Spatiotemporal dynamics between interictal epileptiform discharges and ripples during associative memory processing

Summary: Hippocampal interictal epileptiform discharges in hippocampus acutely impair declarative memory, potentially by hijacking physiological processes essential for encoding and recall.

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ABSTRACT

We describe the spatiotemporal course of cortical high-gamma activity (HGA), hippocampal ripple activity and interictal epileptiform discharges (IEDs) during an associative memory task in 15 epilepsy patients undergoing invasive electroencephalography (iEEG). Successful encoding trials were significantly greater HGA in hippocampus and frontal regions. Successful recall trials manifested sustained HGA in occipital pole and hippocampus compared to failed responses. Hippocampal ripple rates were greater during successful encoding and retrieval trials. IEDs during encoding were associated with decreased odds of remembering in hippocampus (-19%), temporal pole (-18%) or middle temporal gyrus (-15%). Hippocampal IEDs during retrieval predicted 33% decreased odds of remembering. Odds of remembering were further reduced if IEDs occurred during the 500-2000 ms window of encoding or retrieval. Hippocampal IEDs were followed by a transient decrease in ripple rate. We hypothesize that IEDs impair associative memory in a regionally and temporally specific manner by decreasing physiologic hippocampal ripples necessary for effective encoding and recall. Because dynamic memory impairment arises from pathological IED events competing with physiological ripples, IEDs represent a promising therapeutic target for memory remediation in patients with epilepsy.

INTRODUCTION

Memory dysfunction affects 40–50% of epilepsy patients. In a community-based survey, patients ranked memory problems as the most important cognitive comorbidity of epilepsy, adversely affecting daily functioning, work participation, and school performance(*1*). These subjective complaints range from difficulties with remembering names and phone numbers (semantic memory) to what happened during last year's family vacation (episodic memory) (*2*). While there are multiple factors are involved(*3*), interictal epileptiform discharges (IEDs), pathological bursts of neuronal activity between seizures, can dynamically impair cognition. In 1939, Schwab demonstrated that 'subclinical EEG discharges' increased reaction time or resulted in failure to respond to the stimulus. Subsequently, Aarts introduced the term 'transitory cognitive impairment' (TCI) to describe this functional disruption. Because IEDs are transiently associated with memory impairment, they may serve as a target for therapeutic intervention(*4*).

Intracranial EEG (iEEG) studies with epilepsy surgery patients have advanced our understanding of human cognition, including the deleterious impact of IEDs. iEEG offers high spatiotemporal precision and signal-to-noise ratio (Lachaux 2012) for characterizing the neurophysiology of memory, and records directly from deep structures (e.g., hippocampus and entorhinal cortex) inaccessible by other methods. Increased gamma activity in dominant mesial temporal and frontal regions predicts successful encoding of word lists(*5, 6*) or word pairs(*7*). Recently, hippocampal sharp-wave ripple events have been correlated with successful retrieval of word pairs(*8, 9*) and visual episodic memories(*10*). However, these iEEG studies describing physiological processes including gamma activity and ripples typically exclude trials with IEDs, discarding them as "noise."

Accumulating evidence demonstrates that IEDs can impair encoding, maintenance, consolidation, and retrieval of verbal learning.(*4, 11-15*) Left temporal and parietal neocortical IEDs are associated with impaired memory for word list items and word pairs (*12, 15*). IEDs outside the seizure onset zone (SOZ) in higher order visual processing regions have been associated with impaired encoding and retrieval performance for words (*15*). Despite this, our understanding of the relationship of IEDs and human memory is largely correlational(*11, 12, 16*), without a clear mechanism of disruption. Studies assessing word-list learning or verbal paired associate tasks found the greatest effects of IEDs occurring in higher-order visual neocortical areas (i.e. fusiform gyrus, inferior temporal gyrus). It is unclear whether IEDs disrupt sensory processing of words or memory function per se and if they do, the mechanism by which they exert their deleterious effect is unknown (*16*). IEDs may be more

frequent during drowsy or distracted states, and thus only indirectly associated with poor memory performance (*16, 17*).

In this study, we aimed to establish the relationship between high gamma activity and hippocampal ripples and pathological interictal epileptiform discharges (IEDs). Previously, physiological and pathological events have been investigated independently. We hypothesized that characterizing the spatiotemporal course of physiological activity during a memory task would reveal when and where in the brain IEDs exert the greatest impact, and provide a potential mechanism for how IEDs disrupt cognitive processing. We selected a face-profession association task, which potentially represents a more clinically relevant probe of declarative memory than word-list recall or word-pair association tasks.(*5-7, 11, 15, 18*) Our face-profession task depends on bilateral hippocampal(*19-21*) function, thus permitting an opportunity to test how IEDs, often abundant in the mesial temporal lobe, and frequently sampled in intracranial recordings, interrupt mnemonic processes. We examined the spatiotemporal time course of high gamma activity (HGA), a robust index of local cortical activity (*22*) across widespread brain areas during encoding and retrieval, distinguishing between successfully remembered versus forgotten pairs. As hippocampal activation was critical for encoding and retrieval, we next compared the hippocampal ripple rate of successful versus failed trials. To ensure that detected HGA and ripple rate were physiological events and not pathological high frequency oscillations (HFOs, 80-150), which are increased in epileptogenic cortex (*23, 24*) and can co-occur with IEDs (*23*), we performed this initial analysis by excluding electrodes inside the seizure onset zone (SOZ) and trials with IEDs. Next, we evaluated the impact of IEDs by brain region and with respect to the seizure onset zone (SOZ). Because hippocampal IEDs had the greatest adverse effect on memory, we examined their impact by time course, predicting a greater impact on memory if IEDs occurred during the trial when hippocampal activity was critical. Finally, to investigate how IEDs may disrupt memory function, we examined the temporal relationship between IEDs and hippocampal ripples.

RESULTS

Data Collection

We recorded from fifteen patients with epilepsy undergoing iEEG monitoring for surgical evaluation from New York University Langone Hospital (NYULH). All study activities were approved by the NYU Langone Institutional Review Board and all patients provided informed consent to participate in the study. We included a total of 7 males and 8 females, average age of 30.5 (range 15-55, SD 12.4). Fourteen were right-handed and one was ambidextrous; average IQ was 98.8 (range 82-132, SD 15.6). Table 1 summarizes additional demographic and clinical characteristics. Most patients scored below normative values on a standardized verbal memory task, the Rey Auditory Verbal Learning Test (RAVLT, z=-1.8, SD=2.4, Table S1). Patients' implantations included a combination of subdural grids, strips and depth (hippocampal and other) electrodes (Fig. 1). We analyzed 1646 electrodes in this study. Seizure onset zones (SOZ) were diverse (Table 1). Eight patients underwent surgical resection, six were offered a responsive neurostimulator (RNS), and one patient did not receive a surgical intervention due to failure to record clinical seizures.

	Subj	Age	Sex	Handness	Avg. Set Size	IQ	Coverage	Seizure Onset Zone (SOZ)	Outcome
1	NY609	45	F	R	2.2	95	Bilateral	R mesial temporal	R anterior temporal lobe resection
2	NY639	18	M	R	8.8	91	Bilateral	L hemisphere	RNS

3	NY645	38	M	R	4.3	82	Bilateral	R mesial temporal	RNS
4	NY652	20	F	R	4.1	74	R hemisphere	R temporal, parietal, occipital	R temporal, parietal, occipital corticectomy
5	NY661	28	M	R	9.2	132	R hemisphere	R temporal	R anterior temporal lobe resection
6	NY704	55	F	R	3.5	108	L hemisphere	L basal and lateral temporal neocortex	Tailored L anterior temporal lobe resection
7	NY708	41	F	R	1.4	116	L hemisphere	Unclear Non-epileptic seizures	No surgical intervention
8	NY717	49	F	R	3.3	115	Bilateral	R temporal pole and hippocampus	RNS
9	NY723	26	M	R	2.4	NA	Bilateral	B mesial temporal lobes	RNS
10	NY733	15	M	R	4	107	R hemisphere	R orbitofrontal, cingulate, insula	Tailored R frontal corticectomy
11	NY736	29	M	R	4	96	LH depths	L mesial temporal cortex	L anterior temporal lobe resection
12	NY737	20	F	R	4	91	L hemisphere	R middle frontal, cingulate, pars triangularis/opercularis, precentral	R frontal corticectomy
13	NY741	24	M	B	2.1	82	L hemisphere	L frontal, parietal, temporal, occipital	RNS, VNS, or DBS
14	NY743	30	F	R	2	98	L hemisphere	L posterior insula, periopercular	RNS
15	NY748	19	F	R	3.4	96	L hemisphere	L temporal neocortical	Tailored L post inferior temporal corticectomy

Table 1. Demographic and Clinical Characteristics of Subjects.
Fifteen (15) subjects were recruited from a single epilepsy center. Subjects had an average age of 30.5 years (range 15 to 55, SD 12.4), 53% female, right-handed, with a mean IQ of 98.8 (Range 82-132, SD 15.6). Patients were implanted with a combination of strategies: bilateral strips and depths; right and left hemisphere grids, strips, and depths. Seizure onset zones determined by intracranial EEG monitoring and clinical outcomes are reported, which could include surgery or a therapeutic device (RNS: Responsive Neurostimulation, DBS: Deep Brain Stimulation or VNS: Vagal Nerve Stimulation).

All patients performed a face-profession visual association task (Fig. 2A). The face-profession task robustly activates both hippocampi in healthy subjects(*21*). Since epilepsy patients typically have impaired performance compared to healthy subjects, (*11-13, 25*) we calibrated the task difficulty by individual subjects to achieve a balanced distribution between successful and failed encoding trials. Subject performance varied from one trial per set to ten trials per set. Because trial set size was adjusted for subject performance to obtain a similar number of correct and failed trials, direct comparisons of performance across subjects was not a goal.

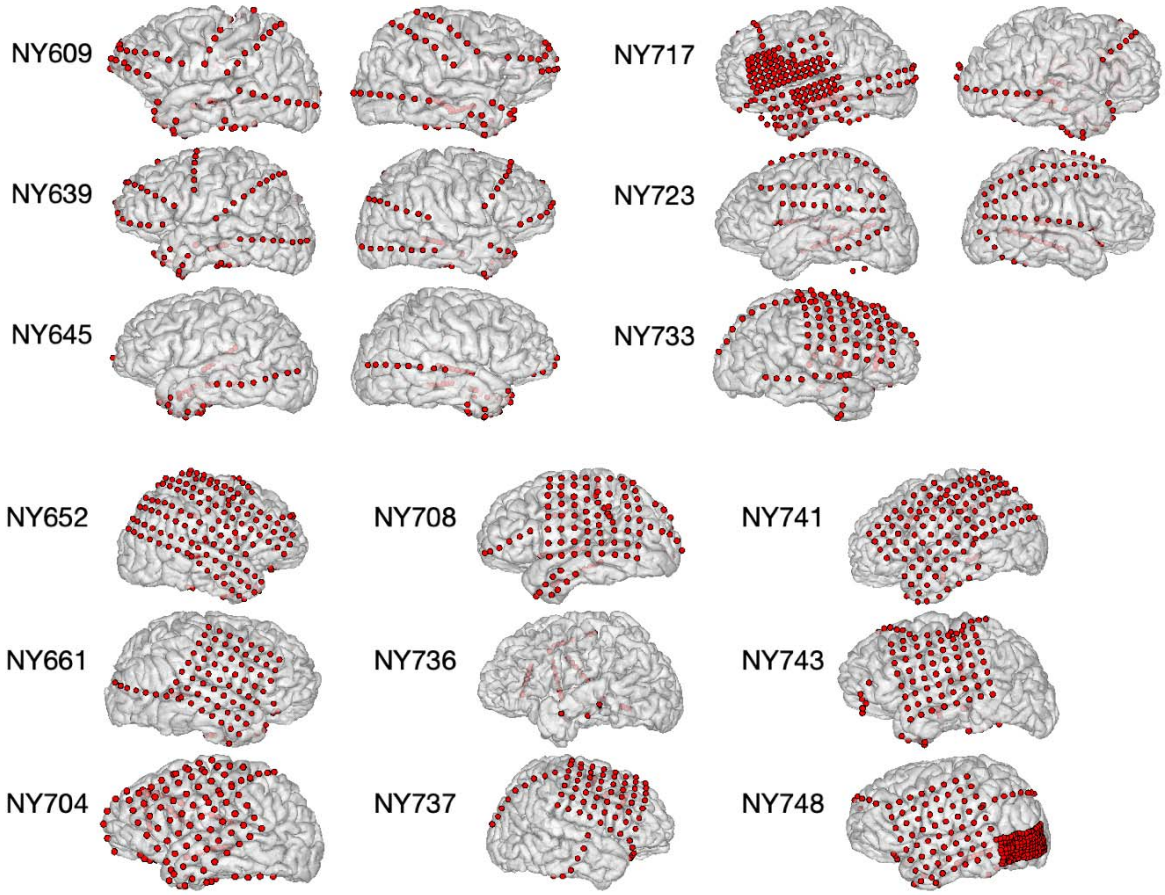

Fig. 1. Electrode coverage for Fifteen Subjects.
We recorded from a total of 1646 electrodes, from 15 subjects. Five patients had bilateral depths and strips (NY609, NY639, NY645, NY723, NY736). Six patients had left hemisphere subdural grids, strips, and depths (NY 704, NY 708, NY717, NY741, NY743, NY748). Four patients had right hemisphere subdural grids, strips, and depths (NY 652, NY661, NY733, NY737).

We tested for memory function using a cued recall paradigm. This paradigm allows greater experimental control compared to free recall designs, including the ability to precisely measure the spatiotemporal relationship between physiological and pathological events. A cued recall paradigm may be more sensitive to clinical memory dysfunction compared to recognition memory tasks (*26*). During recall, subjects were shown only faces from the prior set and asked to speak aloud the associated profession. The cued recall segment lasted for as long as the subject needed to provide a response. Sets during which subjects freely stated the associated profession paired with the face stimulus were scored as correct trials. Subjects participated in between 24 to 119 trials total.

Differences in High Gamma Activity in Hippocampus and Frontal Regions Distinguish Successful versus Failed Remembering.

iEEG recordings were segmented into encoding and cued recall periods, comparing trials which were later successfully recalled versus forgotten. As expected, high gamma activity (HGA, 60-170 Hz) demonstrated an early increase several cortical areas, including primary visual cortex and visual association cortices, such as fusiform gyrus and inferior temporal gyrus, immediately after stimulus presentation (Fig. 2C). In contrast, HGA in hippocampus, beginning at + 0.80s after stimulus presentation, distinguished successful and failed encoding

trials (exceedance mass sum(T)=66.7, p=0.01, see Fig. S4). Increased HGA in the superior frontal region beginning at +1.69 s also characterized successful encoding (sum(T) = 122, p=0.003, Fig. 2C). During cued recall, increased HGA at +0.80s after stimulus presentation in inferior frontal, postcentral, superior and middle temporal gyri, and later at +1.10s in hippocampus and postcentral gyrus distinguished successful and failed recall trials (Fig. 2C). To disambiguate the cognitive from the motor vocalization response component and to account for variable response times, we examined the difference between correct and incorrect responses timed to the vocalization for 10 patients with adequate voice recordings. We found a difference in hippocampal HGA occurring before vocalization, starting at -250 ms before vocalization (Fig. 2C). In addition, an early difference in HGA activity was observed -500 ms before vocal onset in the lateral occipital region. However, this difference may be due to the tendency for earlier responses, closer to stimulus onset, observed for correct trials (Fig. S3).

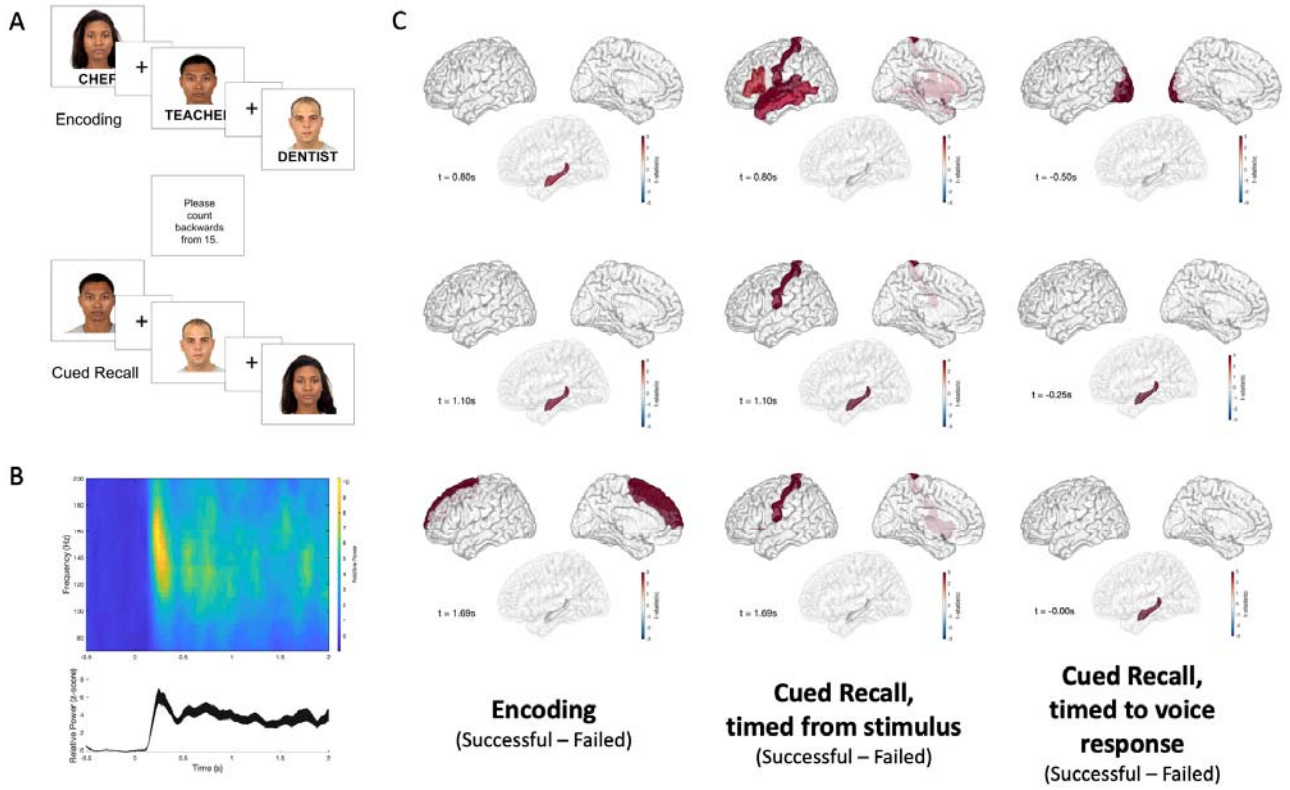

Fig. 2. Task Design and Differences in High Gamma Activity (HGA) between Successful and Failed Associative Memory. (A) A computerized program presented task stimuli and recorded subject spoken responses. During encoding, each face-profession pair was shown for 5 seconds, with a 1 second inter-stimulus interval (ISI) which was marked by a plus sign. To ensure attention and sensory processing of test stimuli, subjects were instructed to read the profession aloud and make a mental association. To prevent rehearsal, a brief distraction task followed the encoding block, during which subjects were asked to count backwards from 15. During cued recall, subjects were shown only the faces from the prior set and asked to say aloud the associated profession. The cued recall period lasted for as long as the subject needed to provide a response. Voice response was recorded and scored for accuracy. Given the highly variable performance between subjects and to achieve a balanced distribution between successful and failed trials, the number of pairs presented per set was calibrated to the individual patient's performance, ranging from 1 to 10 pairs per set. (B) Example spectrogram of high gamma activity (HGA 70-180 Hz) recorded in the occipital cortex, normalized to the -500 pre-stimulus baseline, with a peak at 250 ms after stimulus presentation. (C) **Left.** Group-level differences in HGA by time for correctly versus incorrectly recalled face-profession pairs during encoding and recall. During encoding, increased HGA in hippocampus beginning at +0.80s after stimulus presentation, with increased HGA in superior frontal region beginning at +1.69 s distinguished between successful and failed trials. **Middle**. During cued recall, increased HGA at +0.80s after face stimulus presentation in inferior frontal gyrus, postcentral, superior temporal and middle temporal gyrus, and later at +1.10s in hippocampus distinguish between successful and failed trials. **Right.** To disambiguate the

contribution of vocalization from recall, the difference between successful and failed trials was determined, timed in response to the vocalization. A difference in hippocampal HGA was see beginning at -250 ms prior to vocalization.

Hippocampal Ripples Increased in Successful versus Failed Remembering

Hippocampal ripples were measured from the pair of depth electrodes within or closest to the anterior hippocampus for each patient. Ripple detection was performed using a published method that has demonstrated the relationship between ripples in hippocampus and middle temporal gyrus and successful retrieval(*8*). We detected 12,972 hippocampal ripple events across all test blocks for all patients (mean=997 ±420), after excluding electrodes in the SOZ and all trials with IEDs. An example raw trace of a detected ripple event is shown in Fig. 3A**.** Ripples are brief events possessing oscillatory features characterized by a spectral centroid occurring between 80-120 Hz (Fig. 3B, bottom panel). Ripples had a median duration of 33 ms (±17 ms, Inter-quartile range) and showed a skewed log distribution (Fig 2B middle panel).

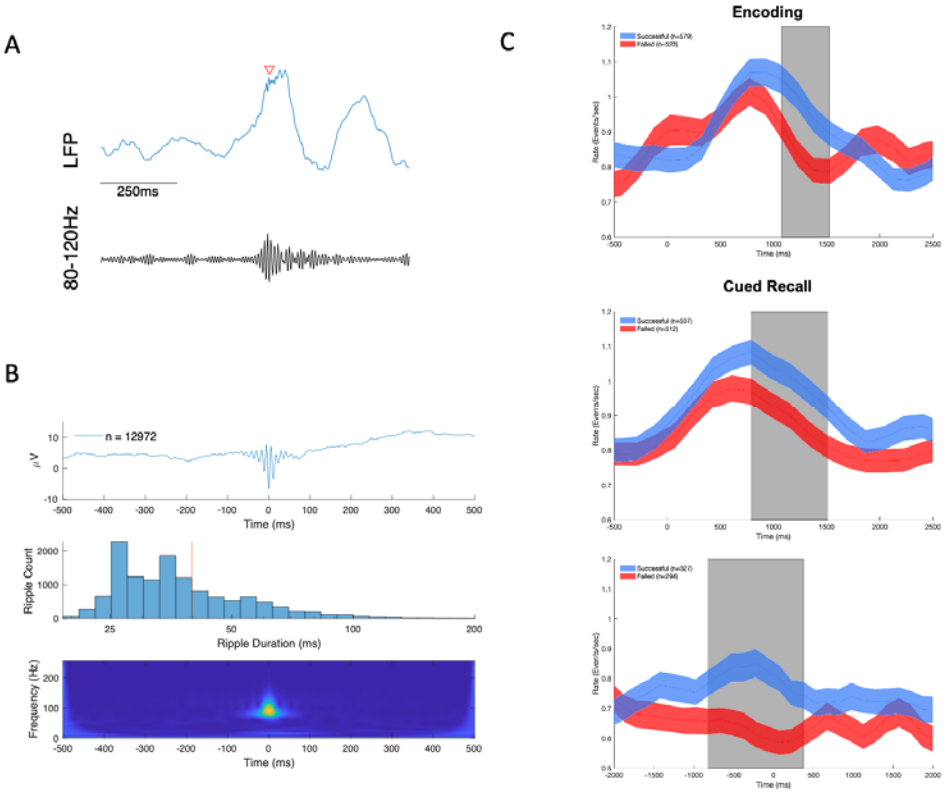

Fig. 3. Hippocampal Ripples During Encoding and Recall Predict Successful Associative Memory.
Ripple events were detected using a bipolar montage from the two electrodes located in or closest to the anterior hippocampus, using a previous published method (80 Hz-120 Hz, 20-200 ms duration, Vaz 2019). To reduce the detections of pathological high frequency oscillations (HFOs), detections were restricted to regions outside of seizure onset zone, and with trials which did not contain an interictal epileptiform discharge. (A) Sample raw EEG tracing (blue) with detected ripple event (RED ARROW), with bandpass filtered (80-120 Hz) tracing (black). (B) Characteristics of all detected hippocampal ripples. A total of 12,972 ripple events were detected across all patients during the encoding trials. TOP PANEL. Sample filtered ripple event reveals oscillatory characteristics. MIDDLE PANEL. Histogram showing detected ripple duration, which follows skewed log distribution. Mean ripple duration 39.8 ms, SD 18.3 ms. BOTTOM. Spectrogram of detected ripple demonstrates a peak frequency between 80-100 Hz. (C) Difference in Ripple Rate between Successful and Failed Associative Memory. TOP PANEL. Successful encoding is characterized by a higher ripple rate (BLUE) compared to failed encoding (RED) between 900-1500 ms after stimulus presentation (GRAY BOX). MIDDLE PANEL. Successful cued recall is characterized by a higher ripple rate (BLUE) compared to failed cued recall (RED) between +650 ms and +1500 ms after stimulus presentation (GRAY BOX). BOTTOM PANEL. Successful cued recall is characterized by a higher ripple rate from -800 ms to +400 ms to voice response.

To examine whether the incidence of detected hippocampal ripple events during encoding and retrieval stages correlated with memory performance, we computed the ripple rate (Hz) of detected events in 150-ms bins starting from -500 ms to 2000 ms relative to the picture onset. While baseline ripple rates in the 500 ms preceding stimulus presentation were similar preceding all trials, successful encoding trials were characterized by a greater increase in ripple rate occurring at the +1000 to +1500 ms interval after stimulus presentation($p=0.01$) (Fig. 3C). Likewise, successful recall trials were characterized by a greater increase in ripple rate occurring at approximately +700 until +1500 ms after stimulus presentation ($p=0.002$, Fig. 3C). For the ten patients with voice recording, successful trials had significantly increased ripple events in the -800 ms preceding the vocal response, lasting +400 ms after vocalization onset ($p=0.002$, Fig. 3C).

Hippocampal ripples in the SOZ during encoding and cued recall did not differ between successful and failed trials (Fig. S1). However, even in the SOZ, ripple rate differentiated successful and failed trials when trials were aligned to the vocal response (Fig. S1).

IEDs in Hippocampus, Temporal Pole, and Middle Temporal Gyrus Decrease Odds of Remembering

IEDs occurring during either the encoding or retrieval stages of the associative memory task were identified and pooled by anatomical region. We detected 13484 IEDs across all test blocks and electrodes for all patients (mean across patients, 898 ± 342 events). We blindly reviewed approximately 12% of detected events, classifying them as a true or a false IED detection (AL, SH). This analysis revealed a positive predictive rate of 92% and false positive rate of 8% among the detected IEDs. Fig. 3A shows the raw tracing of an example IED and its spectrogram.

SOZ was determined clinically by correlating seizure behavior to ictal iEEG changes. All IEDs occurring in any brain region outside the SOZ during encoding decreased the odds of remembering (odds ratio 0.95 ± 0.03, $p=0.0024$, Fig. 3B). IEDs occurring in any brain region during the cued recall stage was associated with a trend towards poorer performance ($p=0.076$, Fig. 3B). Further, an IED occurring in the right, but not left, hemisphere during encoding was associated with significantly decreased odds of remembering (OR 0.91 ± 0.04, $p=0.0002$). There was a non-significant negative correlation between the frequency of IEDs and trial set size ($r=-0.49$, $p=0.06$, Fig. 4C). Verbal IQ did not predict trial set size.

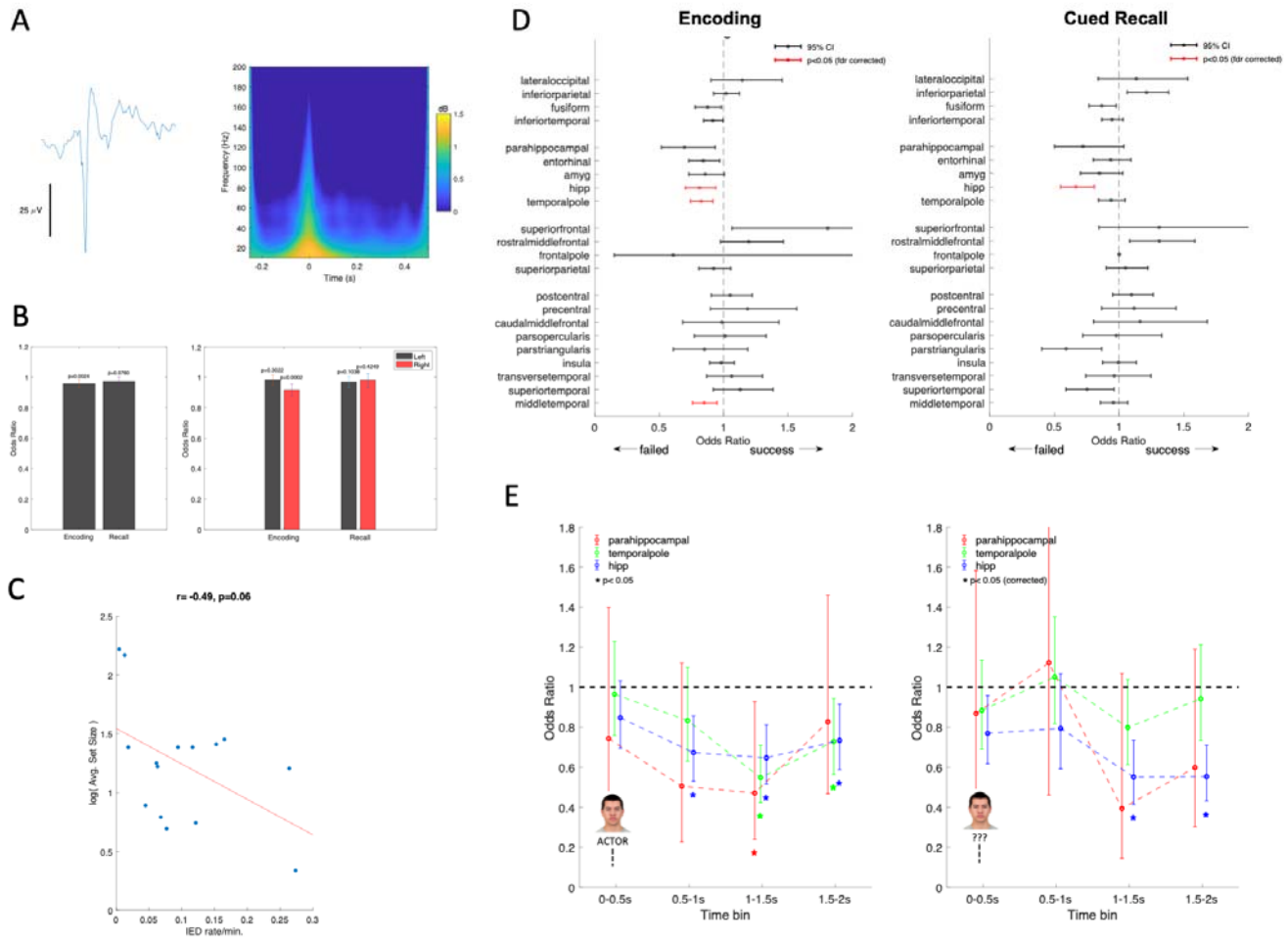

Fig. 4. Interictal epileptiform discharges (IEDs) and effect on memory performance. (A) Example raw tracing and spectrogram of a detected IED. (B) LEFT. IEDs recorded in any brain region during encoding predicted a 5% decreased odds of remembering (p=0.0024). IEDs in any brain region during cued recall trended toward decreased odds of remembering (p=0.0760). RIGHT. IEDs occurring in right hemisphere predicted a 9% decreased odds of remembering (p=0.0002). There was no difference in odds of remembering for IEDs in left hemisphere during encoding, or either hemisphere during recall. (C) Relationship between block size, IQ, and IED rate. Subjects varied in performance, ranging between 1 to 10 stimuli presented per block, with the higher number of stimuli indicating superior task performance between patients. There was a trend toward a negative correlation between IED rate and log set size (r= -0.49, p=0.06) (D) Odds of successful memory for IEDs occurring during encoding and recall, by brain region. Mean odds of successful memory per IED occurring during Encoding (LEFT) and Cued Recall (RIGHT), with 95% CI. Odds less than 1 indicate a decrease in odds of successful performance per spike. After correction for multiple comparisons, significant changes indicated in red (FDR correction p<0.05). (E) Odds of successful memory for IEDs occurring in selected brain regions, by 500 ms time window. Mean odds of successful memory per IED occurring during Encoding (LEFT), demonstrate that odds of remembering are further decreased by 27-46% if IEDs occurred in hippocampus, parahippocampal gyrus, and temporal pole occur between 500-2000 ms. During recall, mean odds of successful memory per IED in hippocampus decreased by 40%-60% when IEDs occur between 1000-2000 ms after stimulus presentation. After correction for multiple comparisons, significant changes indicated by an asterisk (FDR correction p<0.05).

When evaluating the odds of remembering related to IEDs occurring in distinct brain regions during the encoding period, the largest impact on performance when IEDs occurred in the hippocampus, temporal pole, and middle temporal gyrus. An IED in these three regions decreased odds of remembering by 19% (95% CI: 6%-30%), 18% (8-26%), and 15% (5-24%), respectively (Fig. 4D). During cued recall, an IED in hippocampus and outside of SOZ reduced odds of remembering by 33% (19-45%) (Fig. 4D).

Given the time course of HGA and hippocampal ripple activity predicting successful versus failed trails, we predicted that IEDs during critical time windows would have an even greater effect. When the impact of IEDs during encoding was evaluated in a more time-resolved manner, we found that an IED in hippocampus occurring during the 500 ms to 1500 ms window after stimulus presentation was associated with decreased odds of remembering between 27% to 36% (Fig. 4E). IEDs in the temporal pole during the 1000 ms to 2000 ms window decreased odds of remembering by 28% to 46%. IEDs in parahippocampal cortex during the 1000-1500 ms after stimulus were associated with decreased odds of 53%. Similarly, during cued recall, IEDs in hippocampus during the 1000-2000 ms window decreased odds of recall by approximately 45% (Fig. 4E).

Hippocampal IEDs Slow Response Time

In general, response times for all correct trial responses were delivered more quickly compared to incorrect responses or responses where subjects "passed" (mean = 1.74 s ±1.6 SD for correct trials vs. mean = 5.20 s ± 4.6 for incorrect/pass trials). Response times for correct trials which included an IED did not differ from correct trials without IED (Fig. S3). However, for incorrect responses and for responses signaled as "pass,", trials with an IED were slower compared to trials without an IED, when trials were pooled across patients ($Z= -2.55$, $p=0.01$; $Z = -2.87$, $p= 0.004$, respectively; Wilcoxon rank sum test).

Hippocampal IEDs Decrease Ripple Rate

Because both IEDs and ripple rates inversely correlated with memory performance, we examined their temporal relationship on a finer temporal scale, by 500 ms time bins (Fig. 4). Hippocampal ripples generally decreased after the IED for during encoding and recall (Fig. 5). However, this decrease in ripple rate reached significance during the 1-1.5 second time bin during encoding and demonstrated the greatest decrease after IEDs occurring in the 500 ms before and after the voice aligned cued recall (Fig. 5, bottom panel).

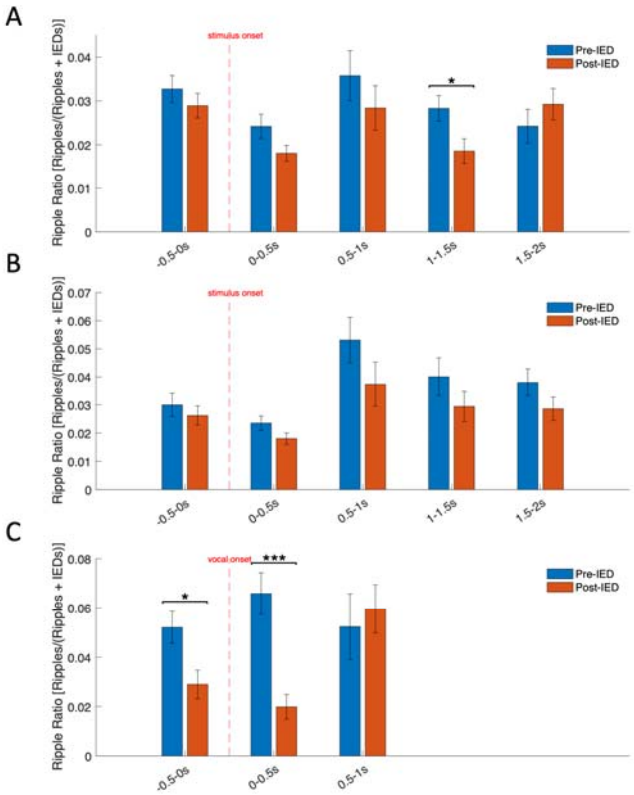

Fig. 5. Average Ripple Ratio (Ripple-to-IED ratio) in the 500ms Pre- vs. 500ms Post-IED window during Encoding & Recall. Average ripple ratio in the 500ms pre- (blue) vs. 500ms post-IED (red), binned by location of detected IEDs (500ms bin windows) for IEDs detected during Encoding (top), Cued Recall (middle), and Cued Recall timed to voice response (Bottom). A reduction in ripple rate after an IED event was found during the 1-1.5s window during encoding. In addition, ripple ratios were significantly reduced immediately preceding (-0.5-0s) and during (0-0.5s) vocalization during cued recall.

DISCUSSION

We examined the role of physiological (high gamma activity and hippocampal ripples) and pathological (IED) events in successful and failed associative memory in epilepsy patients. An increase in frontal and hippocampal high gamma activity and hippocampal ripple rate predicted successful memory. During the encoding and cued recall stages, physiological differences between successful and error trials peaked around 1000 ms after stimulus presentation, or 500 ms before the spoken response. Conversely, pathological IEDs occurring in hippocampus, temporal pole, and middle temporal gyrus reduced the likelihood of remembering. The odds of remembering were decreased by IED in hippocampus (-19%, CI 6-30%), temporal pole (-18%), and middle temporal gyrus (-15%) during encoding. An IED in the hippocampus during retrieval predicted a 33% (CI 19-45%) decreased odds of remembering. IEDs occurring during the 500-2000 ms window of encoding or retrieval had an even greater negative impact. Hippocampal IEDs observed during encoding and recall were generally followed by a decrease in ripple rate, although this difference was only significant between 1000-1500 ms during encoding and -500 to +500 ms with recalled. Overall, our findings suggest that IEDs impair associative memory in a regionally and temporally specific manner, likely by disrupting physiological memory processes (i.e. hippocampal ripples) needed to encode and recall.

Hippocampal Ripples Predict Associative Memory Performance

Our findings advance understanding of the contribution of physiological ripples to memory performance. Hippocampal ripple events detected from local field potential (LFP) recordings in humans undergoing invasive monitoring for epilepsy surgery correlate with successful retrieval of word pairs (*8, 9*) and visual episodic memories(*10*). Recently, LFP ripples in the middle temporal gyrus have been shown to organize sequences of single unit firing activity in humans in a phase-locked manner during successful memory retrieval(*9*). The sequence of single unit firing carries item-specific information, with the temporal order of unit firing during encoding replayed during retrieval in remembered trials(*9*). Similar to prior studies (*8-10*), we also observed an increase in ripple activity during the 800 ms prior to voiced retrieval predicting successful memory. Together, these studies represent a translational link to ripple activity observed in rodents during spatial navigation, which are replayed during wakefulness (*27*) and sleep (*28, 29*).

Whereas previous human studies demonstrated ripples' contribution to retrieval processes, we extend these findings to demonstrate the role of ripple events in successful encoding and retrieval. To verify that our methods captured physiological, and not pathological, high frequency oscillations, we excluded SOZ electrodes. We also excluded trials with IEDs, which often have superimposed pathological HFO events overriding the peak of the waveform (*30, 31*). Concordant with previous results, we found that ripples possessed an oscillatory waveform, a centroid peak between 80-100 Hz, a mean duration of ~30 ms, and followed a skewed log distribution. These features resemble ripples in rodents (*30*) suggesting that the events are not filtered high gamma events. The detected ripple rate at our threshold was approximately 1 event per second, comparable to previous human studies (*8, 10*). Most importantly, physiological ripple events had a strong temporal correlation with successful encoding and recall.

Our finding that ripple rate from hippocampus within SOZ only distinguished between successful and error trials when examining the recall responses aligned to the voice response suggests that SOZ maintains some preserved function, albeit less than tissue outside SOZ (*32*).

Hippocampal IEDs decrease memory performance and prolong reaction time

Our work supports and extends prior work on the role of IEDs in memory dysfunction by detailing IED spatiotemporal dynamics, especially regarding the role of the hippocampus. Early studies using intracranial depth recordings in humans demonstrated that hippocampal IEDs during a Sternberg (letter) working memory experiment impaired performance if they occurred during the maintenance or recognition stage(*11*). One study including 80 surgical patients across multiple research sites demonstrated that IEDs during the encoding and recall epochs impaired verbal memory performance, with stronger effects seen for left hemisphere IEDs occurring in inferior temporal, medial temporal, and parietal regions(*12*). However, hippocampal IEDs predicted reduced memory only if they occurred during the recall phase, but not encoding phase(*12*). Another study in epilepsy surgical patients showed that IEDs occurring in the left fusiform gyrus, and middle and inferior temporal gyrus, and outside of SOZ, during encoding of a word list impaired recall. IEDs decreased odds of recall by 8-15% per IED event (*15*). The authors hypothesized that IEDs disrupted visual encoding or recognition of word forms. In prior works, it is surprising that hippocampus and parahippocampal gyrus have been inconsistently implicated in IED-related memory disruption, especially given their critical role in temporarily binding information acquired from neocortex with later retrieval (*33-35*). It is unclear from previous studies why IEDs disrupt one stage of learning but not the other within the same task.

We show consistent and large effects of IEDs in hippocampus and adjacent neocortical regions during both encoding and recall. Our large effect sizes may be due to the appropriate choice of a face-profession association task, which differs from working memory paradigms and verbal free recall in several ways: 1) the task is associative in nature and demands linking semantic and visual information (a key function of the hippocampus) (*33, 35*), and 2); 2) it is a cued recall paradigm, allowing for more precise temporal mapping of HGA, ripple

events, and IEDs in relationship to stimulus presentation and spoken response. Here, we examined how the HGA and hippocampal ripple time courses could predict when and where IEDs might have maximal impact. We found that IEDs in mesial temporal structures occurring within 500-1000 ms—around the same time when HGA and ripple activity distinguished successful from failed memory--had an even larger deleterious effect, decreasing odds of recall by 30-50% per IED. This is a truly large effect, implying that a IEDs occurring within critical time windows will interfere with the recall process with a high probability.

We demonstrated associations were more likely to be forgotten, and patients showed slower reaction times during trials with IEDs. Slower responses may reflect disruption in associative computation, but alternatively slower processing of the visual stimuli or execution of the motor command. Focal and generalized IEDs can significantly prolong reaction times in a driving simulation task (*36, 37*), and can increase crash rate when a virtual obstacle is presented (*37*) IEDs prolonged reaction time in a variable manner, with generalized discharges affecting RT greater than focal discharges (*37*); and longer and higher voltage IEDs exerting a greater effect (*38*).

Hippocampal IEDs outside the SOZ Impair Memory Performance

Similar to a previous reports(*15*), we found that IEDs within the SOZ were not negatively associated with memory performance. Only IEDs outside of SOZ impaired performance. This may be interpreted by assuming that physiological processes, such as ripples, were already seriously impaired in the seizure zone in all aspects of the task. We also found a positive relationship with hippocampal ripple activity and memory performance when SOZ tissue was excluded from analysis. However, when hippocampal tissue within SOZ was analyzed, there was no relationship between ripple rate during encoding or recall with performance(Fig. S1). Physiological high gamma activity is retained within the SOZ(*32*). Our findings also indicate some preserved function in SOZ compared to surrounding brain tissue outside of the SOZ, as ripple rate increased in relationship to the voice-aligned recall (Fig. S1). The decreased reserve in SOZ is possibly due to greater neuronal loss and damage (*39*).

Hippocampal IEDs decrease ripple rate

By relating the temporal evolution of IEDs to hippocampal ripples, we demonstrated a potential mechanism for IED-induced disruption of mnemonic processing. Previous studies focused on either physiological HGA or ripple activity (*8, 10*) or IEDs (*11, 12, 15*). By examining the fine-grained spatiotemporal course of gamma and ripple activity, particularly in the hippocampus and related structures, we discovered that the most deleterious effects of IEDs occur within 1000-2000 ms after stimulus onset. This window corresponds to the critical increase of physiological HGA and ripples required for remembering, suggesting that IEDs interfere with key physiological mechanisms needed for successful memory encoding and recall. In support of this hypothesis, we found a decrease in ripple activity after IEDs, especially during these critical windows. The close temporal coupling between hippocampal IEDs and ripples imply that IEDs are not merely an epiphenomenon of a drowsy or distracted state(*16*), but rather trigger decreases in physiological ripples necessary for memory.

Limitations

The limitations of our study include a moderate sample size of patients, which limit analysis of how clinical and demographic factors--such as gender, epilepsy duration and severity, and education--affect memory performance. In addition, given that intracranial recordings are composed of LFPs, we could not measure the impact of neuronal sequences associated with ripples. We relied on the features of the filtered ripple event such as duration and frequency, their correlation with memory performance, and previous studies combining LFP with single unit recordings (*9*) to deduce that the signals were indeed physiological ripples. Finally, a study in humans is limited by the inability to induce timed IEDs and prove their causative role in disrupting physiological models to impact memory.

Conclusions

Earlier animal studies found that most hippocampal IEDs act as pathological ripples, recruiting a much larger population of the neuronal pool and in a narrower time window than the physiologically protracted events during ripples (*40*). The competition between physiological ripples and pathological IED rate in a kindling model led to deterioration of performance on a cheeseboard maze task (*14*). In line with this, a recent human iEEG study suggested that hippocampal IEDs modulate single unit recordings, particularly of inhibitory interneurons in the medial temporal lobe (*41*). Together, these findings suggest that epileptic IEDs hijack physiological processes essential for effective encoding and recall of declarative memories.

Assuming that transient memory impairment arises from pathological IED events competing with physiological ripples, hippocampal IEDs represent a promising therapeutic target for memory remediation in patients with epilepsy and Alzheimer's Disease (*42*). However, before IEDs can be considered to be a clinical endpoint, assessment of performance in a real-time manner using a wider variety of clinically meaningful memory tasks is needed. Furthermore, closed-loop termination of IEDs during cognitive testing in rodents and humans (*43*) are needed to demonstrate that reducing IEDs can restore memory.

MATERIALS AND METHODS

Face-profession association task. We employed 120 color images of distinct human faces with neutral expression from the Chicago Face Database (Fig. 2A)(*44*). The image set comprised 59 male, 61 female, and an equal proportion of White, Black, Hispanic, and Asian faces, paired with 120 emotionally neutral, single-word professions, 4–10 letters long, selected from the US Bureau for Labor Statistics database. Since epilepsy patients typically have impaired performance compared to healthy subjects, (*11-13, 25*) we calibrated the task difficulty by individual subjects to achieve a balanced distribution between successful and failed encoding trials. Trial sets ranged from 1 to 10 pairs per set. Task stimuli and subject's spoken responses were presented and recorded by computer (Psychophysics Toolbox). Each face-profession pair was shown for 5 seconds, with a 1 second interstimulus interval which was marked by a plus sign. To ensure attention and sensory processing of test stimuli, patients were instructed to read the profession aloud and make a mental association. To prevent rehearsal after the encoding block, a brief distraction task was presented ("Count backwards from 15").

We tested for memory function using a cued recall paradigm. During recall, subjects were shown only faces from the prior set and asked to speak aloud the associated profession. The cued recall segment lasted for as long as the subject needed to provide a response. Sets during which subjects freely stated the associated profession paired with the face stimulus were scored as correct trials.

The task laptop sent a pulse to a trigger input channel in the EEG amplifier to synchronize task stimuli with the electrophysiological recordings. The time stamps associated with the pulses were used to annotate the iEEG recordings, then later analyzed with the voice responses to measure response times.

Antiseizure medications were reduced to record seizures during the patient's hospital stay. Cognitive testing was performed >= 6 hours after the last seizure. If a patient had a seizure or non-epileptic seizure during testing, all concurrent and subsequent trials were excluded from analysis. All participants provided informed consent with procedures approved by the institutional review board at NYU Langone.

Electrodes and Amplifier. Brain activity was recorded from implanted stainless steel or platinum-iridium depth electrodes or subdural electrode grids embedded in silastic sheets. Decisions for implantation, placement of electrodes, and the duration of monitoring were made by the clinical team and without reference to this study. Subdural grids and strips covered extensive portions of lateral and medial frontal, parietal, occipital, and temporal cortices of both hemispheres (Fig. 1). Recordings were made using: (i) Natus NicoletOne C64 clinical

amplifier, bandpass filtered from 0.16–250 Hz, with a 512 Hz sampling rate or a (ii) Natus Quantum clinical amplifier, with a 2000 Hz sampling rate, which was later down sampled to 512 Hz following anti-aliasing filtering.

iEEG Analysis. Standard artifact rejection techniques, such as notch filtering for line noise and harmonics (60, 120, 180 Hz), detrending, and baseline correction were applied. In addition, EEG artifacts were removed by omitting trials where the raw signal exceeded 5 SD above the mean(*45*). Finally, visual inspection of individual trials excluded trials with excessive non-physiological noise. iEEG analysis focused on identifying differences in the spectral-temporal features between successful and failed encoding trials. All analyses were performed using a bipolar montage, conducted across regions and trials. Electrode localization used an established technique (*46*) and verified by expert inspection (AL, DF, SH). After identifying electrodes in the hippocampus, entorhinal cortex, and regions of the neocortex, we performed time-frequency analyses on discrete task windows, including from -500 ms to 2000 ms during encoding, and -500 to +2000 ms during cued recall, with time 0 designated as the time of the cue presentation. We also derived response times from cue presentation to start of spoken responses (correct, incorrect, and pass), which were manually marked from the audio recordings.

iEEG recordings were segmented into encoding and cued recall periods, comparing trials which were later successfully recalled versus forgotten. HGA activity of the raw EEG traces was estimated using multi-taper spectral analysis (Chronux Toolbox, 250 ms windows, 10 ms steps; 60-170 Hz), normalized per frequency bin to the -0.5 to -0.05 s pre-stimulus baseline, and then averaged across frequency bands. To assess for differences between conditions (successful vs. failed encoding), a non-parametric cluster-corrected permutation test was used to determine significance of any power changes between conditions(*47*)

Seizure onset zone. We sought to identify electrodes within the seizure onset zone (SOZ), which has impaired function compared to non-SOZ areas(*15*). The SOZ was determined by the clinical team's correlation of clinical seizures and intracranial EEG seizure discharges. SOZ electrodes were excluded from primary analysis correlating hippocampal ripples and IEDs with memory performance.

IED Detection. Given the significant inter-rater variability in IED annotation even among experts (*48*), we used an automated IED detection algorithm (*49*) combined with validation by 2 experts (AL, SH). All spikes in the -500 ms to +2000 ms encoding window were pooled by condition (correct/incorrect). Spikes were also pooled by anatomical brain region, as determined by the MNI coordinates of the electrodes co-registered from the post-implantation CT scan or MRI Brain to the pre-implant T1-weight MRI Brain scan (*46*). Spikes in more than one region were considered independently (*15*). Electrodes which were clinically determined to be in the SOZ were treated separately in the IED analysis.

Ripple Detection. Hippocampal electrodes were determined by a combination of automated processes with expert validation. An electrode pair (bipolar) located within or closest to the anterior hippocampus was selected for analysis for each patient. Ripple detection was performed using a method that has previously demonstrated a relationship between ripples in hippocampus and middle temporal gyrus and successful retrieval(*8*). The raw iEEG was filtered between 80 Hz and 120 Hz and the power envelope extracted using a Hilbert transform. Events where the envelope of the filtered response exceeding 2 SDs and 20-200 ms in duration were marked as ripple events. These filter settings reduced the potential of detecting pathological high frequency oscillations (HFOs), which have a centroid peak between 150-200 Hz (*32*). HFOs are potential biomarkers of epileptogenicity and inversely correlate with high gamma activity and memory performance (*32*). To further reduce the likelihood of detecting pathological ripples, electrodes determined to reside within the SOZ and trials with IEDs were excluded from initial ripple detection. Ripple duration and spectral qualities were inspected.

A secondary analysis examined the impact of IEDs on ripples during encoding and retrieval, comparing the normalized hippocampal ripple rates before and after the IED detection. First, all IEDs were binned in 500 ms windows within encoding, recall, and voice aligned trials, from 500 ms before to 2000 ms after cue onset. We then compared the ripple activity rate normalized by the total number of ripples and IEDs (i.e. ripple ratio = ripple rate / (# of ripples + # IEDs)) in the 500 ms window before and after each IED was detected. Ripples surrounding the 50 ms around the IED were excluded to avoid detection of pathological HFOs. This measure tested the null hypothesis that the ripple ratio before and after the IED were the same.

Statistical Analysis and Modeling. We also modelled the effect of spikes on memory performance on a trial by trial basis. A generalized linear model (GLM) with a logit link function permitted modelling of a binary outcome (remembered versus forgotten)(*15*). The GLM was fit to predict recall with IED location (e.g. entorhinal, hippocampal, neocortical) as fixed effects. Subject was considered a random effect. Effect sizes (odds ratio, OR) and confidence intervals (CI) were calculated with significance determined by Wald statistics and FDR corrected. Likelihood ratios were reported when testing single parameters (regional analysis).

ACKNOWLEDGEMENTS
The authors would like to acknowledge Lucia Melloni and Lila Davachi for early advice on task design.

FUNDING
SH, AS, HB, and AL receive support from by K23-NS 104252, RO1 MH 107396, the Zimin Foundation. AF receives support by R01 NS 109367, R01 NS125641, R21 MH122829, and NSF 1912286. DF receives support from NIH R01 NS06209207, NIH R01 NS109367, CDC U48DP006396-01SIP 19-003, Neuropace, Inc, Epilepsy Foundation, Epitel. OD receives support from R01 MH107396, U01 NS099705, R01 MH111417, U01 NS090415, R01 MH116978, R01 HL151490, Tuberous Sclerosis Alliance, Epilepsy Foundation of American, and the National Science Foundation. GB receives support from U01 NS090583, R01 MH107396, R01 MH122391. WD receives support from R01 NS062092 and R01 MH116978.

COMPETING INTERESTS
OD has equity and/or compensation from the following companies: Privateer Holdings, Tilray, Receptor Life Sciences, Qstate Biosciences, Tevard, Empatica, Engage, Egg Rock/Papa & Barkley, Rettco, SilverSpike, and California Cannabis Enterprises (CCE). He has received consulting fees from GW Pharma, Cavion and Zogenix.

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