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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 is fundamental to the formation and retrieval of episodic memories.


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During encoding, participants are tasked with forming an associative link between an image of an object, a face, and a scene. During retrieval, participants are presented with the verbal stimulus at encoding and retrieval (blue outline). Electrophysiological analysis was conducted during the presentation of the verbal stimulus. It was found that periods of increased fast gamma activity enhance connectivity between the entorhinal cortex (MEC) and the CA3 subfield of the hippocampus (30 to 50 Hz) has been proposed to facilitate memory retrieval (7, 31, 32). Slow gamma activity originates from the CA3 subfield of the hippocampus and may play a pivotal role in pattern completion (33, 34). The tradeoff in amplitude between these 2 gamma oscillations is thought to dictate whether encoding or retrieval takes place (35). Evidence suggests that periods of increased fast gamma activity enhance connectivity between CA1 and the entorhinal cortex (31, 36) (allowing information to flow into the hippocampus; Fig. 1B) and aid representational binding through STDP (28, 30). Meanwhile, periods of enhanced slow gamma activity see an increase in connectivity between CA1 and CA3 (allowing for the transfer of completed memory pattern into the neocortex; Fig. 1B) (31, 36). In conjunction, these findings and theories would suggest that fast and slow gamma rhythms differentially support the hippocampal ability to associate and reactivate discrete elements of an episodic memory. Here, we investigated the coordination between alpha/beta power decreases in the anterior temporal lobe and gamma power increases in the hippocampus during episodic memory formation and retrieval. Specifically, we tested 4 central hypotheses derived from a series of conceptual frameworks, computational models, and rodent studies: 1) fast gamma oscillations (60 to 100 Hz) will support encoding while slow gamma oscillations (30 to 45 Hz) will support memory retrieval (7, 31); 2) neocortical power decreases [reflecting information processing (5)] and hippocampal power increases [reflecting representational binding (6, 7, 26, 27)] will accompany episodic memory formation and retrieval when contrasted against memories that were not successfully encoded/retrieved; 3) neocortical power decreases will precede hippocampal power increases during memory formation (reflecting information processing preceding representational binding); and 4) hippocampal power increases will precede neocortical power decreases during retrieval (reflecting pattern completion preceding information reinstatement) (3, 4).

Twelve patients implanted with stereotactic electroencephalogram (EEG) electrodes for the treatment of medication-resistant epilepsy completed 1 of 2 associative memory tasks (Fig. 1C and D; n = 7 in task 1; n = 5 in task 2). In task 1, they related life-like videos or sounds to words that followed. Following a short distractor task, participants attempted to recall the previously presented videos/sounds using the words as cues. In task 2, they related an object to pairs of visual stimuli that followed (face–place, face–face, or place–place). Following a short distractor task, participants attempted to recall both stimuli, using the object as a cue. While external stimulation is different between the 2 tasks, the underlying cognitive and neural processes relating to our hypotheses are consistent: Both tasks require sensory processing followed by representational binding during memory formation, and hippocampal pattern competition prior to neocortical reinstatement during memory retrieval. As such, the data from the 2 tasks were pooled together for analysis. We conducted these analyses in 2 regions of interest (ROIs) (Fig. 1E): the hippocampus (a hub for representational binding) and the anterior temporal lobe [ATL; a hub for semantic-based information object and 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%; recalled both associated items on 66.2% of trials). 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, partial r = 0.294; 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 = 0.025, d = 0.862; Fig. 2F), followed by an increase in slow gamma power (800 to 1,000 ms, P = 0.007, d = 1.177; 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 bands trend 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 = 0.035, d = 0.858; 400 to 600 ms after stimulus onset; 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 = 0.042, d = 0.777; 1,000 to 2,100 ms, P = 0.039, d = 0.849; 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 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 ($P_{fdr} = 0.006$) 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 completion 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 ($P_{fdr} = 0.037, d = 0.73; \text{Fig. 4B}$), 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 lag. 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 fast gamma power in a group-level, nonparametric, permutation test. This revealed an interaction whereby ATL power decreases preceded hippocampal power increases during encoding ($P_{fdr} = 0.005, d = 1.15; 100$ to $200$ ms) but hippocampal power increases preceded ATL power decreases during retrieval ($P_{fdr} = 0.025, d = 0.855; 200$ to $300$ ms) ($\text{Fig. 4C}$). 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, $2 \times 2$ repeated-measures ANOVA (memory operation $\times$ 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 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 (interiepileptical 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 power, but importantly not neocortical alpha/beta and hippocampal slow gamma power. 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 (3, 5, 7, 26). Here, we show that these 2 processes exist 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., ref. 47) 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

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**Fig. 3.** ATL alphabeta activity during encoding and retrieval. (A) Time series of memory-related alphabeta power for encoding and retrieval. In both cases, decreases in alphabeta power relate to greater memory ($P_{fdr} < 0.05$). (B) Raincloud plots depicting the difference in alphabeta power between remembered and forgotten items. Colored circles represent participants who took part in experiment 1. Uncolored triangles represent participants who took part in experiment 2.
alpha/beta power decreases during encoding reflects the need for
the ATL to process semantic details prior to the hippocampus
binding this information into a coherent representation of the
event (26, 27). In contrast, we posit that the ATL delay in response
to hippocampal gamma power increases during retrieval
reflects the need for the hippocampal representational code to be
reactivated prior to reinstating highly detailed stimulus-specific
information about the event (48). Anatomically speaking, this re-
ciprocal communication may be facilitated by the “direct intra-
hippocampal pathway”—a route with reciprocal connections
between the ATL and hippocampus via the entorhinal cortex (49, 50).
These anatomical connections would allow the ATL and
hippocampus to cooperate during episodic memory formation and
retrieval, facilitating the flow of neocortical information into the
hippocampus during encoding and the propagation of hippocam-
pal retrieval signals into the neocortex during retrieval.

We also found distinct gamma rhythms supporting human
episodic memory formation and retrieval (7, 35). Specifically, we
found greater fast gamma oscillatory activity (60 to 80 Hz) during
encoding and greater slow gamma oscillatory activity (40 to 50 Hz)
during retrieval, generalizing earlier rodent findings (e.g., ref. 31)
to humans. We uncovered similar distinctions in fast and slow
gamma-band activity when investigating memory-related changes
in power and neocortical-hippocampal cross-correlations, pro-
viding additional evidence for such a distinction. Earlier rodent
studies have suggested that the distinction between the 2 gamma
bands reflects a difference in CA1 coupling (31); fast gamma os-
cillations support CA1–entorhinal cortex coupling, facilitating
the transfer of information into the hippocampus, while slow gamma
oscillations support CA1–CA3 coupling, facilitating the reac-
tivation of stored information. We speculate that these patterns of
connectivity extrapolate to humans and explain the observed dif-
fences in gamma frequency relating to episodic memory for-
mation and retrieval. In sum, our results suggest that fast and slow
gamma activity relates to distinct processes in the successful for-
mation and retrieval of episodic memory.

In combination, the cross-correlation and gamma-band analyses
produce a detailed picture of information flow during episodic
memory formation and retrieval. Based on earlier frameworks
(3, 7) and models (4), we postulate that the link between neo-
cortical alpha/beta power decreases and hippocampal fast gamma
power increases during memory formation reflects the flow of
semantic information (processed in the ATL) to the entorhinal
cortex (27) via the direct intrahippocampal pathway (49, 50),
where fast gamma synchrony between the entorhinal cortex and
CA1 passes this information on to the hippocampus (31, 51).
In contrast, the link between hippocampal slow gamma power in-
creases and neocortical alpha/beta power decreases during mem-
ory retrieval reflects the flow of reactivated representational codes
from CA3 to CA1 [via slow gamma synchrony (31, 51)], which
propagates out into the neocortex (48) via reciprocal connections
in the direct intrahippocampal pathway, reinstating semantic de-
tails in the desynchronized ATL. However, future research with
direct recordings from these hippocampal subregions in humans is
needed to empirically test this proposed flow of information dur-
ing episodic memory formation and retrieval.

Two questions remain, however. First, do similar bidirectional
streams of information flow exist between the hippocampus and
other neocortical regions? As it was not medically necessary,
electrode coverage did not expand to every neocortical region
linked to episodic memory. Therefore, we could not test this
theory. We speculate, however, that similar bidirectional links do
exist. For example, hippocampal gamma power increases may
encoding, a reduction in ATL alpha/beta activity precedes an increase in
hippocampal fast gamma power. During retrieval, an increase in hippo-
campal slow gamma power precedes a decrease in ATL alpha/beta activity.

Fig. 4. Hippocampal–neocortical time-series cross-correlations. (A) Mean cross-
correlation (with shaded SEM; Left) between the hippocampal fast gamma power
and ATL alpha/beta power during encoding (**Psub < 0.01). ATL power decreases
precede hippocampal fast gamma power increases. Raincloud plot (Right) depicts
the difference in cross-correlation between remembered and forgotten items.
Colored circles represent participants who took part in experiment 1. Uncolored
triangles represent participants who took part in experiment 2. (B) Mean cross-
correlation (with shaded SEM; Left) between the hippocampal slow gamma
power and ATL alpha/beta power during retrieval (*Psub < 0.05). Hippocampal
slow gamma power increases precede ATL alpha/beta power decreases. Raincloud
plot (Right) depicts the difference in cross-correlation between remembered
and forgotten items. Colored circles represent participants who took part in experi-
ment 1. Uncolored triangles represent participants who took part in experiment
2. (C) The contrast of cross-correlation activity between encoding and retrieval
(+$P_{sub} < 0.05, **P_{sub} < 0.01). (D) Mean cross-correlation between neocortical alpha/
beta power and hippocampal gamma power (slow in purple; fast in red; with
SEM) as a function of memory operation (Top, subject-level; Bottom, electrode
pair-level). A repeated-measures ANOVA reveals an interaction between hip-
 pocampal gamma frequency and memory task when predicting memory-related
 hippocampal–neocortical cross-correlation (**P < 0.01). (E) Filtered single-trial
 traces at encoding (Left) and retrieval (Right) in the ATL (Top) and hippo-
campus (Middle). The envelopes of these traces are plotted (Bottom). During

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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 (n = 8 from Queen Elizabeth Hospital; n = 4 from University Hospital Erlangen; 41.7% female; mean age, 35.5 y; range, 24 to 53 y) undergoing treatment for medication-resistant epilepsy took part in the exploring further on an imagined association they had just created. The accuracy of their choice (i.e., scored 1 on the 4-point confidence scale) was used for all reported P values. 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. The data squared was used as a measure of effect size for all ANOVAs (denoted partial $\eta^2$). For reference, partial $\eta^2 = 0.25$ indicates a large effect, partial $\eta^2 = 0.09$ indicates a medium effect, and partial $\eta^2 = 0.01$ 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 side that was positioned in white matter (determined by visual inspection of participant anatomy; see below). The use of a common reference electrode for both the hippocampus and neocortex ensured that any difference in electrophysiological signal from the 2 regions could not be explained by a difference in reference. Finally, the data were visually inspected and any trials exhibiting artifact activity were excluded from further analysis. Any electrodes exhibiting persistent ictal and interictal activity (as identified through visual inspection) were discarded from analysis.

Electrode Localization. First, hippocampal and white matter contacts were defined based on anatomical location through visual inspection of the T1-weighted anatomical scan (nb., one participant had no hippocampal contacts, given electrode placement from all hippocampal-based contacts). Then, the native space coordinates of all remaining contacts were determined by visual inspection of each participant’s postimplantation T1 scan. These contact coordinates were then transformed from native space to Montreal Neurological Institute (MNI) space using a transform matrix obtained by normalizing the native space coordinates of all remaining contacts (separately for the hippocampus and ATL). Peaks of 1/f noise were rereferenced to an electrode on the same shaft that was positioned in white matter (determined by visual inspection of participant anatomy; see below). The use of a common reference electrode for both the hippocampus and neocortex ensured that any difference in electrophysiological signal from the 2 regions could not be explained by a difference in reference. Finally, the data were visually inspected and any trials exhibiting artifact activity were excluded from further analysis. Any electrodes exhibiting persistent ictal and interictal activity (as identified through visual inspection) were discarded from analysis.

Spectral Power Analysis. For all spectral power analyses (i.e., encoding and retrieval), the data underwent wavelet convolution, 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 1 s bins of 200 ms and the 2 conditions were contrasted using the same nonparametric 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 ATL was computed using the MATLAB function crosscorr() with a lag of 300 ms (meaning the 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 each participant and split into 2 groups (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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