Hippocampal synchrony and neocortical desynchrony cooperate to encode and retrieve episodic memories

Benjamin J. Griffiths[1], Sebastian Michelmann*[1], Frederic Roux*[1], Ramesh Chelvarajah[2], David T. Rollings[2], Vijay Sawlani[2], Hajo Hamer[3], Stephanie Gollwitzer[3], Gernot Kreiselmeyer[3], Bernhard Staresina[1], Maria Wimber[1], & Simon Hanslmayr[1]

** denotes equal contribution*

1) School of Psychology, University of Birmingham, Birmingham, United Kingdom.
2) Complex Epilepsy and Surgery Service, Neuroscience Department, Queen Elizabeth Hospital, Birmingham, United Kingdom.
3) Epilepsy Center, Department of Neurology, University Hospital Erlangen, Erlangen, Germany.

Main text: 5,080 words

Methods: 2,522 words

Contact Information / Corresponding Author

Simon Hanslmayr

s.hanslmayr@bham.ac.uk

+44 121 4146203

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 two processes are thought to be supported by neocortical alpha/beta desynchronisation and hippocampal theta/gamma synchronisation, respectively. Intuitively, these two processes should interact to successfully build and retrieve episodic memories, yet this hypothesis has not been tested empirically. Here, we address this question by analysing human intracranial EEG data recorded during an associative memory task. Our findings indicate that neocortical alpha/beta (8-20Hz) desynchronisation reliably precedes and predicts hippocampal "fast" gamma (60-80Hz) synchronisation during episodic memory formation; during episodic memory retrieval however, hippocampal "slow" gamma (40-50Hz) synchronisation reliably precedes and predicts later neocortical alpha/beta desynchronisation. We speculate that this cooperation reflects the flow of information from neocortex to hippocampus during memory formation, and hippocampal pattern completion inducing information reinstatement in the neocortex during memory retrieval.

An episodic memory is a high-detailed memory of a personally-experienced event[1,2]. The formation and retrieval of such memories hinge upon: a) the processing of information relevant to the event, and b) the binding of this information into a coherent episode. A recent framework[3] and computational model[4] suggest that the former of these processes is facilitated by the desynchronisation of neocortical alpha/beta oscillatory networks (8-20Hz; reflected in decreases in oscillatory power)[5], while the latter is facilitated by the synchronisation of hippocampal theta and gamma oscillations (3-7Hz; 40-100Hz; reflected in increases in oscillatory power and theta-gamma phase-amplitude coupling)[6,7] [see fig. 1a]. Critically, the framework posits that these two mechanisms need to cooperate, as an isolated failure of either of these mechanisms would produce the same undesirable outcome: an incomplete memory trace. Here, we test this framework and provide the first empirical evidence of an interaction between neocortical desynchronisation and hippocampal synchronisation during the formation and retrieval of human episodic memories.

Within the neocortex, desynchronised alpha/beta activity is thought to facilitate information processing[5]. This hypothesis is based on the principles of information theory[8], which proposes that a system of unpredictable states (e.g. desynchronised neural activity) is optimal for information coding (see fig. 1b). In support of this hypothesis, many studies have observed neocortical alpha/beta desynchronisation during successful episodic memory formation[9–17] and retrieval[18–23]. For example, the degree of neocortical alpha/beta desynchronisation scales with the depth of semantic processing during episodic memory formation[17]. Critically, disrupting neocortical desynchronisation via repetitive transcranial

magnetic stimulation impairs both episodic memory formation and retrieval, suggesting that alpha/beta desynchronisation plays a causal role in these processes[19,24]. In short, these studies suggest that neocortical alpha/beta desynchronisation underpins the processing of event-related information, allowing for the formation and later recollection of highly detailed episodic memories.

Within the hippocampus, synchronised gamma activity, nested within ongoing theta oscillations, is hypothesised to form a neural code capable of binding event-related information into a cohesive episode[6,7,25,26]. More specifically, each theta cycle provides a window where discrete elements of the event (coded by individual gamma cycles) can be organised, related and maintained (see fig. 1b). Critically, it is hypothesised[3] that gamma cycles lock to the part of the theta cycle optimal for long-term potentiation (LTP), enhancing the synaptic strengthening between neural populations coding for each element of the event and thereby optimising encoding. During later retrieval, the cuing of one element of this theta-gamma code is thought to reactivate the code in its entirety[25], reinstating the memory. Studies in both animals[27–29] and humans[30,31] support these ideas. Interestingly, two distinct gamma rhythms are thought to couple to theta, with faster gamma rhythms (60-100Hz) supporting episodic encoding and slower gamma rhythms (30-45Hz) supporting episodic retrieval[7,32,33]. Evidence suggests that “fast” gamma boosts connectivity between CA1 and the entorhinal cortex (allowing information to flow into the hippocampus for representational binding), while “slow” gamma boosts connectivity between CA1 and CA3 (facilitating pattern completion)[34]. In conjunction, these findings and theories would suggest that the synchronisation of “fast” and “slow” gamma rhythms to an ongoing theta cycle would support the hippocampal ability to associate and reactivate discrete elements of an episodic memory.

Here, we investigated the co-ordination between neocortical alpha/beta desynchronisation (i.e. decreases in oscillatory power) and hippocampal theta/gamma synchronisation (i.e. increases in oscillatory power and phase-amplitude coupling) during episodic memory formation and retrieval. Specifically, we tested four central hypotheses derived from a series of conceptual frameworks, computational models and rodent studies: 1) alpha/beta oscillations will dominate the neocortex while theta and gamma oscillations dominate the hippocampus[5,6,35]; 2) “fast” gamma oscillations (60-100Hz) will support encoding while “slow” gamma oscillations (30-45Hz) will support memory retrieval[7,34]; 3) both neocortical power decreases (reflecting information processing[5]) and hippocampal power increases/phase-amplitude coupling increases (reflecting representational binding[6,7,25,26]) will support episodic memory formation and retrieval; 4) neocortical power decreases will precede hippocampal power increases during memory formation (reflecting information processing preceding

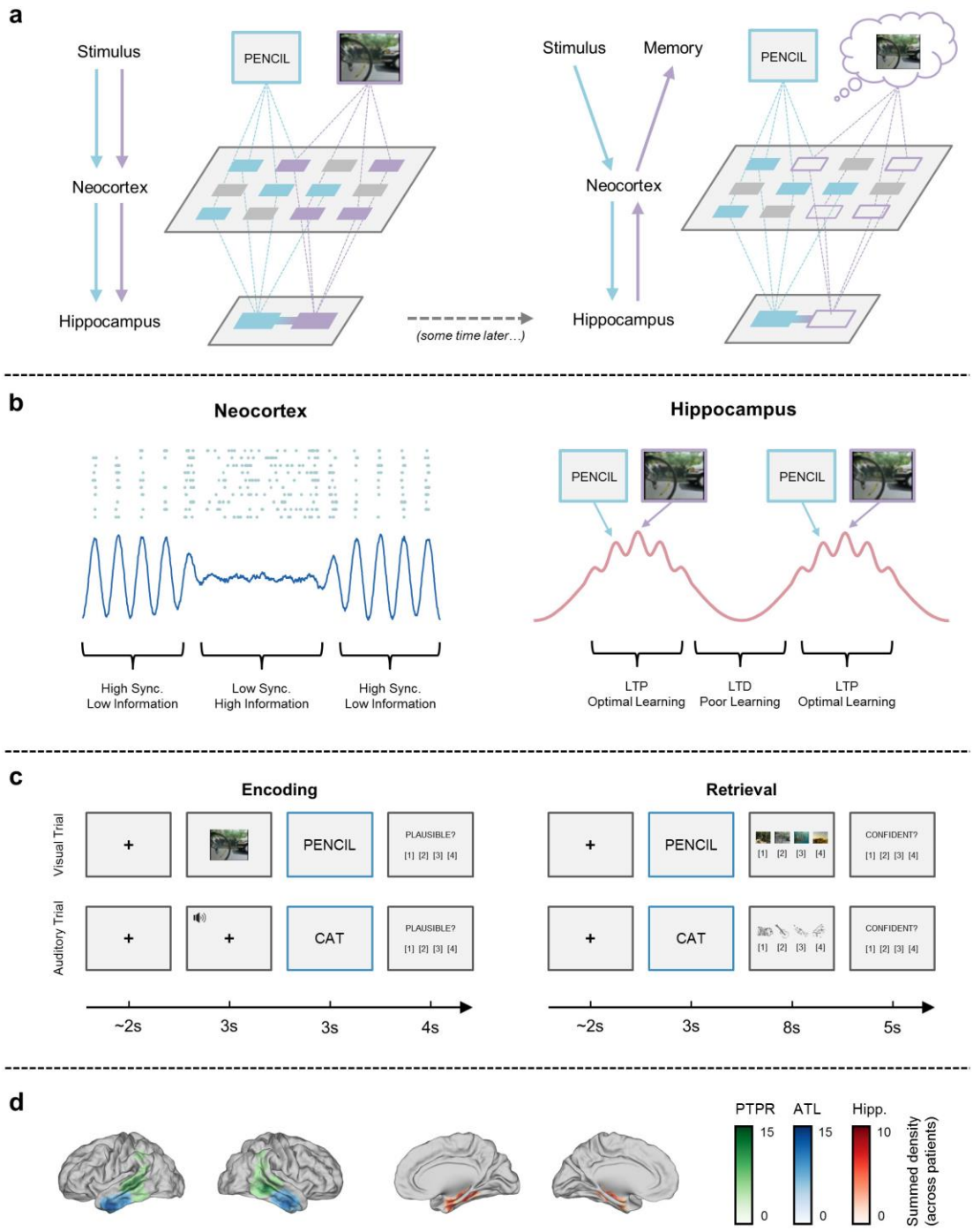

Figure 1. The sync-desync framework. **(a)** this framework explains the encoding (left) and retrieval (right) of associative episodic memories. Incoming stimuli are independently processed by relevant sensory regions of the neocortex. These neocortical representations are then passed onto the hippocampus where they are bound together. At a later stage, a partial cue reactivates the hippocampal associative link, which in turn reactivates neocortical patterns coding for the memory representation, giving rise to conscious recollection. **(b)** a pictographic representation of hypothesised oscillatory dynamics. Reduced oscillatory synchronisation (blue line) within the neocortex allows individual neurons (blue dots) to fire more freely and create a more flexible neural code. Gamma cycles lock to a part of the theta phase (red line) optimal for long-term potentiation (LTP), allowing individual elements to be organised and bound in relation to one another. **(c)** the trial outline for encoding (left) and retrieval (right) tasks. During encoding, participants are tasked with forming an associative link between a life-like dynamic stimulus (either a video or sound) and a subsequent verbal stimulus. During retrieval, participants are presented with verbal stimuli from the previous encoding block and asked to retrieve the associated dynamic stimulus. Electrophysiological analysis was conducted during the presentation of the verbal stimulus at encoding and retrieval (blue outline). **(d)** summed density of electrode coverage of the anterior temporal lobe (blue), posterior temporal/parietal regions (green) and hippocampus (red) [see methods for details on quantification].

representational binding), and hippocampal power increases will precede neocortical power decreases during retrieval (reflecting pattern completion preceding information reinstatement)[3,4].

Nine patients, implanted with hippocampal depth electrodes for the treatment of medication-resistant epilepsy, completed a simple associative memory task (see fig. 1c) where they related life-like videos or sound s to words that followed. Following a short distractor, participants attempted to recall the previously presented videos/sounds using the words as cues. Of these nine patients, eight were included in all neocortical analyses, and seven were included in all hippocampal and neocortical-hippocampal interaction analyses. Electrophysiological analysis was centred on verbal stimulus presentation at both encoding and retrieval. By keeping external stimulation consistent between encoding and retrieval, any differences in oscillatory dynamics must be driven by internal influences. We conducted these analyses in three ROIs (see fig. 1d): 1) the hippocampus (a hub for representation binding), 2) the anterior temporal lobe (ATL; a hub for semantic-based information processing[36]), and 3) the posterior temporal/parietal region (PTPR; a hub for retrieval-related attentional processes[37–40]). 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, revealing the first empirical evidence of an interaction between these two mechanisms during human episodic memory formation and retrieval.

Results

Alpha/beta oscillations dominate the neocortex; theta oscillations dominate the hippocampus

We first sought to empirically define the peak frequencies in our three regions of interest. Broadband spectral power (1-100Hz) was computed across a 1500ms window starting at the onset of the verbal stimulus (at encoding and retrieval). To help identify spectral peaks, the 1/f noise was then subtracted from the data[41–43] (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 distinct slow-theta peak could be observed in the hippocampus at ~2.5Hz and an alpha/beta peak could be observed in the two neocortical regions between 8-20Hz (see figure 2a). We defined the peak frequency of each ROI for each participant individually and conducted all subsequent analyses on these peak frequencies (see supplementary table 1 for individual peak frequencies).

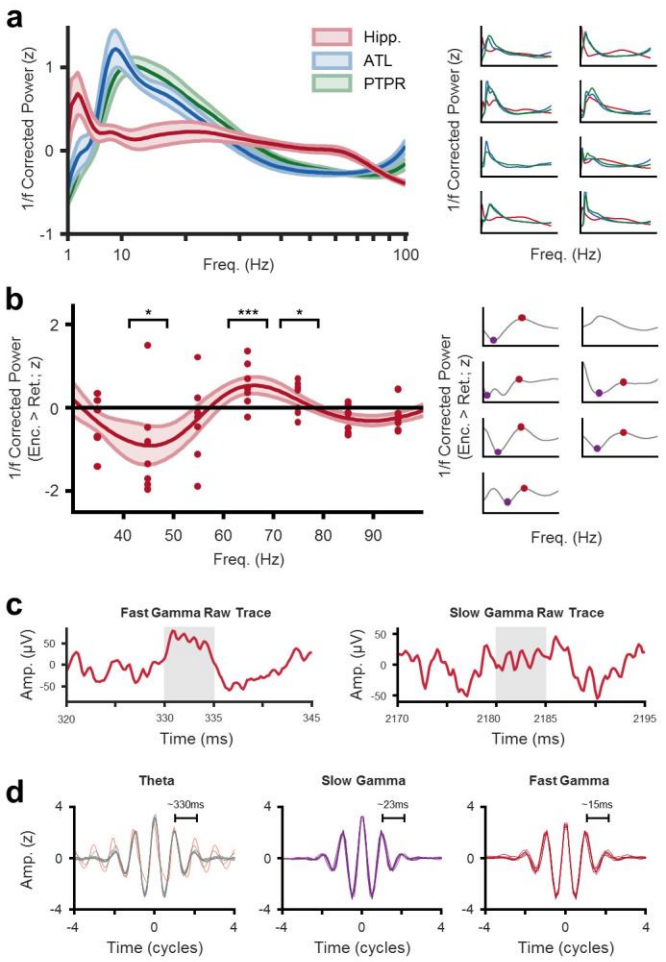

Figure 2. Dominant frequencies in neocortex and hippocampus. **(a)** the mean 1/f corrected power spectrum (with shaded standard error of the mean) across all encoding and retrieval trials reveals a theta peak (~2.5Hz) in the hippocampus and an alpha/beta peak (8-20Hz) peak in the two neocortical ROIs. Individual subject power spectra displayed on right. **(b)** the mean difference in gamma power (with shaded standard error of the mean) between encoding and retrieval reveals a peak in encoding-related, "fast" gamma at 60-80Hz and a peak in retrieval-related, "slow" gamma at 40-50Hz (*p_{fdr} < 0.05). Dots indicate bin-averaged difference for each participant. Individual subject power spectra displayed on right; red dot indicates peak "fast" gamma frequency, and purple dot indicates peak "slow" gamma frequency. **(c)** raw signal during encoding (top) and retrieval (bottom) from a hippocampal contact of "patient 1". The shaded grey region indicates a period of 50 milliseconds (x-axis indicates time relative to word onset). **(d)** peak-locked averaged signal per participant for theta (left; observed data in grey, rodent theta in orange), "slow" gamma" (middle) and "fast" gamma (right). The in-graph time scale indicates the approximate duration of one cycle in milliseconds.

Distinct hippocampal gamma-band frequencies underlie encoding and retrieval processes

We then investigated whether distinct gamma frequency bands support encoding and retrieval processes[7,34]. To test this, the absolute broadband hippocampal gamma power (30-100Hz) was contrasted between encoding and retrieval epochs of successfully remembered pairs. "Fast" hippocampal gamma frequencies (60-80Hz) exhibited significantly greater power during encoding, relative to retrieval, trials (60-70Hz, p_{fdr} = 0.001; 70-80Hz, p_{fdr} = 0.045; see fig. 2B). In contrast, "slow" hippocampal gamma frequencies (40-50Hz) exhibited greater power during retrieval, relative to encoding, trials (p_{fdr} = 0.045). No significant difference between encoding and retrieval could be observed during the epochs of forgotten stimuli (minimum p_{fdr} = 0.335; see supplementary figure 1). 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 supplementary table 1 for individual peak frequencies). These findings provide the first empirical evidence

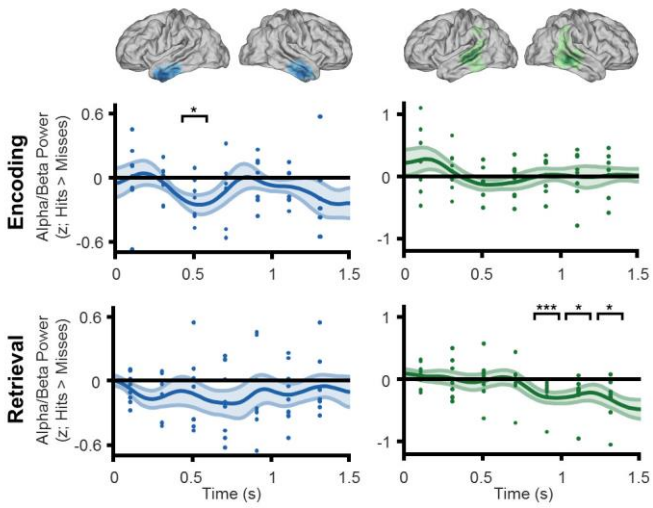

Figure 3. The difference in neocortical desynchronisation between later remembered and later forgotten items during episodic memory formation (top) and retrieval (bottom) in two regions of interest: the anterior temporal lobe (left) and posterior temporal/parietal region (right) [*p_{fdr} < 0.05]. Dark line indicates mean across participants; shaded area indicates standard error of the mean; individual points represent bin-averaged difference in power for each participant.

that two 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, channels and trials. These weights were then contrasted between encoding and retrieval in a random effects, non-parametric permutation-based t-test. This test revealed no significant difference in the beta weights for remembered items (p = 0.311) or for forgotten items (p = 0.458), suggesting the distinction in gamma rhythms between encoding and retrieval was not driven by differences in the 1/f slope.

Neocortical alpha/beta desynchronisation tracks the successful formation and retrieval of episodic memories

We then investigated whether neocortical alpha/beta desynchronisation accompanies the successful encoding and retrieval of episodic memories. Peak alpha/beta power was computed across a 1500ms window commencing at verbal stimulus onset. As above, the 1/f characteristic was subtracted, eliminating the possibility that any condition differences were driven by differences in broadband spectral power fluctuations[44]. The alpha/beta power was z-transformed across the entire session for each channel-frequency pair separately, smoothed to attenuate trial-by-trial variability in temporal/spectral responses, and then split into "hits" and "misses" for contrasting. A random effects, non-parametric permutation-based t-test revealed a significant decrease in anterior temporal lobe (ATL) alpha/beta power during encoding (p_{fdr} = 0.041; 400-600ms after verbal stimulus onset, see fig. 3 for difference line plot; see supp. fig. 2 for separate hit/miss line plots) for remembered stimuli relative to forgotten stimuli, possibly reflecting the processing of semantic information related to incoming stimuli[45]. No similar difference was observed in the posterior temporal/parietal

region (PTPR; $p_{fdr} > 0.5$). During retrieval, a permutation-based t-test revealed a significant decrease in PTPR alpha/beta power (800-1000ms, $p_{fdr} = 0.001$; 1000-1200ms, $p_{fdr} = 0.026$; 1200-1400ms, $p_{fdr} = 0.038$; see fig. 3 for difference line plot; see supp. fig. 2 for separate hit/miss line plots) for remembered stimuli relative to forgotten stimuli, perhaps reflecting retrieval-related attentional processes[37–40]. No similar difference was observed in the ATL ($p_{fdr} = 0.209$). These results replicate earlier findings implicating neocortical alpha/beta desynchronisation in the encoding[9–17] and retrieval[18–23] of human episodic memories.

Hippocampal theta/gamma power changes track the successful formation and retrieval of episodic memories

We used two approaches to investigate how hippocampal theta/gamma synchronisation underpins episodic memory formation and retrieval. First, we examined whether hippocampal power increases relate to episodic memory using the same analytical approach implemented to assess neocortical desynchronisation during memory formation and retrieval. A random effects, non-parametric permutation-based t-test revealed no significant difference between remembered and forgotten items in hippocampal theta power during episodic memory formation ($p_{fdr} = 0.125$; see fig. 4a). However, a significant increase in hippocampal theta power was observed during successful episodic memory retrieval (600-800ms, $p_{fdr} = 0.026$; 800-1000ms, $p_{fdr} = 0.026$; 1000-1200ms, $p_{fdr} = 0.036$).

To examine the distinction between “fast” and “slow” gamma power during episodic memory encoding and retrieval, we conducted a non-parametric, permutation-based, 2x2 repeated measures ANOVA that investigated the influence of 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. However, a random effects (RE) analysis did not reveal a significant interaction ($p = 0.126$). To rule out the possibility of limited statistical power yielding a false negative, we reassessed the interaction with a fixed effects (FE) analysis, where each hippocampal channel was considered as an individual sample point. The fixed effects approach revealed a significant interaction ($p = 0.013$, see figure 4b), indicating that “fast” and “slow” gamma exhibited dissimilar memory-related power fluctuations during encoding and retrieval. Notably however, the fixed effects approach lacks generalisability to the population level. To rectify this, bootstrapping resampling methods[46] were used to estimate population-level reliability (see methods for details). In 1000 resamples, 97% of instances showed evidence that the observed interaction between

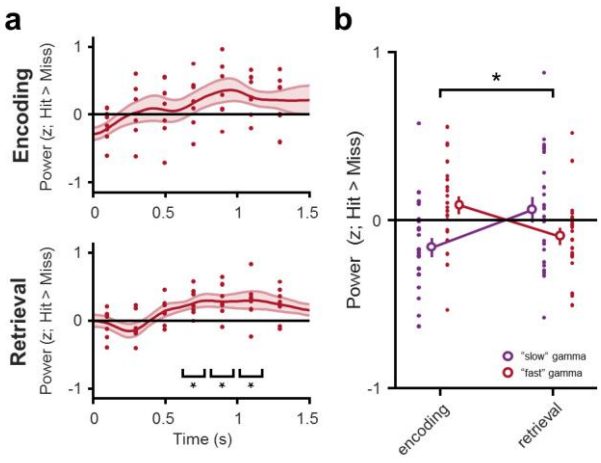

Figure 4. Hippocampal power fluctuations during episodic memory formation and retrieval. **(a)** the mean difference (with standard error of the mean and individual patient data points) in theta power between remembered and forgotten items [*p < 0.05]. **(b)** the mean difference in "fast" and "slow" gamma power (with bars indicating standard error of the mean) during encoding and retrieval. Fixed effects analysis revealed a significant interaction where memory-related "fast" gamma dominates during encoding and memory-related "slow" gamma dominates during retrieval [*p < 0.05].

memory task and gamma frequency was greater than chance, indicating a high degree of population-level reliability.

Intriguingly, it appeared that the interaction was not simply driven by an increase in "fast" gamma during encoding and an increase in "slow" gamma during retrieval, but also a decrease in the opponent gamma, i.e. "slow" gamma during encoding and "fast" gamma during retrieval. We therefore examined the time-courses of memory-related "fast" and "slow" gamma power. These analyses revealed a simultaneous increase in "fast" gamma power (1000-1200ms, RE p_{fdr} = 0.053, FE p_{fdr} = 0.041) and decrease in "slow" gamma power (1000-1200ms, RE p_{fdr} < 0.001, FE p_{fdr} = 0.009; 1200-1400ms, RE p_{fdr} < 0.001, FE p_{fdr} = 0.009) during episodic memory formation. However, we only uncovered a small "fast" gamma band decrease during successful memory retrieval (RE p_{fdr} = 0.302, FE p_{fdr} = 0.036).

Hippocampal theta/gamma phase-amplitude coupling correlates with the successful formation of episodic memories

The section above demonstrates that both theta and gamma band activity correlate with episodic memory functions. However, numerous theories suggest that it is the interaction between these two bands that is essential for episodic memory. To address this hypothesis, we investigated whether functional coupling between hippocampal theta phase and gamma power can be observed during these same time windows. To test this, we computed the phase-locking value between the hippocampal theta phase and the hippocampal gamma envelope of each participant (separately for "fast" and "slow" gamma bands)[47]. When analysing phase-amplitude coupling between theta and "fast" gamma, a significant increase was observed for later remembered, relative to later forgotten, stimuli during the encoding of the verbal stimulus (p < 0.001; see fig 5a-c), but not during the encoding of the dynamic stimulus (p = 0.188). Control analyses revealed no difference in phase-amplitude coupling

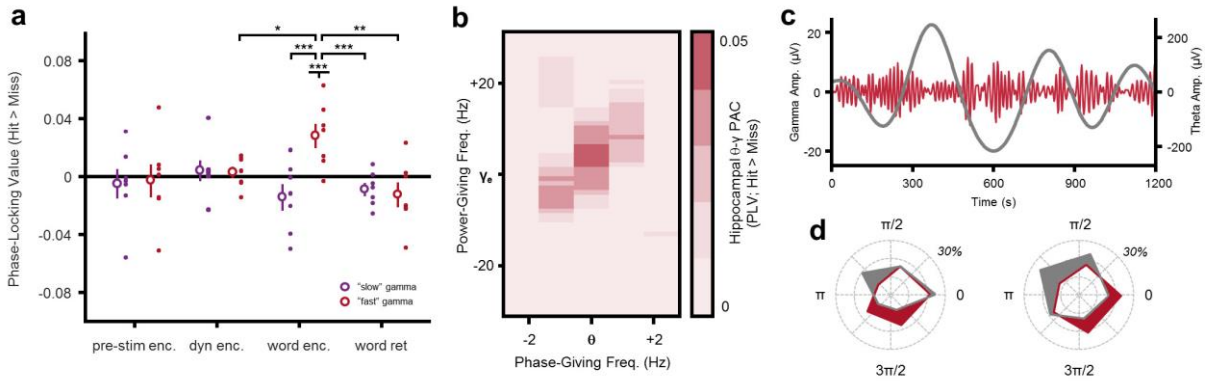

Figure 5. Hippocampal theta-gamma phase amplitude coupling during episodic memory formation and retrieval. **(a)** the mean difference (with standard error of the mean and individual patient data points) in phase-amplitude coupling between hits and misses for theta locked to "fast" gamma (red) and "slow" gamma (purple) [*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$]. **(b)** a co-modulogram showing the difference in phase-amplitude coupling between hits and misses as a function of theta phase and encoding-related, "fast" gamma power during the presentation of the verbal stimulus at encoding. **(c)** a hippocampal recording from "patient 1" depicting an increase in gamma amplitude (red; filtered with band-pass FIR at 67±5 Hz) during the trough of the ongoing theta cycle (grey; filtered with band-pass FIR at 2.5±0.5 Hz). **(d)** preferred theta phase for gamma power locking in patient 2 (left) and 7 (right; proportion of trials; hits in red; misses in grey).

between remembered and forgotten trials during the encoding pre-stimulus interval ($p > 0.5$) or during the presentation of the verbal stimulus at retrieval ($p > 0.5$). When analysing phase-amplitude coupling between theta and "slow" gamma, no difference between remembered and forgotten items was observed in any time window (verbal stimulus at encoding: $p > 0.5$; dynamic stimulus at encoding: $p = 0.262$; pre-stimulus interval at encoding: $p > 0.5$; verbal stimulus at retrieval: $p > 0.5$).

Importantly, if the hippocampus supports episodic binding[e.g.25], we would anticipate that theta-gamma coupling is only prevalent during the presentation of the second (i.e. verbal) stimulus, as both stimuli need to be presented before inter-item binding can occur. To test this, we contrast the memory-related "fast" gamma PAC effect during verbal stimulus presentation with the same effect observed during dynamic stimulus presentation. In support of the representational binding account, we found a significant increase in memory-related "fast" gamma PAC during the presentation of the verbal stimulus, relative to the presentation of the dynamic stimulus ($p = 0.014$).

To test whether the verbal encoding PAC effect was restricted to the "fast" gamma band, memory-related "fast" gamma PAC was contrasted with "slow" gamma PAC during the period when the verbal stimulus was presented at encoding. Indeed, we found significantly greater PAC in the "fast" gamma band relative to the "slow" gamma band ($p < 0.001$), providing further evidence that "fast" gamma is functionally distinct from "slow" gamma during episodic memory formation.

Lastly, while we anticipated observing similar coupling during retrieval based on earlier accounts[7], its absence conforms to other claims that theta-gamma coupling is more prevalent during encoding relative to retrieval[6]. To directly test these claims, we contrasted the "fast" gamma verbal PAC subsequent memory effect with the "fast" and "slow" gamma PAC retrieval success effect. Conforming to the notion that PAC is predominately restricted to encoding, we found significantly greater "fast" gamma PAC at encoding than "fast" or "slow" gamma PAC at retrieval ($p = 0.008$ and $p < 0.001$ respectively).

Phase-amplitude coupling is an analytical method susceptible to several confounds[48]. To avoid a cumbersome results section, we have resolved concerns about trial number imbalances, event-related potentials, asymmetric waveforms, power differences between conditions, meaningful phase/power-giving frequencies and bandwidth in the supplementary materials.

Hippocampal theta/gamma synchronisation and neocortical alpha/beta desynchronisation cooperate during the encoding and retrieval of human episodic memories

So far, we have demonstrated that both neocortical desynchronisation and hippocampal synchronisation are prevalent during episodic memory processes. Critically however, the synchronisation/desynchronisation framework[3] would predict that, during encoding, these two markers correlate such that the degree of neocortical desynchronisation can predict the degree of hippocampal synchronisation. On a cognitive level, this would signify information processing within the neocortex preceding representational binding in the hippocampus. To test this theory, we cross-correlated the neocortical alpha/beta power time-series with the hippocampal theta and gamma power time-series. This analysis offsets the neocortical time-series relative to the hippocampal time-series in an attempt to identify at what time lag the two time-series most strongly correlate. The cross-correlation was computed for every trial, and the subsequent memory effect (SME) was calculated by subtracting the mean cross-correlation across forgotten items from the mean cross-correlation across remembered trials. By calculating the SME, any correlation between the two time-series that is driven by shared noise (originating from a shared reference) is removed, as this correlation is consistent across remembered and forgotten trials. Furthermore, the SME highlights memory-specific dynamics in neocortical-hippocampal links, rather than general, memory-unspecific connectivity. Relative to later forgotten items, later remembered items showed a significant negative cross-correlation between ATL alpha/beta power and hippocampal "fast" gamma power ($p_{fdr} = 0.037$; see fig. 6a for difference line plot; see supp. fig. 3 for separate hit/miss line plots). Critically, this cross-correlation suggests that alpha/beta power decreases precede "fast" gamma power increases by approximately 100-200ms. No link was observed

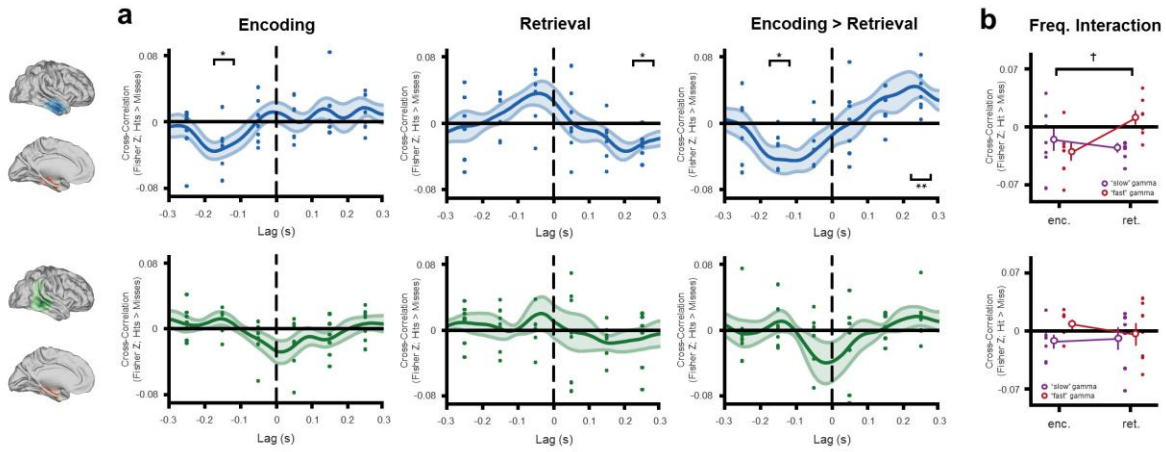

Figure 6. Hippocampal-neocortical time-series cross-correlations. **(a)** mean cross correlation (with shaded standard error of the mean) between the hippocampal gamma power and neocortical alpha/beta power (anterior temporal lobe in blue; posterior temporal/parietal region in green). Dots represent individual patient means. A negative lag indicates that neocortical power fluctuations precede hippocampal fluctuations; a positive lag indicates the reverse. During encoding (left), ATL power decreases precede hippocampal "fast" gamma power increases. During retrieval (middle), ATL power decreases follow hippocampal "slow" gamma power increases. The contrast of activity between encoding and retrieval (right) confirms this interaction [$*p_{fdr} < 0.05$]. **(b)** Mean gamma power ("slow" in purple; "fast" in red; with standard error of the mean) as a function of memory operation. A repeated-measures ANOVA reveals an interaction between hippocampal gamma frequency and memory task when predicting memory-related hippocampal-neocortical cross-correlation ($^{\dagger}p = 0.051$).

between ATL alpha/beta power and hippocampal "slow" gamma power ($p_{fdr} = 0.419$). Alpha/beta power in the PTPR did not cross-correlate with hippocampal "fast" or "slow" gamma power ($p_{fdr} = 0.247$ and $p_{fdr} = 0.216$ respectively). No link was observed between hippocampal theta and ATL/ PTPR alpha/beta power (both $p_{fdr} > 0.5$). These results indicate that a unique connection exists between the ATL and the hippocampus during episodic memory formation, where ATL alpha/beta desynchronisation precedes hippocampal "fast" gamma synchronisation.

We then investigated whether this relationship reverses (i.e. hippocampal synchronisation precedes neocortical desynchronisation) during episodic memory retrieval. 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 retrieval success effect (RSE) by subtracting the mean cross-correlation across forgotten items from the mean cross-correlation across remembered trials. The RSE was calculated for the same reasons as the SME (see above). Relative to forgotten items, remembered items showed a significant negative cross-correlation between ATL alpha/beta power and hippocampal "slow" gamma power ($p_{fdr} = 0.042$; see fig. 6a for difference line plot; see supp. fig. 3 for separate hit/miss line plots), where an increase in hippocampal gamma

power would precede a decrease in ATL alpha/beta power by 200-300ms (see sup. fig. 2 for separate remembered and forgotten cross-correlations). No link was observed between ATL alpha/beta power and hippocampal "fast" gamma power (p_{fdr} > 0.5), nor between PTPR alpha/beta power and hippocampal "fast" or "slow" gamma power (p_{fdr} > 0.5 and p_{fdr} = 0.217 respectively). No link was observed between hippocampal theta and ATL/ PTPR alpha/beta power (both p_{fdr} > 0.5). These results indicate that hippocampal "slow" gamma synchronisation precedes ATL alpha/beta desynchronisation 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 random effects, non-parametric, permutation-based t-test. This revealed an interaction whereby ATL desynchrony preceded hippocampal synchrony during encoding (p_{fdr} = 0.024; 100-200ms) but hippocampal synchrony preceded ATL desynchrony during retrieval (p_{fdr} = 0.001; 200-300ms) [see fig. 6a for difference line plot; see supp. fig. 3 for separate hit/miss line plots]. No interaction was observed when analysing the PTPR-hippocampus cross-correlation. These results support those reported in the previous two paragraphs; 1) ATL alpha/beta desynchronisation precedes hippocampal "fast" gamma synchronisation during episodic memory formation and 2) hippocampal "slow" gamma synchronisation precedes ATL alpha/beta desynchronisation 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 non-parametric, permutation-based, 2x2 repeated measures ANOVA (memory operation x gamma frequency), taking encoding-related activity from the -200 to -100ms time bin and retrieval-related activity from the 200 to 300ms time bin. Analysis revealed a trending interaction between the two factors (p = 0.051). Figure 6b 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.

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 two processes are accomplished by neocortical oscillatory desynchronisation (reflected by decreases in alpha/beta oscillatory power) and hippocampal oscillatory synchronisation (reflected by increases in theta/gamma oscillatory power and theta-gamma phase-amplitude coupling) respectively[3,5,7,25]. Here, we provide the first empirical evidence that these two processes co-exist and interact. During successful episodic memory formation, alpha/beta power decreases in the anterior temporal lobe (ATL) reliably precedes "fast" hippocampal gamma power increases (60-80Hz) by 100-200ms. In contrast, "slow" hippocampal gamma power increases (40-50Hz) precede alpha/beta power decreases by 200-300ms during successful episodic memory retrieval. These findings demonstrate that the cooperation between neocortical desynchronisation and hippocampal synchronisation underpins the formation and retrieval of episodic memories.

Our central finding demonstrates that ATL alpha/beta desynchronisation and hippocampal theta/gamma synchronisation cooperate during the formation and retrieval of episodic memories. This result draws together a multitude of conflicting studies, some which indicate that synchronisation benefits memory[e.g.27,30,31] and others which indicate that desynchronisation benefits memory[e.g.12,23,49], and provides a possible empirical resolution to the so-called "synchronisation-desynchronisation conundrum"[3]. These findings are in line with previous observations demonstrating that hippocampal gamma synchrony precedes hippocampal alpha desynchrony during associative memory retrieval[50]. However, we are the first to show that this sequence reverses during encoding, and to link these two mechanisms across brain regions (via simultaneous hippocampal-neocortical recordings unavailable to [50]). We speculate that the delay in hippocampal response relative to ATL alpha/beta desynchronisation 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[25,26]. In contrast, we posit that the ATL delay in response relative to hippocampal gamma synchrony during retrieval reflects the need for the hippocampal representational code to be reactivated prior to reinstating highly-detailed semantic information about the event[51]. Anatomically speaking, this reciprocal communication may be facilitated by the "direct intrahippocampal pathway" – a route with reciprocal connections between the ATL and hippocampus via the entorhinal cortex[52,53] (parsimoniously, the absence of connections between the PTPR and hippocampus via this pathway may explain why no similar PTPR-hippocampus cross-correlation was observed). 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 hippocampal retrieval signals into the neocortex during retrieval.

We also uncovered the first empirical evidence of distinct gamma rhythms supporting human episodic memory formation and retrieval[7,32]. Specifically, we found that "fast" gamma oscillatory activity (60-80Hz) dominates encoding while "slow" gamma oscillatory activity (40-50Hz) dominates retrieval, generalising earlier rodent findings [e.g.34] to humans. We uncovered similar distinctions in "fast" and "slow" gamma band activity when investigating memory-related changes in power, phase-amplitude coupling and neocortical-hippocampal cross-correlations, providing additional evidence for the distinction. Earlier rodent studies have suggested that the distinction between the two gamma bands reflects a difference in CA1 coupling[34]; "fast" gamma oscillations support CA1-entorhinal cortex coupling, facilitating the transfer of information into the hippocampus, while "slow" gamma oscillations support CA1-CA3 coupling, facilitating the reactivation of stored information. We speculate that these patterns of connectivity extrapolate to humans and explain the observed differences in gamma frequency relating to episodic memory formation and retrieval. Intriguingly, our findings also suggest that successful memory formation is accompanied not only by an increase in "fast" gamma power, but also a reduction in "slow" gamma power. Specific to this experiment, the reduction in "slow" gamma power may translate to an attenuation of retrieval-related interference induced by the reactivation of different verbal stimuli associated with the same dynamic stimulus. Peculiarly, we did not see the anticipated time-locked "slow" gamma power increase effect at retrieval. This could be explained by the greater temporal variability in neural responses to retrieval relative to encoding masking the effect. In sum, our results suggest that "fast" and "slow" gamma activity relates to distinct processes in the successful formation 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 neocortical alpha/beta desynchronisation and hippocampal "fast" gamma synchronisation during memory formation reflects the flow of semantic information (processed in the desynchronised ATL) to entorhinal cortex[26] via the direct intrahippocampal pathway[52,53], where "fast" gamma synchronicity between the entorhinal cortex and CA1 passes this information onto the hippocampus[34,54]. In contrast, the link between hippocampal "slow" gamma synchronisation and neocortical alpha/beta desynchronisation during memory retrieval reflects the flow of reactivated representational codes from CA3 to CA1 (via "slow" gamma synchronicity[34,54]), which propagates out into the neocortex[51] via reciprocal connections in the direct intrahippocampal

pathway, reinstating semantic details in the desynchronised ATL. However, future research with direct recordings from these hippocampal sub-regions in humans is needed to empirically test this proposed flow of information during episodic memory formation and retrieval.

In addition to these novel findings, we uncovered evidence for an increase in theta-"fast" gamma phase-amplitude coupling during the formation of episodic memories. As phase-amplitude coupling is an analytical method subject to numerous physiological[55] and analytical[48] confounds that can produce spurious results, we have conducted numerous control analyses (see supplementary materials) to support our finding of hippocampal theta-gamma phase-amplitude coupling in human episodic memory. Previous accounts have suggested that hippocampal theta-gamma phase-amplitude coupling underpins the representational binding of discrete elements of an event into a coherent episodic memory. We find support for this hypothesis by identifying the presence of memory-related phase-amplitude coupling during the presentation of the verbal stimulus (where verbal-to-dynamic stimulus binding could occur), and not identifying the same phase-amplitude coupling during the presentation of the dynamic stimulus (where verbal-to-dynamic stimulus binding could not occur, as the verbal stimulus has yet to be presented). Moreover, we observed a significant increase in memory-related phase-amplitude coupling during the presentation of the verbal stimuli relative to the dynamic stimuli. In conjunction, these results provide strong support for the notion that theta-gamma phase-amplitude coupling relates to representational binding in episodic memory. Whether this coupling reflects item-to-item binding or a more holistic binding of the entire event remains an open question however. Concerns that this coupling is driven by stimulus modality (i.e. verbal vs. visual/audio) are unfounded as no coupling is observed during presentation of the same verbal stimuli at retrieval. Similarly, concerns that the observed hippocampal coupling reflects the maintenance of the previously presented dynamic stimulus[56,57] are unfounded as no hippocampal coupling was observed during the presentation of the retrieval cue, a period when patients must maintain the recalled dynamic stimulus for later response. Rather, it would appear that the hippocampal theta-gamma phase-amplitude coupling observed during successful memory formation is uniquely linked to the binding of disparate elements into a coherent episodic memory.

Lastly, we found that ATL alpha/beta desynchronisation accompanies the successful formation and retrieval of episodic memories, supporting a wealth of research preceding our findings (for reviews, see [3,5]). Importantly, while alpha/beta desynchronisation could be reliably predicted by verbal stimulus onset during episodic memory formation, the same was not true for retrieval. We speculate that this is due to greater temporal variability in

neocortical desynchrony during retrieval relative to encoding. As retrieval requires hippocampal pattern completion prior to the neocortical information reinstatement (an intermediary step absent for encoding), any temporal variability in the pattern completion process would impair our ability to time-lock neocortical desynchrony to verbal stimulus onset. Under this assumption however, we would also expect ATL desynchrony to lock to hippocampal activity relating to pattern completion, such as hippocampal gamma activity[33,50]. Our cross-correlation results support this idea, demonstrating that ATL alpha/beta desynchronisation can be reliably predicted by preceding hippocampal "slow" gamma synchronisation during episodic memory retrieval. In short, these findings suggest that ATL alpha/beta desynchronisation accompanying episodic memory encoding and retrieval may time-lock to different events.

Three questions remain however: First, why does neocortical alpha/beta desynchronisation cross-correlate with hippocampal gamma synchronisation, but not hippocampal theta synchronisation? We argue that it is not theta power but theta phase that is most important for memory formation and retrieval. This stance conforms to several existing theories of episodic memory that posit that hippocampal theta phase, not power, facilitates representational binding and organisation[6,7,25].

Second, do similar bi-directional 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 bi-directional links do exist. For example, hippocampal gamma synchronisation may co-ordinate with alpha/beta desynchronisation in the visual cortex to facilitate the encoding and retrieval of visual memories[19]. Speculating further, hippocampal gamma synchronisation may be the metaphorical spark that lights the fuse of memory replay, coded in desynchronised neocortical alpha phase patterns[18].

Third, why is human hippocampal theta (~2.5Hz) "slow" in comparison to rodent hippocampal theta (~8Hz), but similar "slowing" is not observed within the gamma band? The notion that human hippocampal theta is slower than that of rodents is not controversial[58,59]. It has been proposed that the "slowing" of hippocampal theta oscillations is beneficial as it compensates for conduction delays within the hippocampus (a by-product of massive brain scaling resulting from evolution). In contrast, the "slowing" of hippocampal gamma oscillations may be detrimental for learning. Speculatively, a slower gamma rhythm would mean that interacting neurons no longer fire at a rate optimal for spike-timing dependent plasticity (STDP; a form of long-term potentiation), limiting synaptic strengthening. In support of these ideas, empirical evidence suggests that theta rhythms

"slow" to a much greater degree than gamma rhythms as brain size increases (see fig. 2B in [59]). In short, theta rhythms "slow" to facilitate communication over greater distances, while gamma rhythms remain consistent to preserve STDP.

In summary, we deliver the first empirical evidence that neocortical desynchronisation and hippocampal synchronisation cooperate during the formation and retrieval of episodic memories, providing evidence that may help resolve the so-called "synchronisation-desynchronisation conundrum"[3]. Furthermore, we provide the first evidence that distinct hippocampal gamma oscillations service human episodic memory formation and retrieval, with faster (~60-80Hz) oscillations supporting encoding and slower (~40-50Hz) oscillations supporting retrieval. In conjunction, these results further illuminate our understanding of how co-ordinated oscillatory synchronisation and desynchronisation help build and retrieve memories of our past experiences.

Methods

Participants

Nine participants (n = 7 from Queen Elizabeth Hospital Birmingham, UK; n = 2 from University Hospital Erlangen, Germany; 55.6% female; mean age = 35.8 years, range = 24 to 53 years) undergoing treatment for medication-resistant epilepsy took part in the experiment. These participants had intracranial depth electrodes implanted for diagnostic purposes. Ethical approval was granted by the NHS 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.

Behavioural paradigm

Each participant completed a paired associates task (see fig. 1d). During encoding, participants were presented with one of four videos or sounds followed by a word in the participant's native language (English, n = 7; German; n = 2). Due to time restraints, some participants only completed the experiment using one modality of dynamic stimulus (sound, n=1; video, n=5; both, n=3). Participants were asked to "vividly associate" these two 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 two stimuli (the plausibility judgement was used to keep participants on task rather than to yield a meaningful metric). After encoding, participants completed a 2-minute distractor task which involved making odd/even judgements for random integers ranging from 1 to 99. During retrieval, participants were presented with every word that was presented in the earlier encoding stage and, 3 seconds later, asked to identify the associated video/sound. 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 two 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 patient that had fewer than 10 "remembered" or 10 "forgotten" trials after iEEG pre-processing were excluded from further analysis (n=1).

Behavioural analysis

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). Participants, on averaged, recalled 52.0% of all pairs (standard deviation = 17.1%), a percentage much greater than what would be expected by chance (25%).

iEEG acquisition and preprocessing

First, the raw data was epoched; for encoding trials, epochs began 2 seconds before the onset of the visual/auditory stimulus and ended 4 seconds after verbal stimulus onset (9 seconds in total); for retrieval trials, epochs began 2 seconds before, and ended 4 seconds after, the onset of the verbal cue (6 seconds in total). Second, the data was filtered using a 0.2Hz finite-impulse response high-pass filter and 3 finite-impulse response band-pass filters at 50±1Hz, 100±1Hz and 150±1Hz, attenuating slow-drifts and line noise respectively. Third, as the iEEG data was sampled at the physician's discretion (512Hz, n=1; 1024Hz, n=8), all data was down-sampled to 500Hz. Fourth, the data from each electrode was re-referenced to an electrode on the same shaft that was positioned in white matter (determined by visual inspection of the patient anatomy; see below). Finally, the data was visually inspected and any trials exhibiting artefactual activity were excluded from further analysis. Any channels exhibiting persistent ictal and interictal activity were discarded from analysis.

Electrode localisation

First, hippocampal and white matter contacts were defined based on anatomical location through visual inspection of the T1 scan (N.B. one patient had no hippocampal contacts, and therefore was excluded from all hippocampal-based analyses). Then, the native space co-ordinates of all remaining contacts were determined by visual inspection of each patient's post-implantation T1 scan. These contact co-ordinates were then transformed from native space to MNI space using a transform matrix obtained by normalising patient T1 scans in SPM 12. These contacts were then marked as within the anterior temporal lobe (ATL), posterior temporal/parietal region (PTPR), or elsewhere (this latter group was excluded from further analysis).The ATL was defined as all parts of the temporal lobe (as defined by the *wfupickatlas* plugin[60] for SPM 12; http://fmri.wfubmc.edu/software/pickatlas) anterior to a plane perpendicular to the long axis of the temporal lobe[45]. The plane was slightly shifted from that described in [45] to [y=-5, z=-30; y=15, z=-5] for the pragmatic reason of ensuring that all participants had electrode contacts in the ATL ROI. The PTPR was defined as the temporal and parietal lobe (as defined by the *wfupickatlas* plugin[60] for SPM 12) posterior to this same plane. For visualisation in figure 1d, every electrode from every patient was given a diameter of 1cm and then placed in a

template brain registered in MNI space. The number of electrodes in each voxel was then summed to provide a measure of summed density.

1/f correction

Memory-related differences in power have been shown to be influenced by broadband changes in the power spectrum[44]. To rule out the possibility that our power-related memory effects are driven by broadband spectral dynamics, we subtracted the 1/f power characteristic from all wavelet-based analyses. Spectral power was computed using 199 linearly-spaced 5-cycle wavelets ranging from 1 to 100Hz. The time-frequency decomposition method was kept consistent across all frequency bands to ensure that only a single slope (characterising the full extent of the 1/f dynamic) needed to be calculated and subsequently subtracted from the signal (in line with previous experiments that have extracted the 1/f characteristic from the signal [e.g.42,43]). A vector containing values of each wavelet frequency (*A*) and another vector containing the power spectrum for each channel-sample pair (*B*) were then log-transformed. The linear equation $Ax = B$ was solved using least squares regression, where x is an unknown constant describing the curvature of the 1/f characteristic (the function used can be found in the Github repository listed in the *Code Availability* section below). The 1/f curve (Ax) was then subtracted from the log-transformed power-spectrum (*B)*. This approach removes the 1/f curve while retaining oscillatory peaks in the power spectrum (see fig. 2A for 1/f-corrected power-spectra).

Peak frequency analysis

To identify dominant frequencies within the hippocampus and neocortex, the raw signal recorded at every contact for each epoch was convolved with a 5-cycle wavelet (0 to 1500ms post-stimulus [padded with real data for lower frequencies], in steps of 25ms; 1Hz to 100Hz, in steps of 0.5Hz). The 1/f noise was subtracted using the method described above to help pronounce the peaks in the power-spectrum. The data was then smoothed using a Gaussian kernel (200ms; 1Hz) to attenuate inter- and intra-individual differences in spectral responses[61,62] and to help approximate normally distributed data (an assumption frequently violated in small samples). The data was averaged across all time-points, trials and contacts (separately for the hippocampus, ATL and PTPR). Peaks of 1/f corrected absolute power were then visually identified for each participant. To allow group comparisons (e.g. in figure 2), the power-spectrum of each participant was z-transformed using the mean and standard deviation across trial/contact/time-averaged frequencies prior to plotting.

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 (200ms, 5Hz). The absolute power for the averaged retrieval epochs was subtracted from the absolute power for the averaged encoding epochs and the encoding-related/retrieval-related gamma peaks were visually identified for each participant.

To quantify the difference in "fast"/"slow" gamma, the power-spectra for encoding and retrieval were collapsed in seven 10Hz bins ranging from 30Hz to 100Hz and then contrasted in a random effects, non-parametric permutation-based t-test (5000 randomisations; for details, see Maris and Oostenveld,

2007). The multiple comparison issue was solved using the false-discovery rate correction [64]. To confirm that this difference was related to memory as opposed to a difference in task, this analysis was repeated using the "forgotten" trials.

Selection of peak frequencies

All subsequent analyses are based on individual 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: 1-7Hz; alpha/beta: 8-20Hz; "slow" gamma: 30-60Hz; "fast" gamma: 60-100Hz). This led to the successful identification of peaks for all frequency bands, in all patients, apart from the "fast" and "slow" gamma peak for patient 2. Consequently, we used the average "fast" and "slow" gamma peak frequency for this patient. The bandwidths of these peaks were kept consistent across participants, and were determined through inspection of the group-averaged bandwidth of the peaks (theta: ±0.5Hz; alpha/beta: -1Hz/+5Hz [capturing the observed asymmetry in the peak]; "slow"/"fast" gamma: ±10Hz). Individual peak frequencies are reported in Supplementary Table 1.

Spectral power analysis

For all spectral power analyses (i.e. encoding and retrieval epochs), the data underwent the same wavelet convolution, 1/f correction, and smoothing approaches described in the *peak frequency analysis* section. The data was then z-transformed. To this end, the means and standard deviations of each channel-frequency pair was derived by collapsing each trial over time, and then calculating the statistic across trials[13]. The time-frequency resolved data was then averaged over channels to provide a time-series for each "ROI" x "peak frequency band" pair.

For time-series statistical analysis, trials were split into two groups based on whether the stimuli were remembered or forgotten. Then, the time-series were collapsed into seven time bins of 200ms ranging from verbal stimulus onset to 1400ms after onset. The two conditions were then contrasted using the same non-parametric statistical procedure described in the *peak frequency analysis* section.

For statistical analyses of the interaction between memory task (encoding vs. retrieval) and gamma frequency ("fast" vs. "slow"), the difference between remembered and forgotten stimuli was calculated. Then, this memory-related power was averaged over time and entered into a non-parametric, permutation based 2x2 repeated measures ANOVA. First, the observed interaction term was derived, Second, for each of the 5000 permutations, the values for each category (encoding-"fast; encoding-"slow"; retrieval-"fast"; retrieval-"slow") were randomly permuted and the interaction term was computed again. Lastly, the p-value was derived by examining the position of the observed F-statistic against the permuted F-statistic distribution.

For population-reliability analyses, we took inspiration from Efron[46]. Efron ran a bootstrapping test where participant data was resampled with replacement and then subjected to Bayesian analysis. Each resample that yielded a positive log Bayes factor was viewed as evidence in favour of the alternative hypothesis. We integrated this approach with our interaction analysis described in the paragraph above. The channel data was resampled with replacement and then subjected to the interaction analysis. The observed F-statistic was then contrasted with the median of the permuted F-

statistic distribution. Like Efron, any observed F-statistic that yielded an F-statistic greater than the median permuted F-statistic was viewed as evidence for the alternative hypothesis. The resampling procedure was conducted 1000 times and the percentage of times where the procedure yielded evidence for the alternative hypothesis was computed. This percentage was interpreted as the population-level reliability.

Phase-amplitude coupling analysis

Theta-gamma phase amplitude coupling within the hippocampus was assessed for every trial using phase-locking value [47]. The consistency between the angles of the peak theta phase (±0.5Hz) and the peak gamma (±5Hz) power envelope was computed for windows of 1000ms (reducing concerns of non-stationarity introduced by long epochs), with an overlap of 750ms between bins, for each individual trial (for further details, see [47]). By calculating phase-locking value on a single-trial level, issues with trial number imbalances between conditions can be side-stepped as each phase-locking value is calculated on the same number of samples. That said, single-trial analysis could mean gamma is locked to different phases of the theta cycle on each trial, and therefore would not serve any mechanistic purpose. To alleviate these concerns, we tested for non-uniformity in gamma-power-to-theta-phase-locking (i.e. phase preference), and have included individual polar plots detailing the distribution of the preferred phase for gamma-locking (see figure 4d for examples, see supplementary figure 4 for all patients). Across subjects, a Rayleigh test revealed that later remembered items demonstrated a significant deviation from uniformity ($z = 3.714$, $p = 0.018$), suggesting gamma power peaked at a preferred phase of the theta cycle during successful memory formation. No deviation from uniformity was observed for later forgotten items ($z = 1.354$, $p = 0.267$). Phase-amplitude coupling was computed for four time windows (word at encoding [500ms to 2500ms], dynamic stimulus at encoding [500ms to 2500ms], word at retrieval [500ms to 2500ms], and encoding pre-stimulus interval [-2000ms to 0ms]). The first 500ms after stimulus onset was excluded to alleviate concerns that any observed phase-amplitude coupling may be driven by non-stationarity induced by the event-related potential. The observed phase-locking values for each contact were averaged to provide a single measure of phase-amplitude coupling in the hippocampus per trial. For statistical analysis, trials were split based on whether they were later remembered or later forgotten and contrasted using the same non-parametric statistical procedure described in the *peak frequency analysis* section.

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 the *spectral power analysis* section, with two exceptions: 1) wavelet convolution occurred in steps of 10ms rather than 50ms (enhancing temporal resolution), and 2) the temporal aspect of the smoothing kernel was reduced to 50ms to avoid excessive smoothing obscuring the temporal dynamics of the neocortical-hippocampal cross-correlation. For each “trial x channel combination” pair, the cross-correlation between the hippocampus and the ATL, and the cross-correlation between the hippocampus and PTPR, was computed using the Matlab function crosscorr() with a lag of 300ms (meaning the

correlation between hippocampus and neocortex was considered for every offset from where the neocortex preceded the hippocampus by 300ms to where the neocortex lagged behind the hippocampus by 300ms). This returned a time-series of Pearson correlation values describing the relationship between hippocampus and neocortex at all considered lags. These correlation values were then averaged over channels and split into two groups: remembered and forgotten. These two groups were individually averaged over trials for each participant, collapsed into bins of 100ms, and then contrasted using the same non-parametric statistical procedure described in the *peak frequency analysis* section. 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" x "lag-lead" difference, we contrasted the subsequent memory cross-correlation with the retrieval success using the same non-parametric statistical procedure described in the *peak frequency analysis* section.

Lastly, to test the influence of the "memory task" x "gamma frequency" interaction on the memory-related cross-correlation differences, we conducted a non-parametric, permutation-based 2x2 repeated measures ANOVA in the same manner as described in the *spectral power analysis* section.

Acknowledgements

Thanks to data provided courtesy of Ehren Newman, who provided additional data for analysis (Indiana University Bloomington, Department of Psychological and Brain Sciences).

Author Contributions

B.J.G. designed the experiment, carried out research and analysis, and wrote the paper. S.M. designed the experiment, and provided feedback on paper. F.R. guided cross-frequency coupling analysis, and provided feedback on paper. D.T.R, R.C., V.S., H.H., S.G., & G.K. helped recruit patients, implement the testing setup and provided technical guidance on recording the iEEG data. M.W. & B.S. provided feedback on paper. S.H. designed the experiment, wrote the paper, and guided data analysis.

Competing Interests

The authors declare no competing interests.

Data Availability

All correspondence and material requests should be addressed to Simon Hanslmayr (s.hanslmayr@bham.ac.uk). The datasets analysed during the current study are available from the corresponding author on reasonable request.

Code Availability

All analyses scripts have been made openly available on GitHub (https://github.com/benjaminGriffiths/ieeg_sync_desync) [N.B. folder will be made public on manuscript acceptance].

References

1. Tulving, E. Episodic memory: from mind to brain. *Annu. Rev. Psychol.* **53,** 1–25 (2002).

2. Tulving, E. & Thomson, D. Encoding specificity and retrieval processes in episodic memory. *Psychol. Rev.* **80,** 352–373 (1973).

3. Hanslmayr, S., Staresina, B. P. & Bowman, H. Oscillations and episodic memory – Addressing the synchronization/desynchronization conundrum. *Trends Neurosci.* **39,** 16–25 (2016).

4. Parish, G., Hanslmayr, S. & Bowman, H. The Sync/deSync model: How a synchronized hippocampus and a de-synchronized neocortex code memories. *bioRxiv* 1–35 (2017). at <http://www.biorxiv.org/content/early/2017/09/06/185231>

5. Hanslmayr, S., Staudigl, T. & Fellner, M.-C. Oscillatory power decreases and long-term memory: the information via desynchronization hypothesis. *Front. Hum. Neurosci.* **6,** 1–12 (2012).

6. Nyhus, E. & Curran, T. Functional role of gamma and theta oscillations in episodic memory. *Neurosci. Biobehav. Rev.* **34,** 1023–1035 (2010).

7. Colgin, L. L. Theta-gamma coupling in the entorhinal-hippocampal system. *Curr. Opin. Neurobiol.* **31,** 45–50 (2015).

8. Shannon, C. E. & Weaver, W. *A mathematical theory of communication*. (University of Illinois Press, 1949).

9. Greenberg, J. A., Burke, J. F., Haque, R., Kahana, M. J. & Zaghloul, K. A. Decreases in theta and increases in high frequency activity underlie associative memory encoding. *Neuroimage* **114,** 257–63 (2015).

10. Guderian, S., Schott, B. H., Richardson-Klavehn, a. & Duzel, E. Medial temporal

theta state before an event predicts episodic encoding success in humans. *Proc. Natl. Acad. Sci.* **106,** 5365–5370 (2009).

11. Fellner, M.-C., Bäuml, K.-H. T. & Hanslmayr, S. Brain oscillatory subsequent memory effects differ in power and long-range synchronization between semantic and survival processing. *Neuroimage* **79,** 361–370 (2013).

12. Hanslmayr, S. *et al.* The relationship between brain oscillations and BOLD signal during memory formation: A combined EEG-fMRI study. *J. Neurosci.* **31,** 15674–15680 (2011).

13. Griffiths, B., Mazaheri, A., Debener, S. & Hanslmayr, S. Brain oscillations track the formation of episodic memories in the real world. *Neuroimage* **143,** 256–266 (2016).

14. Weiss, S. & Rappelsberger, P. Long-range EEG synchronization during word encoding correlates with successful memory performance. *Cogn. Brain Res.* **9,** 299–312 (2000).

15. Lega, B., Germi, J. & Rugg, M. D. Modulation of oscillatory power and connectivity in the human posterior cingulate cortex supports the encoding and retrieval of episodic memories. *J. Cogn. Neurosci.* **29,** 1415–1432 (2017).

16. Noh, E., Herzmann, G., Curran, T. & De Sa, V. R. Using single-trial EEG to predict and analyze subsequent memory. *Neuroimage* **84,** 712–723 (2014).

17. Hanslmayr, S., Spitzer, B. & Bauml, K.-H. Brain oscillations dissociate between semantic and nonsemantic encoding of episodic memories. *Cereb. Cortex* **19,** 1631–1640 (2009).

18. Michelmann, S., Bowman, H. & Hanslmayr, S. The temporal signature of memories: Identification of a general mechanism for dynamic memory replay in humans. *PLOS Biol.* **14,** e1002528 (2016).

19. Waldhauser, G. T., Braun, V. & Hanslmayr, S. Episodic memory retrieval functionally relies on very rapid reactivation of sensory information. *J. Neurosci.* **36,** 251–260 (2016).

20. Burgess, A. P. & Gruzelier, J. H. Short duration power changes in the EEG during recognition memory for words and faces. *Psychophysiology* **37,** 596–606 (2000).

21. Dujardin, K., Bourriez, J. L. & Guieu, J. D. Event-Related Desynchronization (ERD) patterns during verbal memory tasks: effect of age. *Int. J. Psychophysiol.* **16,** 17–27 (1994).

22. Zion-Golumbic, E., Kutas, M. & Bentin, S. Neural dynamics associated with semantic and episodic memory for faces: evidence from multiple frequency bands. *J. Cogn. Neurosci.* **22,** 263–277 (2010).

23. Khader, P. H. & Rösler, F. EEG power changes reflect distinct mechanisms during long-term memory retrieval. *Psychophysiology* **48,** 362–369 (2011).

24. Hanslmayr, S., Matuschek, J. & Fellner, M.-C. Entrainment of prefrontal beta oscillations induces an endogenous echo and impairs memory formation. *Curr. Biol.* **24,** 904–909 (2014).

25. Lisman, J. E. & Jensen, O. The theta-gamma neural code. *Neuron* **77,** 1002–1016 (2013).

26. Davachi, L. Item, context and relational episodic encoding in humans. *Curr. Opin. Neurobiol.* **16,** 693–700 (2006).

27. Tort, A. B. L., Komorowski, R. W., Manns, J. R., Kopell, N. J. & Eichenbaum, H. Theta-gamma coupling increases during the learning of item-context associations. *Proc. Natl. Acad. Sci.* **106,** 20942–20947 (2009).

28. Shirvalkar, P. R., Rapp, P. R. & Shapiro, M. L. Bidirectional changes to hippocampal theta-gamma comodulation predict memory for recent spatial episodes. *Proc. Natl. Acad. Sci. U. S. A.* **107,** 7054–7059 (2010).

29. Igarashi, K. M., Lu, L., Colgin, L. L., Moser, M. B. & Moser, E. I. Coordination of entorhinal-hippocampal ensemble activity during associative learning. *Nature* **510,** 143–147 (2014).

30. Heusser, A. C., Poeppel, D., Ezzyat, Y. & Davachi, L. Episodic sequence memory is supported by a theta-gamma phase code. *Nat. Neurosci.* **19,** (2016).

31. Staudigl, T. & Hanslmayr, S. Theta oscillations at encoding mediate the context-dependent nature of human episodic memory. *Curr. Biol.* **23,** 1101–1106 (2013).

32. Colgin, L. L. Do slow and fast gamma rhythms correspond to distinct functional states in the hippocampal network? *Brain Res.* **1621,** 309–315 (2015).

33. Colgin, L. L. & Moser, E. I. Gamma oscillations in the hippocampus. *Physiology* **25,** 319–329 (2010).

34. Colgin, L. L. *et al.* Frequency of gamma oscillations routes flow of information in the hippocampus. *Nature* **462,** 353–357 (2009).

35. Colgin, L. L. Rhythms of the hippocampal network. *Nat. Rev. Neurosci.* **17,** 239–249 (2016).

36. Visser, M., Jefferies, E. & Lambon Ralph, M. Semantic processing in the anterior temporal lobes: a meta-analysis of the functional neuroimaging literature. *J. Cogn. Neurosci.* **22,** 1083–1094 (2010).

37. Spaniol, J. *et al.* Event-related fMRI studies of episodic encoding and retrieval: Meta-analyses using activation likelihood estimation. *Neuropsychologia* **47,** 1765–1779 (2009).

38. Cabeza, R. Role of parietal regions in episodic memory retrieval: The dual attentional processes hypothesis. *Neuropsychologia* **46,** 1813–1827 (2008).

39. Ciaramelli, E., Grady, C. L. & Moscovitch, M. Top-down and bottom-up attention to memory: A hypothesis (AtoM) on the role of the posterior parietal cortex in memory retrieval. *Neuropsychologia* **46,** 1828–1851 (2008).

40. Vilberg, K. L. & Rugg, M. D. Memory retrieval and the parietal cortex: A review of evidence from a dual-process perspective. *Neuropsychologia* **46,** 1787–1799 (2008).

41. Hughes, A. M., Whitten, T. A., Caplan, J. B. & Dickson, C. T. BOSC: A better oscillation detection method, extracts both sustained and transient rhythms from rat hippocampal recordings. *Hippocampus* **22,** 1417–1428 (2012).

42. Manning, J. R., Jacobs, J., Fried, I. & Kahana, M. J. Broadband shifts in local field potential power spectra are correlated with single-neuron spiking in humans. *J. Neurosci.* **29,** 13613–13620 (2009).

43. Zhang, H. & Jacobs, J. Traveling theta waves in the human hippocampus. *J. Neurosci.* **35,** 12477–12487 (2015).

44. Burke, J. F., Ramayya, A. G. & Kahana, M. J. Human intracranial high-frequency activity during memory processing: Neural oscillations or stochastic volatility? *Curr. Opin. Neurobiol.* **31,** 104–110 (2015).

45. Rice, G. E., Ralph, M. A. L. & Hoffman, P. The roles of left versus right anterior temporal lobes in conceptual knowledge: An ALE meta-analysis of 97 functional neuroimaging studies. *Cereb. Cortex* **25,** 4374–4391 (2015).

46. Efron, B. Bootstrap methods: Another look at the jackknife. *Ann. Stat.* **7,** 1–26 (1979).

47. Jiang, H., Bahramisharif, A., van Gerven, M. a. J. & Jensen, O. Measuring directionality between neuronal oscillations of different frequencies. *Neuroimage* **118,**

359–367 (2015).

48. Aru, J. *et al.* Untangling cross-frequency coupling in neuroscience. *Curr. Opin. Neurobiol.* **31,** 51–61 (2014).

49. Spitzer, B., Hanslmayr, S., Opitz, B., Mecklinger, A. & Bäuml, K.-H. Oscillatory correlates of retrieval-induced forgetting in recognition memory. *J. Cogn. Neurosci.* **21,** 976–990 (2009).

50. Staresina, B. P. *et al.* Hippocampal pattern completion is linked to gamma power increases and alpha power decreases during recollection. *Elife* **5,** 1–18 (2016).

51. Rugg, M. D., Johnson, J. D., Park, H. & Uncapher, M. R. Encoding-retrieval overlap in human episodic memory: A functional neuroimaging perspective. *Prog. Brain Res.* **169,** 339–352 (2008).

52. Duvernoy, H. M. *The Human Hippocampus: Functional Anatomy, Vascularization, and Serial Sections with MRI*. (Springer, 2005).

53. Poppenk, J. & Moscovitch, M. A hippocampal marker of recollection memory ability among healthy young adults: Contributions of posterior and anterior segments. *Neuron* **72,** 931–937 (2011).

54. Kemere, C., Carr, M. F., Karlsson, M. P. & Frank, L. M. Rapid and Continuous Modulation of Hippocampal Network State during Exploration of New Places. *PLoS One* **8,** e73114 (2013).

55. Jensen, O., Spaak, E. & Park, H. Discriminating valid from spurious indices of phase-amplitude coupling. *eNeuro* **3,** 1–8 (2016).

56. Axmacher, N. *et al.* Cross-frequency coupling supports multi-item working memory in the human hippocampus. *PNAS* **107,** 3228–3233 (2010).

57. Roux, F. & Uhlhaas, P. J. Working memory and neural oscillations: Alpha-gamma versus theta-gamma codes for distinct WM information? *Trends Cogn. Sci.* **18,** 16–25 (2014).

58. Jacobs, J. Hippocampal theta oscillations are slower in humans than in rodents: implications for models of spatial navigation and memory. *Philos. Trans. R. Soc. B Biol. Sci.* **369,** 20130304–20130304 (2013).

59. Buzsáki, G., Logothetis, N. & Singer, W. Scaling brain size, keeping timing: Evolutionary preservation of brain rhythms. *Neuron* **80,** 751–764 (2013).

60. Maldjian, J. A., Laurienti, P. J., Kraft, R. A. & Burdette, J. H. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage* **19,** 1233–1239 (2003).

61. Haegens, S., Cousijn, H., Wallis, G., Harrison, P. J. & Nobre, A. C. Inter- and intra-individual variability in alpha peak frequency. *Neuroimage* **92,** 46–55 (2014).

62. Benwell, C. S. Y., London, R. E., Tagliabue, C. F. & Veniero, D. Frequency and power of human alpha oscillations drift systematically and independently with time-on-task. *bioRxiv* 1–34 (2018).

63. Maris, E. & Oostenveld, R. Nonparametric statistical testing of EEG- and MEG-data. *J. Neurosci. Methods* **164,** 177–90 (2007).

64. Benjamini, Y. & Hochberg, Y. Controlling the false discovery rate: A practical and powerful approach to multiple testing. *J. R. Stat. Soc. Ser. B* **57,** 289–300 (1995).