippocampal power as originating from this alpha-band “fluctuation” mechanism. One could alternatively argue that the width of a single oscillator frequency may fluctuate as a function of memory operation, giving an apparent shift in the ratio between fast and slow gamma. However, such an effect should introduce a symmetrical change around the peak. This is not present in our data, which suggests that such an effect is ill-suited to explain the observed difference in fast and slow gamma. In short, while any electrophysiological effect can be interpreted in many ways, it seems the most parsimonious explanation here is that distinct fast and slow gamma bands differentially influence memory operations, as proposed by Colgin (7).

In summary, we demonstrate that neocortical power decreases and hippocampal power increases cooperate during the formation and retrieval of episodic memories, providing evidence that may help resolve the so-called synchronization–desynchronization conundrum (3). Furthermore, we find that distinct hippocampal gamma oscillations service human episodic memory formation and retrieval, with faster (~60 to 80 Hz) oscillations supporting encoding and slower (~40 to 50 Hz) oscillations supporting retrieval. In conjunction, these results further illuminate our understanding of how interactions between the neocortex and hippocampus help build and retrieve memories of our past experiences.

Methods
Participants. Twelve patients (8 from Queen Elizabeth Hospital; n = 4 from University Hospital Erlangen; 41.7% female; mean age, 35.5 ± 14 years; range, 24 to 53 y) undergoing treatment for medication-resistant epilepsy took part in the experiment. All research was conducted with the use of depth electrodes, which had been implanted for diagnostic purposes. Ethical approval was granted by the National Health Service Health Research Authority (15/WM/0219) and the Ethik-Kommission der Friedrich-Alexander Universität Erlangen-Nürnberg (142, 12 B). Informed consent was obtained in accordance with the Declaration of Helsinki.

Behavioral Paradigm: Animal–Face–Place Associative Task. Seven of the 12 participants completed this paired–associates task (Fig. 1C). During encoding, participants were presented with a 3–s video or sound, followed by a word in the participant’s native language (English, n = 7; German; n = 1; presented for 3 s). There was a total of 4 videos and 4 sounds, repeated throughout each block. All 4 videos had a focus on scenery that had a temporal dynamic, while the 4 sounds were melodies performed on 4 distinct musical instruments. Due to time restraints, some participants only completed the experiment using 1 modality of dynamic stimulus (sound, n = 1; video, n = 5; both, n = 2). Participants were asked to vividly associate these 2 stimuli. For each pairing, participants were asked to rate how plausible (1 for very implausible and 4 for very plausible) the association they created was between the 2 stimuli (the plausibility judgment was used to keep participants on task rather than to yield a meaningful metric). The following trial began immediately after participants provided a judgment. If a judgment was not recorded within 4 s, the next trial began. This stopped participants from elaborating further on an imagined association they had just created. After encoding, participants completed a 2–min distractor task which involved making odd/even judgments for random integers ranging from 1 to 99. Feedback was given after every trial. During retrieval, participants were presented with every word that was presented in the earlier encoding stage and, 3 s later, asked to identify the associated video/sound from a list of all 4 videos/sounds shown during the previous encoding block. The order in which the 4 videos/sounds were presented was randomized across trials to avoid any stimulus-specific preparatory motor signals contaminating the epoch. Following selection, participants were asked to rate how confident they felt about their choice (1 for guess and 4 for certain). Each block consisted solely of video–word pairs or solely of sound–word pairs; there were no multimodal blocks. Each block initially consisted of 8 pairs, with each dynamic stimulus being present in 2 trials. However, the number of pairs increased by steps of 8 if the number of correctly recalled pairs was greater than 60%—this ensured a relatively even number of hits and misses for later analysis. Participants completed as many blocks/trials as they wished. Any participant who had fewer than 10 “remembered” or 10 “forgotten” trials after intracranial (i) EEG preprocessing was excluded from further analysis.

All participants completed the task on a laptop brought to their bedside. Responses were logged using the “” and “,” which corresponded to the values “1,” “2,” “3,” and “4.” To aid comprehension, snippets of paper were placed on top of each relevant keyboard key with the associated numerical value written upon them. The auditory stimuli were presented via the laptop’s speakers due to concerns that earphones could prove painful to the participants following electrode implantation just above the ear.

Behavioral Paradigm: Animal–Face–Place Associative Task. Five of the 12 participants completed this paired–associates task (Fig. 1D). During encoding, participants were first presented with an image cue of an animal for 2 s, followed by a pair of 2 images made up of any combination of a famous face or a famous place (i.e., face-place, face-face, or place-place pairs; presented for 2 s). There were initially a total of 20 image pairs, repeated throughout each block. This number was reduced if the hit rate fell below 66.25%, or if increased if the hit rate surpassed 73.75%. Participants were asked to vividly associate these 2 stimuli. For each pairing, participants were asked whether the association was plausible or implausible (the plausibility judgment was used to keep participants on task rather than to yield a meaningful metric). Participants were self-paced in providing a judgment, and the following trial began immediately afterward. After encoding, participants completed a distractor task which involved making odd/even judgments for 15 sequentially presented random integers, ranging from 1 to 99. Feedback was given after every trial. During retrieval, participants were presented with every image cue that was presented in the earlier encoding stage and, 2 s later, asked how many of the associated face or place pairs they remembered (participants had the option of responding with 0, 1, or 2). If the participant remembered at least 1 image, they were then asked to select the pair of images from a panel of 4 images shown during the previous encoding block (2 targets and 2 distractors). Participants were self-paced during the retrieval stage, though the experiment ended after a runtime of 40 min in total. All participants completed the task on a laptop brought to their bedside. Any participant who had fewer than 10 remembered or 10 forgotten trials after iEEG preprocessing was excluded from further analysis.

Behavioral Coding. For the first associative task, trials were classified as remembered if the participant selected the correct dynamic stimulus and stated that they were highly confident about their choice (i.e., scored 4 on the 4-point confidence scale). Trials were classified as forgotten if the participant selected the incorrect dynamic stimulus, did not respond, or stated that they guessed their choice (i.e., scored 1 on the 4-point confidence scale). For the second associative task, trials were classified as remembered only if the participant indicated that they remembered both images and subsequently selected both correctly from the panel. Trials were classified as forgotten in all other cases, where the participant indicated that they did not remember at least one image and/or subsequently selected one of the images incorrectly from the panel.

Statistical Analysis. While the 2 tasks differed in external stimulation, the underlying cognitive and neural phenomena relating to hypotheses were expected to be consistent across tasks. Therefore, the data for the 2 tasks were pooled. Unless explicitly stated otherwise in Results, all statistics were conducted on the group level (i.e., random effects) using nonparametric, permutation-based statistical tests. In analyses where multiple comparisons were made (e.g., time-series differences), the false-discovery rate (FDR) correction (54) was applied (denoted FDR). Effect sizes accompany each reported P value; Cohen’s d was used for all t tests (denoted d). For reference, Cohen (55) suggested that d = 0.8 indicates a large effect, d = 0.5 indicates a medium effect, and d = 0.2 indicates a small effect. Partial η² was used as a measure of effect size for all ANOVAs (denoted partial η²). For reference, partial η² = 0.25 indicates a large effect, partial η² = 0.09 indicates a medium effect, and partial η² = 0.01 indicates a small effect.
iEEG Acquisition and Preprocessing. First, the raw data were epoched; for encoding trials, epochs began 2 s before the onset of the visual/auditory stimulus and ended 4 s after verbal stimulus onset (9 s in total); for retrieval trials, epochs began 2 s before, and ended 4 s after, the onset of the verbal cue (6 s in total). Second, the data were filtered using a 0.2-Hz finite-impulse response high-pass filter and 3 finite-impulse response band-pass filters at 50 ± 1 Hz, 100 ± 1 Hz, and 150 ± 1 Hz, attenuating slow drifts and line noise, respectively. Third, as the iEEG data were sampled at the physician's discretion (512 Hz, n = 1, 1,024 Hz, n = 8), all data were downsampled to 500 Hz. Fourth, the data from each electrode were rereferenced to an electrode on the same electrode montage as the electrode from which recording was conducted. Fifth, the data were viewer (median: 1.5 Hz, M1, 0.5 Hz). The 1/θ was convolved with a 5-cycle wavelet (0 to 1,500 ms poststimulus [padded with 1,000 ms of right and left padding to ensure that all waveforms were of equal length]). A 1/θ fit (A(θ)) was then subtracted from the log-transformed power spectrum (B).

Peak Frequency Analysis. Raw signal recorded at every contact for each epoch was convolved with a 5-cycle wavelet (0 to 1,500 ms poststimulus [padded with real data for lower frequencies], in steps of 25 ms; 1 to 100 Hz, in steps of 0.5 Hz). The 1/θ noise was subtracted using the method described above to help pronounce the peaks in the power spectrum. The data were then smoothed using a Gaussian kernel (full-width half-maximum, 200 ms; 1 Hz) to attenuate inter- and intrahippocampal differences in spectral responses (S3) and to help approximate normally distributed data (an assumption frequently violated in small samples). The data were averaged across all time points, trials, and contacts (separately for the hippocampus and ATL). Peaks of 1/θ−corrected absolute power were then identified using the findpeaks() peak-detection algorithm implemented in MATLAB. To identify the memory-related difference in the dominant gamma bands, the power spectra for remembered trials were calculated in an identical manner, except that the Gaussian kernel was expanded to account for the greater variability of high-frequency oscillatory responses (200 ms, 5 Hz). The power spectra for encoding and retrieval were then collapsed into seven 10-Hz bins ranging from 30 to 100 Hz and contrasted in a group-level (i.e., random effects), nonparametric permutation test (58) with 5,000 randomizations. The multiple-comparisons issue was solved using the false-discovery rate correction (54). This analysis was repeated for the forgotten trials.

Selection of peak frequencies. The peak frequencies of each patient were determined using the MATLAB function findpeaks() on the averaged power spectrum around the approximate frequency bands (theta, 1 to 7 Hz; alpha/theta, 8 to 20 Hz; slow gamma, 30 to 60 Hz; fast gamma, 50 to 100 Hz). The bandwidths of these peaks were kept consistent across participants, and were determined through inspection of the group-averaged bandwidth of the peaks (theta, ±0.5 Hz, alpha/beta, −1 Hz/±5 Hz [capturing the observed asymmetry in the peak]; slow/fast gamma, ±10 Hz). Individual peak frequencies are reported in SI Appendix, Table S1.

Spectral Power Analysis. For all spectral power analyses (i.e., encoding, and retrieval), the data were transformed using a log 1/f correction, and smoothing approaches described in Peak Frequency Analysis. The data were then z-transformed using the means and SDs of each electrode-frequency pair (14). The time-frequency–resolved data were then averaged over electrodes of each ROI. For time-series statistical analysis, trials were split into 2 groups based on whether the stimuli were remembered or forgotten. Then, the time series were collapsed into 7 bins of 200 ms and the 2 conditions were contrasted (same nonparametric and bootstrap) using the Statistical procedure described in Peak Frequency Analysis. For statistical analyses of the interaction between memory task (encoding vs. retrieval) and gamma frequency (fast vs. slow), this memory-related difference in power (i.e., SME and RSE) was averaged over time and contrasted in a nonparametric, permutation-based, 2 × 2 repeated-measures ANOVA.

Cross-Correlation Analysis. For all cross-correlation analyses (i.e., encoding and retrieval epochs), the data underwent the same wavelet convolution, 1/f correction, and smoothing approaches described in Spectral Power Analysis, with 2 exceptions: 1) wavelet convolution occurred in steps of 10 ms rather than 50 ms (enhancing temporal resolution), and 2) the temporal aspect of the smoothing kernel was reduced to 50 ms to avoid excessive smoothing obscuring the temporal dynamics of the neocortical–hippocampal cross-correlation. For each "trial × electrode combination" pair, the cross-correlation between the hippocampus and neocortex was considered for every offset from where the neocortex preceded the hippocampus by 300 ms to where the neocortex lagged behind the hippocampus by 300 ms. This returned a time series of Pearson correlation values describing the relationship between the hippocampus and neocortex at all considered lags. These correlation values were then averaged over electrodes and split into conditions (remembered vs. forgotten). These 2 groups were individually averaged over trials for each participant, collapsed into bins of 100 ms, and then contrasted using the same nonparametric statistical procedure described in Peak Frequency Analysis. We term the “remembered > forgotten” difference in cross-correlation for encoding data the “subsequent memory cross-correlation” and the difference for retrieval data the “retrieval success cross-correlation.”

To test the “encoding-retrieval > lag-lead” difference, we contrasted the subsequent memory cross-correlation with the retrieval success using the same nonparametric statistical procedure described in Peak Frequency Analysis. Lastly, to test the influence of the “memory task” × “gamma frequency” interaction on the memory-related cross-correlation differences, we conducted a nonparametric, permutation-based, 2 × 2 repeated-measures ANOVA in the same manner as described in Spectral Power Analysis.

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