

Research Articles: Behavioral/Cognitive

Hippocampal theta and episodic memory

<https://doi.org/10.1523/JNEUROSCI.1045-22.2022>

Cite as: J. Neurosci 2022; 10.1523/JNEUROSCI.1045-22.2022

Received: 31 May 2022

Revised: 16 October 2022

Accepted: 17 November 2022

This Early Release article has been peer-reviewed and accepted, but has not been through the composition and copyediting processes. The final version may differ slightly in style or formatting and will contain links to any extended data.

Alerts: Sign up at www.jneurosci.org/alerts to receive customized email alerts when the fully formatted version of this article is published.

Hippocampal theta and episodic memory

Joseph H. Rudoler¹, Nora A. Herweg^{1,2} and Michael J. Kahana¹

¹Computational Memory Lab, Department of Psychology, University of
Pennsylvania, PA, USA 19104

²Department of Neuropsychology, Institute of Cognitive Neuroscience, Faculty of
Psychology, Ruhr University Bochum, Germany 44780

November 28, 2022

Corresponding Author: Michael J. Kahana, kahana@psych.upenn.edu

20 pages

4 figures

Acknowledgements: The authors would like to acknowledge our funding source for this work, NIH/NINDS Grant U01 NS1113198. Many thanks to Daniel Schonhaut, Josh Jacobs, John Sakon, David Halpern, and Noa Herz for helpful comments on previous versions of this manuscript.

⁰The authors declare no competing financial interests.

Abstract

Computational models of rodent physiology implicate hippocampal theta as a key modulator of learning and memory (Buzsaki & Moser, 2013; J. E. Lisman & Jensen, 2013), yet human hippocampal recordings have shown divergent theta correlates of memory formation. Herweg et al. (2020) suggest that decreases in memory-related broadband power mask narrowband theta increases. Their survey also notes that theta's role in memory appears strongest in contrasts that isolate retrieval processes and when aggregating signals across large brain regions. We evaluate these hypotheses by analyzing human hippocampal recordings captured as 162 neurosurgical patients ($N = 86$ female) performed a free recall task. Using the irregular-resampling auto-spectral analysis to separate broad and narrow-band components of the field potential we show: 1) Broadband and narrowband components of theta exhibit opposite effects, with broadband signals decreasing and narrow-band theta increasing during successful encoding; 2) Whereas low-frequency theta oscillations increase prior to successful recall, higher-frequency theta and alpha oscillations decrease, masking theta's positive effect when aggregating across the full band; 3) Theta's effects on memory encoding and retrieval do not differ between reference schemes that accentuate local signals (bipolar) and those that aggregate across large reference (whole brain average). In line with computational models that ascribe a fundamental role for hippocampal theta in memory, our large-scale study of human hippocampal recordings shows that 3-4 Hz theta oscillations reliably increase during successful memory encoding and prior to spontaneous recall of previously studied items.

Significance statement

Analyzing recordings from 162 patients we resolve a long-standing question regarding the role of hippocampal theta oscillations in the formation and retrieval of episodic memories. We show that broadband spectral changes confound estimates of narrowband theta activity, thereby accounting for inconsistent results in the literature. After accounting for broadband effects, we find that increased theta activity marks successful encoding and retrieval of episodic memories, supporting rodent models that ascribe a key role for hippocampal theta in memory function.

1 Introduction

Since the classic work of (Scoville & Milner, 1957), we have known that the hippocampal formation plays a crucial role in human context-dependent (episodic) memory. Whereas lesion studies reified the single-case study of H.M. (Squire, Knowlton, & Musen, 1993), further advances in our understanding of hippocampal physiology arose from recording field potentials and neuronal spiking in awake behaving mammals (e.g., O’Keefe & Dostrovsky, 1971; Knierim, Kudrimoti, & McNaughton, 1995; McNaughton, Barnes, & O’Keefe, 1983). These studies led to discoveries regarding the role of theta oscillations and place cell activity in animal learning (see J. Lisman, Jensen, & Kahana, 2001, for a review). While human scalp EEG studies had suggested some role for theta rhythms in cognitive processes (e.g., Schacter, 1977) it was only at the turn of the 21st century that depth-electrode recordings in neurosurgical patients specifically implicated theta oscillations in human spatial and verbal memory (Kahana, Sekuler, Caplan, Kirschen, & Madsen, 1999; Sederberg, Kahana, Howard 2003; Ekstrom et al., 2005). The ability to record neural activity from indwelling electrodes synchronized with computer-controlled memory experiments spawned a series of important discoveries regarding the electrophysiology of human learning and memory (Johnson & Knight, 2015)

Despite recent progress in the neurophysiology of human memory, considerable confusion surrounds the role of hippocampal theta activity in key memory processes, such as successful encoding and retrieval. To isolate neural correlates of successful memory encoding, researchers typically sort studied items into two groups: those that are subsequently recalled or recognized and those that are subsequently “forgotten”. Neuroimaging studies employing this contrast have frequently identified the hippocampus as a region of increased haemodynamic activity during successful encoding. To isolate neural correlates of memory retrieval, researchers often compare the period during which recollection occurs with a control period comprising either a matched deliberation interval (Burke, Sharan, et al., 2014) or a period preceding a retrieval error (Long et al., 2017).

In a recent review Herweg et al. (2020) identify a highly inconsistent pattern of findings, particularly with regards to data from direct recordings from the human medial-temporal lobe (MTL). They find that most studies either report negative associations between MTL theta and memory, or mixed patterns of results with some electrodes exhibiting increases and others exhibiting decreases

in theta power. Herweg et al (2020) propose several possible accounts for the discrepancies across these studies. First, they suggest that estimates of theta-band spectral power are confounded with broadband power changes, with the former reflecting synchronous oscillations and the latter reflecting asynchronous broadband activity indicative of greater attentiveness or cognitive engagement (Burke, Ramayya, & Kahana, 2015; Hanslmayr, Staudigl, & Fellner, 2012; Miller et al., 2014; Voytek & Knight, 2015). They claim that the standard subsequent memory effect (SME) analysis will emphasize changes in global attention rather than memory-specific encoding processes, and suggest that negative effects largely reflect broadband activity which masks the positive theta effects in the data. Theta oscillations might emerge after making analytic corrections for broadband changes. They also note that studies looking at retrieval processes - which are not bound to external stimuli and compare more similar attentive states - may be less susceptible to broadband confounds and therefore more suited to identify increases in hippocampal theta. Memory retrieval in a free recall task also depends critically on associative processes that bind items together based on a combination of their temporal and semantic relations (Kahana, 2020), which may themselves be linked to the strength of theta oscillations (Solomon, Lega, Sperling, & Kahana, 2019). Finally, they note that most magnetoencephalography (MEG) and scalp EEG studies find positive theta effects, often overlying frontal regions. While both invasive and non-invasive studies have yielded mixed results, the noticeably greater proportion of non-invasive studies reporting positive theta effects raises questions about how theta is impacted by the spatial resolution of the recording technology and the referencing scheme applied to the signal. It may be that bipolar reference schemes used in many of the studies reporting decreases in theta may have filtered out theta increases that appear synchronously over larger brain areas.

The present paper evaluates these accounts of the discrepant findings concerning hippocampal theta and memory. To do so, we analyze a large dataset comprising 162 neurosurgical patients fitted with hippocampal depth electrodes. Using standard wavelet methods we analyze spectral activity during encoding and retrieval phases of a delayed free recall task. We also separate broadband and narrowband components of spectral activity using irregular-resampling auto-spectral analysis (IRASA) (Wen & Liu, 2016). To evaluate the hypothesized role of hippocampal theta in memory

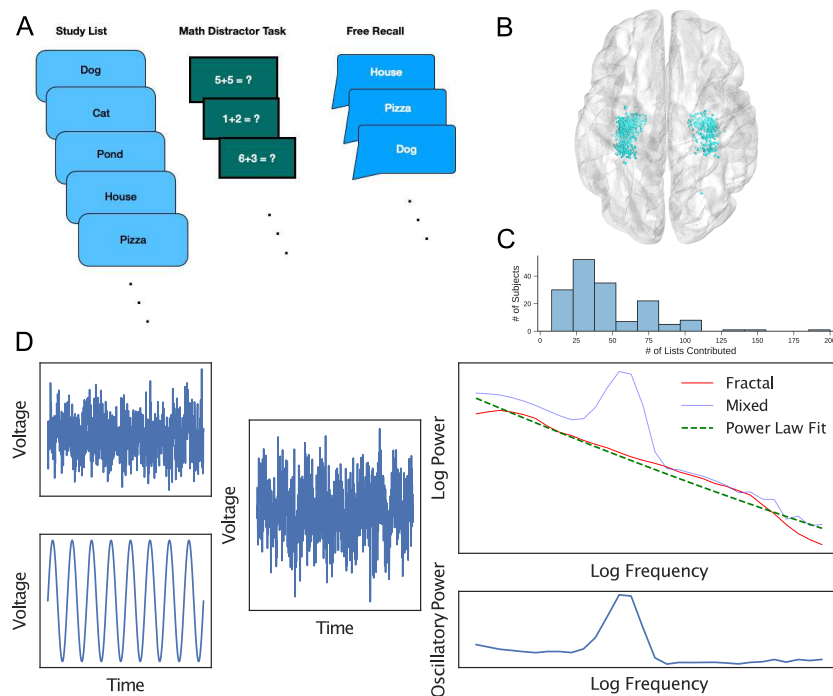
97 encoding, we analyze the period during which an item is studied and compare trials for which the
 98 stimulus is subsequently recalled or forgotten. At retrieval, we compare the period immediately
 99 preceding verbal recall with matched periods of deliberation, when patients are trying to recall but
 100 no items come to mind. Finally, we evaluate the hypothesis that local spatial referencing obscures
 101 theta's role in memory by repeating the above comparisons separately using a global average
 102 reference of implanted electrodes (as compared with a bipolar reference that localizes activity to
 103 the differential voltage between neighboring channels).

104 2 Materials and Methods

105 2.1 Subjects

106 We analyzed hippocampal depth-electrode recordings from 162 patients who participated in the
 107 DARPA-funded *Restoring Active Memory* project (e.g., Ezzyat et al., 2018; Solomon, Stein, et al.,
 108 2019; Solomon, Lega, et al., 2019; Phan, Wachter, Solomon, & Kahana, 2019). This publicly-
 109 shared dataset includes >300 patients with drug-resistant epilepsy who took part in memory
 110 testing while undergoing a neurosurgical procedure to localize seizure activity and functional tis-
 111 sue. These patients ($N = 86$ female, $N = 17$ left-handed) had a mean age of 38 (ranging from
 112 18 to 64). Researchers obtained informed consent from each patient and the research protocol
 113 was approved by the institutional review board (IRB) at the University of Pennsylvania and each
 114 participating hospital.

115 Patients contributed variable numbers of trials (i.e. studied test lists) depending on the length
 116 of their hospitalization and their interest in participating. We analyzed data only from patients
 117 who recalled at least, on average, one word per list; we also limited this study to patients with
 118 at least one bipolar pair consisting of contacts localized within the hippocampus (see *Electrode*
 119 *Recording: Localization and Preprocessing*).



2.2 Experimental Design

Patients completed a free recall task, in which they encoded a sequence of 12 words which appeared on a blank screen for 1600 ms each during a study phase. The spacing between words is jittered between 750 and 1000 ms. Following each study phase patients performed a 20 s arithmetic distractor task in which they solved problems of the form $X + Y + Z = ??$, where X , Y , and Z were positive or negative numbers between 1 and 9. Responses were made on a keypad, with presentation of additional math problems following each response (i.e., a self-paced task). After the delay, a row of asterisks accompanied by an 800 Hz auditory tone signaled the start of the recall period. At this point patients recalled out loud all the words they could remember from the list in 30 seconds. They repeat this sequence 25 times to complete the experiment, but not all patients complete a full 25 trials. Many patients repeat this process for multiple experimental sessions.

2.3 Electrode Recordings: Localization and Preprocessing

Our study focuses specifically on neural recordings from the hippocampus, defined as including regions CA1, CA2, CA3, CA4, dentate gyrus, and subiculum. To localize the recording contacts of depth electrodes, first hippocampal subfields and MTL cortices were automatically labeled in a pre-implant, T2-weighted MRI using the automatic segmentation of hippocampal subfields (ASHS) multi-atlas segmentation method (Yushkevich et al., 2015). Next, post-implant CT images were manually annotated with the voxel coordinates of individual recording contacts in CT-space. Post-implant CT images were coregistered with presurgical T1 and T2 weighted structural scans with Advanced Normalization Tools (Avants, Epstein, Grossman, & Gee, 2008), aligning the locations of individual recording sites to the anatomical labels assigned through automatic segmentation. For the majority of subjects in this dataset, MTL depth electrodes that were visible on overlaid CT and MRI scans were then manually annotated with localizations within MTL subregions by neuroradiologists with expertise in MTL anatomy. The electrodes used in this analysis appear in Figure 1 in transformed MNI coordinate space. Algorithms that perform automatic segmentation and coregistration naturally introduce some imprecision, especially for patients with lesions or

otherwise altered anatomy. Moreover, surgically implanted depth electrodes displace brain tissue and further complicate this task. Our confidence in these localizations stems from the manual work of the research team in visually inspecting the alignments and segmentations for every patient, and from the work of expert neuroradiologists checking the veracity of the anatomical labels.

The original sampling rates for these recordings vary by hospital and patient, but are all at least 500 Hz. For analysis, we resampled each recording to 500 Hz for consistency. We re-referenced the EEG using a bipolar montage in order to mitigate noise and increase the spatial resolution of the recordings, except for one analysis that explicitly compares this bipolar reference to a global (or whole-brain) average reference scheme. Applying a Butterworth bandstop filter of order 4 removed 60 Hz line noise from the recordings.

2.4 Separating broadband and narrowband effects with IRASA

IRASA, introduced by Wen and Liu (2016), is a method for separating oscillations from the pink noise background. We first assume that the EEG timeseries is a mixed signal containing both fractal ($f(t)$) and oscillatory ($x(t)$) components.

$$y(t) = f(t) + x(t)$$

Fractals are mathematically interesting for a number of reasons, but a property of particular importance is that they exhibit *self-affinity*. This means that fractals are scale free; geometrically, magnifying a portion of a fractal will produce qualitatively the same pattern. Expressed mathematically, when a fractal time series is resampled by a factor h ,

$$f_h(t) \triangleq h^H f(t)$$

which means that the statistical distribution of the resampled time series is the same as the statistical distribution of the original time series multiplied by a scaling term (The Hurst exponent H is related to the time series' auto-correlation). In the frequency domain, this self-affinity manifests

even more directly as

$$F_h(\omega) = h^H F(\omega)$$

158 which states that the Fourier transform after resampling is equal to the Fourier transform of the
 159 original time series multiplied by a scaling factor. This property is useful because resampling causes
 160 non-fractal signals to shift in the frequency domain. For an example of how signals typically shift
 161 in frequency space under resampling, consider an oscillation at 5 Hz in a recording sampled at 1000
 162 Hz. This oscillation completes a full cycle every 200 samples. If the recording is downsampled to
 163 500Hz, then essentially every other sample is removed. Now, the same 5 Hz oscillation completes a
 164 cycle in only 100 samples. Without properly correcting for the change in sampling rate, it appears
 165 as if the speed of the oscillation has doubled to 10 Hz. To operationalize the property of self-affinity,
 166 we use the discrete Fourier Transform to compute the autopower spectrum of the time series up-
 167 and down-sampled by a set of non-integer factors h . Taking the median across the full range of h
 168 values removes the shifted oscillatory peaks, leaving exactly the fractal component. Subtracting
 169 this fractal component from the overall power spectrum then isolates oscillations. Figure 1 shows
 170 an example of the method applied to simulated data. We refer the reader to the original methods
 171 paper (Wen & Liu, 2016) for a more mathematically detailed description of IRASA.

172 2.4.1 Isolating rhythmic oscillations

173 In order to isolate the oscillatory components of the neural power spectrum, we applied IRASA
 174 to an epoch of 300-1300ms following word presentation for every event in the task's encoding
 175 phase. To study the electrophysiology of memory retrieval we repeated the analysis for the epochs
 176 from 800-50ms prior to recall vocalization. These time windows were chosen to balance the trade-
 177 off between having a sufficiently long window to assess power in the low theta band and being
 178 sufficiently specific to an individual, temporally punctate behavioral event.

179 IRASA decomposes the power spectrum into fractal and oscillatory components for each event
 180 and channel within every patient. The choice of resampling factors h controls the extent to which
 181 the method is robust to outliers, but trades robustness for spectral smoothing that decreases our
 182 frequency resolution. As we wanted to ensure our analysis did not unintentionally include noise

artifacts created by large oscillations, but are also interested in having a high-resolution spectral decomposition that can distinguish between different narrowband effects, we chose a relatively conservative set of resampling factors from 1.1 to 2.0, linearly spaced by 0.05. This is the default set of resampling factors recommended and used in the original methods paper.

As IRASA explicitly extracts only the fractal component from the power spectrum, in order to isolate the oscillatory component we need to take the difference of the full spectrum and the fractal component. This is simple enough, but poses a challenge when log-transforming to suppress extreme values and normalize the data. If the fractal estimate is greater than the mixed power spectrum, the oscillatory power will be negative and the log transform undefined. We therefore introduce a Shifted Symmetric Log transform (SSL) to achieve the same goals without issue. This transform is defined as follows:

$$SSL(x) = \frac{x}{|x|} \log(1 + |x|)$$

This function retains the useful properties of the logarithm, but it is symmetric about the x -axis and does not go to negative infinity at very small values.

2.4.2 Wavelet power

We computed wavelet power at both encoding and retrieval to serve as a baseline against which we can compare our results using IRASA. We computed power at logarithmically spaced frequencies using Morlet wavelets with a width of 4 cycles. For this analysis, we included buffers on either side which corresponded to at least two cycles at the lowest frequency being analyzed (to avoid edge effects). At retrieval, we excluded recalls which were preceded by a vocalization during the buffer period preceding the epoch; we also implemented a mirrored buffer following the epoch in order to avoid contaminating our spectral estimates with vocalization artifacts from recall onset.

2.5 Statistical Analyses

Our primary question in analyzing item encoding is the following: how does power at a given frequency (e.g. theta) behave as a function of subsequent recall status? In answering this question we want to account for individual differences as well as session-level effects; memory performance

and power might differ across patients or event across different recording sessions for the same individual. Accordingly, we fit a linear mixed effects model for each frequency of interest using the *lmer4* package in R (Bates, Mächler, Bolker, & Walker, 2015) which predicts channel-averaged power as a function of subsequent recall (1 for success and 0 for failure), with random slopes and intercepts for the effects of subject, session, and trial (studied word list). To ensure proper estimation of the effects and their standard errors, we started with a maximal model and incrementally reduced the model complexity to remove zero-variance components and avoid singularities in the estimated variance-covariance matrix (Matuschek, Kliegl, Vasishth, Baayen, & Bates, 2017; Bates, Kliegl, Vasishth, & Baayen, 2018). Our analysis of memory retrieval followed the same procedure and model, but the binary memory success variable represented successful memory retrieval (as opposed to baseline deliberation) rather than successful memory encoding (as determined by subsequent recall).

We report effects at each frequency of interest as β coefficients from this model, and use a Wald test to evaluate statistical significance. We then correct for multiple comparisons by using the Benjamini-Hochberg procedure for controlling false discovery rate. This method is appropriate when tests are positively correlated, as are spectral estimates at similar frequencies.

2.6 Data and Code Availability

Raw electrophysiological data used in this study are available upon request from <https://memory.psych.upenn.edu>. Analysis and data visualization code is also available for direct download from <https://memory.psych.upenn.edu>. The Python implementation of the IRASA method used for this study is publicly available at <https://github.com/pennmem/irasa>, and other custom processing scripts used for this project can be found at <https://github.com/pennmem/>.

3 Results

As our analyses sought to elucidate the role of hippocampal theta oscillations in episodic memory encoding and retrieval, we identified all patients with hippocampal electrodes in the multi-center

226 *Restoring Active Memory* project (see *Methods*). Out of a total of N=281 patients who completed
 227 the same free recall task, 162 had at least one bipolar electrode pairs whose contacts both fell within
 228 the hippocampal formation defined as including regions CA1, CA2, CA3, CA4, dentate gyrus, and
 229 subiculum, but excluding non-hippocampal MTL regions such as perirhinal and parahippocampal
 230 cortices. Each patient performed a memory task in which they studied 12 words which they
 231 attempted to recall following a brief arithmetic distractor task (see Fig.1A for a schematic of
 232 the experimental task). During the 30 s recall period, patients attempted to say as many words
 233 as they could remember from the most recent list, in any order. Each patient contributed data
 234 from multiple study-test trials (see *Methods* for details). As patients performed this memory task,
 235 intraparenchymal depth electrodes captured hippocampal field potentials (Figure 1B; see *Methods*
 236 details regarding electrode localization).

237 The present study seeks to clarify the role of hippocampal neural oscillations in the formation
 238 and retrieval of episodic memories. As most prior work involving direct brain recordings used stan-
 239 dard spectral decomposition procedures (e.g., wavelet transforms, multi-tapers, other windowed
 240 FFT methods, etc.) these studies cannot disambiguate oscillations from broadband components
 241 of neural activity underlying successful mnemonic function. To address this limitation, we ana-
 242 lyzed neural signals using the irregular-resampling auto-spectral analysis (IRASA), which exploits
 243 the fractal properties of the power-law distributed broadband component to isolate it from the
 244 mixed power spectrum (see *Methods*). Figure 1c shows how IRASA decomposes a simulated EEG
 245 trace into broadband and narrowband components. The simulated data in 1c contain a single
 246 sine wave at a known frequency (“narrowband”) and pink noise (“broadband”). IRASA estimates
 247 this broadband component (see *Methods*) and subtracts it from the mixed autopower spectrum to
 248 isolate the residual oscillatory power.

249 The formation of episodic memories occurs when patients study words for a subsequent recall
 250 task. To identify the spectral correlates of successful encoding we examined the 1 second interval
 251 beginning 300 ms following item presentation, thereby excluding brain signals related to perceptual
 252 processing of the presented word. Spectral analyses of hippocampal field potentials during this
 253 encoding period typically show a tilt in the power spectrum, with decreases in low frequency

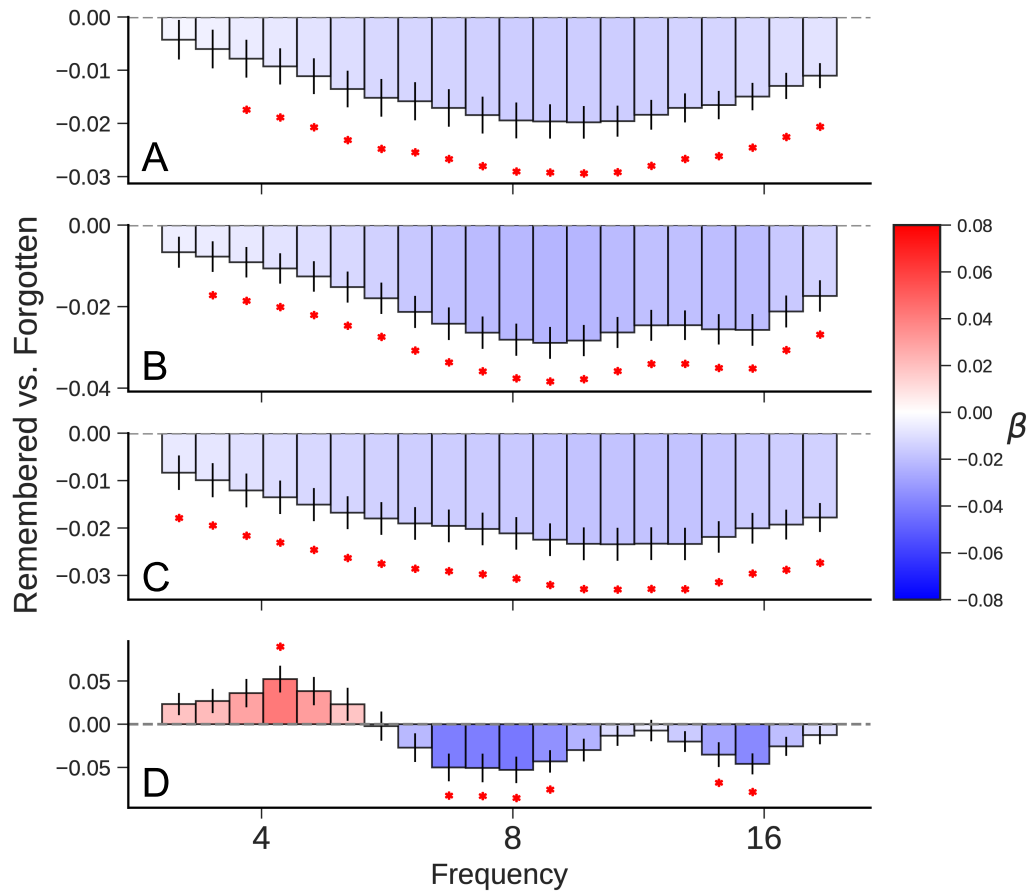


Figure 2: Subsequent Memory Effect. Comparison of spectral power for successful and unsuccessful memory encoding events (remembered - forgotten) based on hippocampal depth electrode recordings from 300-1300ms following item presentation. Values represent fixed effect coefficients for the effect of successful recall on spectral power. A red asterisk indicates that the effect size is significant after correcting for multiple comparisons ($p < .05$). **A)** Power computed using traditional Morlet wavelets. **B)** The mixed power spectrum (before separating broadband and narrowband effects) shows the expected theta and alpha decreases, analogous to the results using wavelets. **C)** The fractal power spectrum (broadband only) likewise shows broad decreases in low frequency. **D)** The oscillatory power spectrum, which is computed as the difference of the mixed and fractal power spectra, exhibits an increase in theta power, while retaining the same decrease in alpha power.

power and increases in high frequency power predicting subsequent recall (Burke, Long, et al., 2014; Ezzyat et al., 2017; Fellner et al., 2019). This spectral tilt manifests as a flattening of the overall spectrum in log-log space, resulting in a change in the power law exponent. IRASA, by isolating the power-law distributed background and removing that component from the power spectrum, reveals a more accurate estimate of the narrowband oscillatory patterns that coexist

259 with broadband changes.

260 As shown in Figure 2, the mixed autopower spectrum - analogous to traditional wavelet or
 261 multitaper methods - shows the expected theta decreases during successful encoding. Likewise,
 262 the isolated broadband component shows decreases in theta power. The oscillatory spectrum,
 263 however, shows theta increases. The estimates of effect size and significance derive from the mixed
 264 effects model described in *Methods*, which predicts power at a frequency of interest as a function
 265 of recall status, while accounting for the effects of subject and session.

266 Our finding of a small but reliable positive theta subsequent-memory effect in the human hip-
 267 pocampus contrasts with previous studies that found predominantly negative theta effects using
 268 wavelet methods and aggregate indices of hippocampal activity. These results confirm the hy-
 269 pothesis offered by Herweg et al. (2020) that broadband decreases in low frequency activity mask
 270 narrowband increases in theta activity. Given that aggregating hippocampal recordings from 162
 271 patients only yielded a modest positive theta SME, it is likely that many studies comprising smaller
 272 samples would not be powered to detect this effect (e.g., Sederberg, Schulze-Bonhage, Madsen, Bromfield, Litt,
 273 2007). We next turn to the question of memory retrieval, asking whether isolation of narrow-band
 274 spectral components can resolve mixed findings regarding theta's role in retrieval processes.

275 We used the same decomposition approach to estimate oscillatory power during a 750 ms
 276 epoch between 800 ms and 50 ms prior to recall onset. The theta increase observed during
 277 encoding is even more pronounced at retrieval; it even shows up in traditional power decom-
 278 positions like Morlet wavelets and IRASA's mixed spectrum (see Figure 3A,B). Positive theta
 279 during retrieval has previously been reported from intracranial electrodes in the right tempo-
 280 ral pole (Burke, Sharan, et al., 2014), but these findings were called into question by subse-
 281 quent studies with far greater statistical power showing either decreases or no significant effect
 282 (Solomon, Lega, et al., 2019; Weidemann et al., 2019). We note that most prior work averaged
 283 wavelet power over the traditional theta band from either 3 or 4 Hz to 8 Hz, which blends together
 284 the positive and negative effects shown in Figure 3. Assessing a more continuous spectrum instead
 285 of averaging within bands, we recover a strong positive effect at low frequencies. So, oscillatory
 286 power obtained with IRASA for the memory retrieval contrast matches the results obtained using

287 traditional wavelet power, though we do obtain somewhat better resolution that reveals multiple
 288 distinct components in the high theta/alpha range.

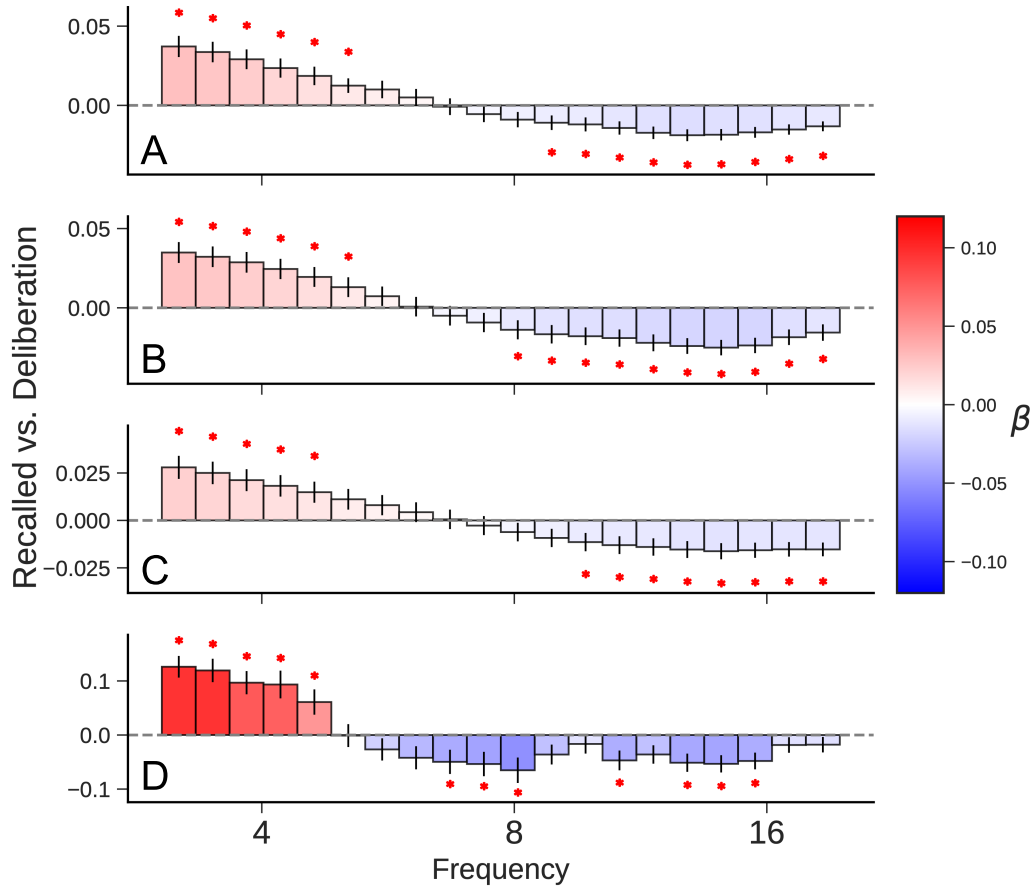


Figure 3: **Memory Retrieval Contrast.** Comparison of successful retrieval events and matched baseline deliberation events which we treat as “failed recall”. Power at logarithmically spaced frequencies were computed for the 750ms preceding recall vocalization. Values represent fixed effect coefficients for the effect of successful recall on spectral power. A red asterisk indicates that the effect size is significant after correcting for multiple comparisons ($p < .05$). Subplots show **A)** wavelet power, **B)** IRASA mixed power, **C)** IRASA fractal power, and **D)** IRASA oscillatory power.

289 Herweg et al (2020) proposed that choice of referencing scheme may potentially contribute
 290 to the apparent inconsistencies between non-invasive and invasive analyses of theta’s role in
 291 memory. Scalp EEG and MEG studies often report positive theta correlates of memory encod-
 292 ing and retrieval (Klimesch, Doppelmayr, Russegger, & Pachinger, 1996; Hanslmayr et al., 2011;
 293 Kaplan et al., 2012; Fellner, Bäuml, & Hanslmayr, 2013; Staudigl & Hanslmayr, 2013; Backus, Schoffelen, Sze

2016) whereas many highly powered intracranial studies have failed to show these effects. The two most commonly employed - and practically distinct - methods of voltage referencing are the bipolar reference and the average reference. In a bipolar scheme, the potential difference is calculated between pairs of neighboring electrodes. This is effectively a spatial filter, as any signal shared by both electrodes will be eliminated by the differencing operation. An average reference is more sensitive to global changes in field potentials; it is calculated by averaging the potential measured at all electrodes, and subtracting that average from each one. Herweg et al (2020) observe that increases in theta power reported in scalp EEG and MEG studies with average referencing often exhibit a broad topography across the scalp, centered around frontal electrodes, and suggest that these effects might have been attenuated in intracranial studies that frequently used bipolar referencing schemes. This is because bipolar referencing acts as a spatial high-pass filter, attenuating theta effects that occur synchronously across neighboring electrodes.

Comparing the memory-related power changes measured with each referencing scheme did not reveal any reliable differences (see Figure 4). An FDR-corrected paired t-test comparing bipolar to average reference (for 126 patients with monopolar recordings) did not identify significant differences between the oscillatory power estimates for the two referencing schemes at any of the frequencies of interest.

4 Discussion

We sought to resolve long-standing controversies regarding the role of hippocampal theta in learning and memory. To do so, we reanalyzed a large dataset of human hippocampal activity recorded as neurosurgical patients performed multiple trials of a verbal delayed free recall task. Our dataset comprised 797 hippocampal recordings across 162 patients. Whereas previous research found inconsistent theta correlates of successful encoding and recall, we find narrow-band 4-Hz oscillations to consistently increase during successful encoding (Figure 2) and preceding spontaneous free recall (as compared with matched deliberation periods, Figure 3). Further, we show that increases in theta activity appear similarly whether measured using a local spatial filter (bipolar referencing) or a more global filter (referencing to the average of all electrodes, see Figure 4).

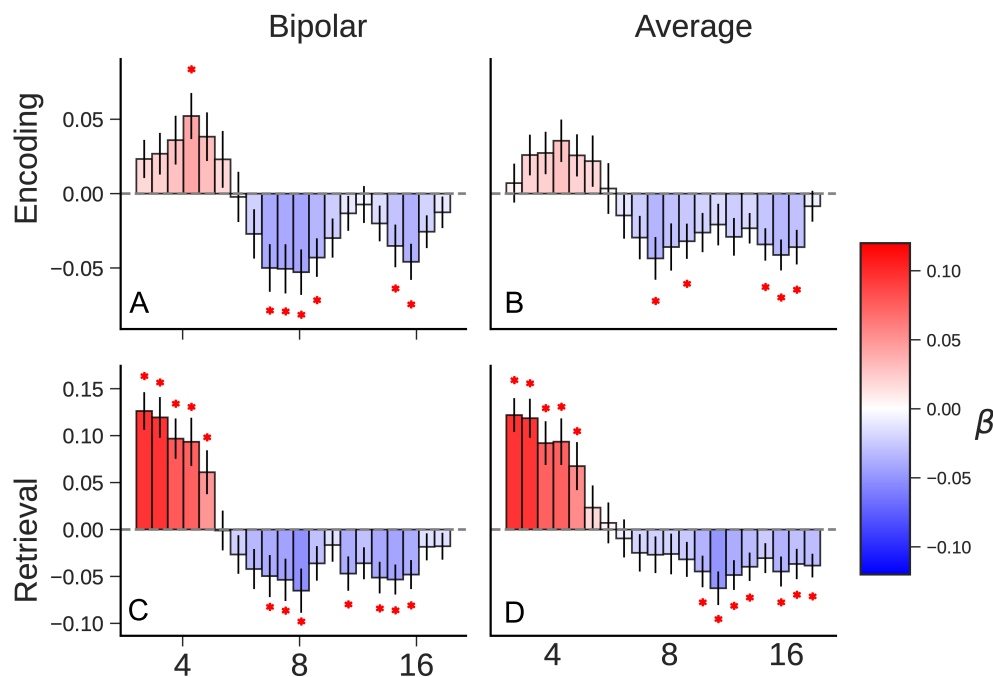


Figure 4: **Comparison of referencing schemes.** Average effect sizes for successful vs unsuccessful memory contrasts **A)** with bipolar reference at encoding, **B)** with average reference at encoding, **C)** with bipolar reference at retrieval, and **D)** with average reference at retrieval. The isolated oscillatory power spectra did not differ significantly based on the spatial filter applied to the data.

321 Although many studies report theta-correlates of memory in broader memory regions, only a
 322 few studies specifically isolate hippocampal signals. Fell et al. (2011) analyzed hippocampal theta
 323 during memory encoding in a continuous recognition procedure. Analyzing ~100 hippocampal
 324 electrodes they found a significant interaction between pre- and post-stimulus presentation changes
 325 in theta power, with significant prestimulus theta increases predicting subsequent recognition.
 326 During the post-stimulus item encoding period they found a modest *decrease* in theta ($p \sim 0.10$) for
 327 subsequently recognized items. Sederberg, Schulze-Bonhage, Madsen, Bromfield, McCarthy, et al.
 328 (2007) analyzed hippocampal subsequent memory effects in a delayed free recall task. Their
 329 study, which included 186 hippocampal recordings detected reliable high-frequency increases during
 330 successful encoding, but they failed to observe reliable theta effects. In a much larger analysis of
 331 hippocampal recordings in delayed recall (401 hippocampal electrodes) Long, Burke, and Kahana
 332 (2014) observed negative theta SMEs during successful encoding, and null-effects in the theta band

333 during successful retrieval (Burke, Long, et al., 2014). Lega, Jacobs, and Kahana (2012) examined
 334 237 hippocampal recordings during delayed free recall (as in Sederberg et al., 2007). Recognizing
 335 the possibility that spectral measures confound broadband and narrowband (oscillatory) effects,
 336 Lega applied an oscillation detection algorithm (Caplan et al., 2003) to filter for electrodes that
 337 exhibited narrowband oscillations in each of several frequency bands. Analyzing these channels
 338 revealed both positive and negative theta effects at different electrodes. Although Lega's study
 339 revealed striking positive theta effects at specific electrodes, it found an even larger number of
 340 hippocampal recordings that exhibited narrow-band decreases, thus offering a potential explanation
 341 for the negative and null-results described above.

342 Standard methods used to analyze spectral EEG power (such as wavelets, multi-tapers and
 343 windowed FFTs) mix narrow-band and broad-band signals, leaving open the possibility that a
 344 negative broadband effect can mask a positive narrowband effect, and vice-versa. When analyzed
 345 in this manner, our study replicated a number of previously published studies in showing *decreased*
 346 hippocampal theta power during the encoding of subsequently forgotten items (e.g., Burke et al.,
 347 2014; Solomon et al., 2019). By using irregular-resampling auto-spectral (IRASA), however, we
 348 revealed a positive relation between 4-Hz theta and successful memory encoding that tends to be
 349 obscured by a large negative relation between broadband power and encoding success.

350 Although we used IRASA to isolate narrow-band power, a number of other methods have
 351 been developed to address this problem, usually by modelling the $1/f$ background and considering
 352 deviations or residuals to be true narrowband, synchronous oscillations. The Better Oscillation
 353 Detection Method (Caplan, Madsen, Raghavachari, & Kahana, 2001) characterizes oscillations by
 354 measuring when narrowband power exceeds a power threshold above the fitted $1/f$ spectrum
 355 for a specified number of cycles at the frequency of interest; a newer method called FOOF
 356 (Donoghue et al., 2020) identifies oscillations by assuming they are Gaussians superposed on top
 357 of a $1/f$ distribution and selecting oscillatory peaks through an iterative fitting algorithm. We
 358 expect that using these related methods would lead to similar results regarding the increase in
 359 theta with successful memory encoding.

360 Comparing the period immediately preceding correct recall of a studied item with matched

361 deliberation intervals revealed that while low-frequency (4 Hz) theta increased, higher-theta band
362 power decreased. In this case, separating narrow- and broad-band power did not prove necessary
363 to uncover the positive correlation between theta activity and successful recall. Finally, Herweg
364 et al hypothesized that bipolar referencing may obscure theta increases by filtering out activity
365 correlated across multiple neighboring electrodes. Our comparison of bipolar and average references
366 reveals clear theta increases irrespective of referencing scheme.

367 This study does not discuss, nor directly account for, differences in epilepsy etiologies across
368 patients or in epileptic activity across trials. While these and other clinical factors are outside the
369 scope of this paper, as they do not bear directly on our hypotheses, they may bear on the study of
370 memory in patients with epilepsy more generally. (Camarillo-Rodriguez et al., 2022; Quon et al.,
371 2021).

372 Hanslmayr et al. (2012) and Hanslmayr, Staresina, and Bowman (2016) propose that broad-
373 band and narrowband spectral activity have distinct and complementary roles in memory encod-
374 ing: broad low-frequency desynchronization across the brain supports increased representation of
375 information content, while narrowband theta power increases reflect the hippocampus organizing
376 and encoding that information. Our data are consistent with this theory, as we observe simulta-
377 neous decreases in broadband, fractal power and increases in narrowband, oscillatory theta power
378 during memory encoding. Numerous other computational models of memory, mostly informed by
379 studies in rodents, assign a prominent role for theta in both memory formation and retrieval. Our
380 decomposition of narrowband and broadband components of human hippocampal field potentials
381 reveals increases in narrow-band theta during both successful encoding and retrieval, supporting
382 the applicability of these models to human episodic memory.

References

- Avants, B. B., Epstein, C. L., Grossman, M., & Gee, J. C. (2008). Symmetric diffeomorphic image registration with cross-correlation: evaluating automated labeling of elderly and neurodegenerative brain. *Medical Image Analysis*, *12*(1), 26–41.
- Backus, A. R., Schoffelen, J.-M., Szebényi, S., Hanslmayr, S., & Doeller, C. F. (2016, February). Hippocampal-prefrontal theta oscillations support memory integration. *Current Biology*, *26*(4), 450–457.
- Bates, D., Kliegl, R., Vasishth, S., & Baayen, H. (2018). Parsimonious mixed models. *arXiv*(arXiv:1506.04967).
- Bates, D., Mächler, M., Bolker, B., & Walker, S. (2015). Fitting linear mixed-effects models using lme4. *Journal of Statistical Software*, *67*(1), 1–48. doi: 10.18637/jss.v067.i01
- Burke, J. F., Long, N. M., Zaghoul, K. A., Sharan, A. D., Sperling, M. R., & Kahana, M. J. (2014). Human intracranial high-frequency activity maps episodic memory formation in space and time. *NeuroImage*, *85*, 834–843. doi: 10.1016/j.neuroimage.2013.06.067
- Burke, J. F., Ramayya, A. G., & Kahana, M. J. (2015). Human intracranial high-frequency activity during memory processing: Neural oscillations or stochastic volatility? *Current Opinion in Neurobiology*, *31*, 104–110. doi: <https://doi.org/10.1016/j.conb.2014.09.003>
- Burke, J. F., Sharan, A. D., Sperling, M. R., Ramayya, A. G., Evans, J. J., Healey, M. K., ... Kahana, M. J. (2014). Theta and high-frequency activity mark spontaneous recall of episodic memories. *Journal of Neuroscience*, *34*(34), 11355–11365. doi: 10.1523/JNEUROSCI.2654-13.2014
- Buzsaki, G., & Moser, E. (2013). Memory, navigation and theta rhythm in the hippocampal-entorhinal system. *Nature Neuroscience*, *16*(2), 130–138.
- Camarillo-Rodriguez, L., Leenen, I., Waldman, Z., Serruya, M., Wanda, P. A., Herweg, N. A., ... Sperling, M. R. (2022). Temporal lobe interictal spikes disrupt encoding and retrieval of verbal memory: A subregion analysis. *Epilepsia*, 1–13. doi: <https://doi.org/10.1111/epi.17334>
- Caplan, J. B., Madsen, J. R., Raghavachari, S., & Kahana, M. J. (2001). Distinct patterns

- of brain oscillations underlie two basic parameters of human maze learning. *Journal of Neurophysiology*, 86, 368–380.
- Caplan, J. B., Madsen, J. R., Schulze-Bonhage, A., Aschenbrenner-Scheibe, R., Newman, E. L., & Kahana, M. J. (2003). Human theta oscillations related to sensorimotor integration and spatial learning. *Journal of Neuroscience*, 23(11), 4726–4736.
- Donoghue, T., Haller, M., Peterson, E. J., Varma, P., Sebastian, P., Gao, R., ... Voytek, B. (2020, November). Parameterizing neural power spectra into periodic and aperiodic components. *Nature Neuroscience*, 23, 1655–1665.
- Ekstrom, A. D., Caplan, J., Ho, E., Shattuck, K., Fried, I., & Kahana, M. (2005). Human hippocampal theta activity during virtual navigation. *Hippocampus*, 15, 881–889.
- Ezzyat, Y., Kragel, J. E., Burke, J. F., Levy, D. F., Lyalenko, A., Wanda, P. A., ... Kahana, M. J. (2017). Direct brain stimulation modulates encoding states and memory performance in humans. *Current Biology*, 27(9), 1251–1258. doi: 10.1016/j.cub.2017.03.028
- Ezzyat, Y., Wanda, P., Levy, D. F., Kadel, A., Aka, A., Pedisich, I., ... Kahana, M. J. (2018). Closed-loop stimulation of temporal cortex rescues functional networks and improves memory. *Nature Communications*, 9(1), 365. doi: 10.1038/s41467-017-02753-0
- Fell, J., Ludowig, E., Staresina, B., Wagner, T., Kranz, T., Elger, C. E., & Axmacher, N. (2011). Medial temporal theta/alpha power enhancement precedes successful memory encoding: evidence based on intracranial eeg. *Journal of Neuroscience*, 31(14), 5392–5397.
- Fellner, M.-C., Bäuml, K.-H. T., & Hanslmayr, S. (2013). Brain oscillatory subsequent memory effects differ in power and long-range synchronization between semantic and survival processing. *NeuroImage*, 79, 361–370.
- Fellner, M.-C., Gollwitzer, S., Rampp, S., Kreiselmeier, G., Bush, D., Diehl, B., ... Hanslmayr, S. (2019). Spectral fingerprints or spectral tilt? Evidence for distinct oscillatory signatures of memory formation. *PLoS Biology*, 17(7), e3000403. doi: 10.1371/journal.pbio.3000403
- Hanslmayr, S., Staresina, B. P., & Bowman, H. (2016, January). Oscillations and episodic memory: Addressing the synchronization/desynchronization conundrum. *Trends In Neurosciences*, 39(1), 16–25.

- Hanslmayr, S., Staudigl, T., & Fellner, M. (2012). Oscillatory power decreases and long-term memory: the information via desynchronization hypothesis. *Frontiers in Human Neuroscience*, 6(74).
- Hanslmayr, S., Volberg, G., Wimber, M., Raabe, M., Greenlee, M. W., & Bäuml, K. H. T. (2011). The relationship between brain oscillations and bold signal during memory formation: A combined eeg-fmri study. *Journal of Neuroscience*, 31(44), 15674-15680.
- Herweg, N. A., Solomon, E. A., & Kahana, M. J. (2020). Theta oscillations in human memory. *Trends in Cognitive Science*, 24(3), 208-227. doi: <https://doi.org/10.1016/j.tics.2019.12.006>
- Johnson, E. L., & Knight, R. T. (2015). Intracranial recordings and human memory. *Current opinion in Neurobiology*, 31, 18-25.
- Kahana, M. J. (2020). Computational models of memory search. *Annual Review of Psychology*, 71(1), 107-138. doi: 10.1146/annurev-psych-010418-103358
- Kahana, M. J., Sekuler, R., Caplan, J. B., Kirschen, M., & Madsen, J. R. (1999). Human theta oscillations exhibit task dependence during virtual maze navigation. *Nature*, 399, 781-784.
- Kaplan, R., Doeller, C. F., Barnes, G. R., Litvak, V., Düzel, E., Bandettini, P. A., & Burgess, N. (2012). Movement-related theta rhythm in humans: Coordinating self-directed hippocampal learning. *PLoS biology*, 10(2), e1001267.
- Klimesch, W., Doppelmayr, M., Russeger, H., & Pachinger, T. (1996). Theta band power in the human scalp EEG and the encoding of new information. *NeuroReport*, 7, 1235-1240.
- Knierim, J., Kudrimoti, H., & McNaughton, B. (1995). Place cells, head direction cells, and the learning of landmark stability. *Journal of Neuroscience*, 15(3), 1648-1659.
- Lega, B., Jacobs, J., & Kahana, M. (2012). Human hippocampal theta oscillations and the formation of episodic memories. *Hippocampus*, 22(4), 748-761. doi: <https://doi.org/10.1002/hipo.20937>
- Lisman, J., Jensen, O., & Kahana, M. J. (2001). Toward a physiologic explanation of behavioral data on human memory. In C. Hölscher (Ed.), *Neuronal mechanisms of memory formation* (pp. 195-223). Cambridge: Cambridge University Press.
- Lisman, J. E., & Jensen, O. (2013). The theta-gamma neural code. *Neuron*, 77(6), 1002-1016.

- Long, N. M., Burke, J. F., & Kahana, M. J. (2014). Subsequent memory effect in intracranial and scalp EEG. *NeuroImage*, *84*, 488–494. doi: 10.1016/j.neuroimage.2013.08.052
- Long, N. M., Sperling, M. R., Worrell, G. A., Davis, K. A., Gross, R. E., Lega, B. C., ... Kahana, M. J. (2017). Contextually mediated spontaneous retrieval is specific to the hippocampus. *Current Biology*, *27*(7), 1074–1079. doi: 10.1016/j.cub.2017.02.054
- Matuschek, H., Kliegl, R., Vasishth, S., Baayen, H., & Bates, D. (2017, June). Balancing type I error and power in linear mixed models. *Journal of Memory and Language*, *94*, 305–315.
- McNaughton, B. L., Barnes, C. A., & O'Keefe, J. (1983). The contributions of position, direction, and velocity to single unit activity in the hippocampus of freely-moving rats. *Experimental Brain Research*, *52*(1), 41–49.
- Miller, K. J., Honey, C. J., Hermes, D., Rao, R. P., den Nijs, M., & Ojemann, J. G. (2014, January). Broadband changes in the cortical surface potential track activation of functionally diverse neuronal populations. *NeuroImage*, *85*, 711–720.
- O'Keefe, J., & Dostrovsky, J. (1971). The hippocampus as a spatial map: Preliminary evidence from unit activity in the freely-moving rat. *Brain Research*, *34*, 171–175.
- Phan, T. D., Wachter, J. A., Solomon, E., & Kahana, M. J. (2019). Multivariate stochastic volatility modeling of neural data. *eLife*, *8*, e42950.
- Quon, R. J., Camp, E. J., Meisenhelter, S., Song, Y., Steimel, S. A., Testorf, M. E., ... Jobst, B. C. (2021). Features of intracranial interictal epileptiform discharges associated with memory encoding. *Epilepsia*.
- Schacter, D. L. (1977). Eeg theta waves and psychological phenomena: A review and analysis. *Biological Psychology*, *5*(1), 47–82.
- Scoville, W. B., & Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery, and Psychiatry*, *20*, 11–21.
- Sederberg, P. B., Kahana, M. J., Howard, M. W., Donner, E. J., & Madsen, J. R. (2003). Theta and gamma oscillations during encoding predict subsequent recall. *Journal of Neuroscience*, *23*(34), 10809–10814. doi: 10.1523/JNEUROSCI.23-34-10809.2003
- Sederberg, P. B., Schulze-Bonhage, A., Madsen, J. R., Bromfield, E. B., Litt, B., Brandt, A., & Ka-

- 495 hana, M. J. (2007). Gamma oscillations distinguish true from false memories. *Psychological*
 496 *Science*, 18(11), 927–932. doi: 10.1111/j.1467-9280.2007.02003.x
- 497 Sederberg, P. B., Schulze-Bonhage, A., Madsen, J. R., Bromfield, E. B., McCarthy, D. C., Brandt,
 498 A., ... Kahana, M. J. (2007). Hippocampal and neocortical gamma oscillations predict
 499 memory formation in humans. *Cerebral Cortex*, 17(5), 1190–1196. doi: 10.1093/cercor/
 500 bhl030
- 501 Solomon, E. A., Lega, B. C., Sperling, M. R., & Kahana, M. J. (2019). Hippocampal theta
 502 codes for distances in semantic and temporal spaces. *Proceedings of the National Academy*
 503 *of Sciences*, 116(48), 24343–24352. doi: <https://doi.org/10.1073/pnas.1906729116>
- 504 Solomon, E. A., Stein, J. M., Das, S., Gorniak, R., Sperling, M. R., Worrell, G., ... Kahana, M. J.
 505 (2019). Dynamic theta networks within the human medial temporal lobe support episodic
 506 encoding and retrieval. *Current Biology*, 29(7), 1100–1111. doi: 10.1016/j.cub.2019.02.020
- 507 Squire, L. R., Knowlton, B., & Musen, G. (1993). The structure and organization of memory.
 508 *Annual Review of Psychology*, 44, 453–495.
- 509 Staudigl, T., & Hanslmayr, S. (2013). Theta oscillations at encoding mediate the context-
 510 dependent nature of human episodic memory. *Current Biology*, 23(12), 1101–1106. doi:
 511 <https://doi.org/10.1016/j.cub.2013.04.074>
- 512 Voytek, B., & Knight, R. T. (2015, June). Dynamic network communication as a unifying neural
 513 basis for cognition, development, aging, and disease. *Biological Psychiatry*, 77(12), 1089-
 514 1097.
- 515 Weidemann, C. T., Kragel, J. E., Lega, B. C., Worrell, G. A., Sperling, M. R., Sharan, A. D., ...
 516 Kahana, M. J. (2019). Neural activity reveals interactions between episodic and semantic
 517 memory systems during retrieval. *Journal of Experimental Psychology: General*, 148(1),
 518 1–12. doi: 10.1037/xge0000480
- 519 Wen, H., & Liu, Z. (2016, Jan). Separating fractal and oscillatory components in the power
 520 spectrum of neurophysiological signal. *Brain Topography*, 29(1), 29(1):13–26.
- 521 Yushkevich, P. A., Pluta, J. B., Wang, H., Xie, L., Ding, S.-L., Gertje, E. C., ... Wolk, D. A.
 522 (2015). Automated volumetry and regional thickness analysis of hippocampal subfields and

523 medial temporal cortical structures in mild cognitive impairment. *Human Brain Mapping*,
524 36(1), 258–287.