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Epilepsia

RESEARCH ARTICLE

Temporal lobe interictal spikes disrupt encoding and retrieval of verbal memory: A subregion analysis

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Abstract

Objective: The medial temporal lobe (MTL) encodes and recalls memories and can be a predominant site for interictal spikes (IS) in patients with focal epilepsy. It is unclear whether memory deficits are due to IS in the MTL producing a transient decline. Here, we investigated whether IS in the MTL subregions and lateral temporal cortex impact episodic memory encoding and recall.

Methods: Seventy-eight participants undergoing presurgical evaluation for medically refractory focal epilepsy with depth electrodes placed in the temporal lobe participated in a verbal free recall task. IS were manually annotated during the pre-encoding, encoding, and recall epochs. We examined the effect of IS on word recall using mixed-effects logistic regression.

Results: IS in the left hippocampus (odds ratio [OR] = .73, 95% confidence interval [CI] = .63–.84, $p < .001$) and left middle temporal gyrus (OR = .46, 95% CI =

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.27–.78, $p < .05$) during word encoding decreased subsequent recall performance. Within the left hippocampus, this effect was specific for area CA1 (OR = .76, 95% CI = .66–.88, $p < .01$) and dentate gyrus (OR = .74, 95% CI = .62–.89, $p < .05$). IS in other MTL subregions or inferior and superior temporal gyrus and IS occurring during the prestimulus window did not affect word encoding ($p > .05$). IS during retrieval in right hippocampal (OR = .22, 95% CI = .08–.63, $p = .01$) and parahippocampal regions (OR = .24, 95% CI = .07–.8, $p < .05$) reduced the probability of recalling a word.

Significance: IS in medial and lateral temporal cortex contribute to transient memory decline during verbal episodic memory.

KEYWORDS

CA1, dentate gyrus, episodic memory, interictal epileptiform discharges, intracranial EEG, lateral temporal cortex, medial temporal lobe

1 | INTRODUCTION

Memory deficits are common among people with epilepsy.[1] Multiple factors potentially affect memory in epilepsy, including interictal spikes (IS), the location and nature of the underlying pathology, antiepileptic drugs, synaptic reorganization, and changes in white matter integrity, which both are related to the age of seizure onset.[2] IS are pathological transient discharge waveforms, clearly distinguished from background activity, with a pointed peak and duration of 20–70 ms.[3] IS have been found to correspond to abnormal synchronous firing of excitatory and inhibitory neurons.[4,5] In animal models of epilepsy, and human subjects, IS have been associated with transient cognitive/memory impairment (TCI/TMI).[5–7]

The TCI/TMI produced by IS have been demonstrated in different tasks[8–10] and even in daily activities such as driving.[11] Multiple mechanisms have been proposed by which IS may cause cognitive impairments.[5,12,13] Various reports have described location-specific effects of IS. In verbal episodic memory tasks, left-sided IS disrupt memory encoding[14,15]; conversely, during spatial or visual tasks, right-sided IS produce TCI/TMI.[6]

The medial temporal lobe (MTL) is a major site for IS in temporal lobe epilepsy and a key structure for forming and retrieving memories.[16] Lesions and dysfunctions in MTL subregions are associated with significant impairments in episodic memory.[17–19] Few studies in humans have assessed the impact of IS in the MTL,[5,20–23] and the results of the relationship between IS in the MTL and memory processes are inconsistent. In some studies, IS had no impact when they occur during the encoding, maintenance, or retrieval periods.[14,23,24] Other studies found that IS in the MTL specifically disrupt retrieval but not encoding,[5,21,22] and one recent study found that IS impact encoding and recall in participants solving a recognition task.[25] Thus, it is unclear whether IS in the MTL disrupt encoding and/or recall, and whether finding this possible effect depends on the task under study, the methods used to detect the IS, or the study sample size.

Key Points

- Interictal temporal lobe spikes produce transient memory and cognitive impairment
- IS in specific mesial temporal lobe subregions determine whether verbal encoding is reduced
- IS in middle temporal gyrus reduced retrieval of verbally encoded information
- Consideration should be given to developing new treatments that suppress IS to prevent their adverse cognitive consequences

In addition, most of these studies have addressed the impact of hippocampal IS on transient cognitive impairment.[12,20,22,26] Nonetheless, in addition to the hippocampus, the MTL comprises the entorhinal, perirhinal, and parahippocampal cortices, and the hippocampus itself contains multiple subregions with different functions.[27] Whether IS in these MTL subregions affect encoding or recall has not been investigated in humans. Identifying the MTL subregions in which IS produce a TCI/TMI would help dissect the critical circuits that serve as the substrate for human memory and may have clinical relevance.

We analyzed intracranial electroencephalographic (iEEG) data from 78 epilepsy patients who participated in a verbal free recall task.[28–30] The free recall task has been used extensively to study the encoding and retrieval of episodically formed associations.[31] In contrast with

other tasks, the free recall task requires an active retrieval process in which patients recall items based on semantic relatedness and temporal contiguity of the recalled items. We used expert validation to annotate all IS during the memory encoding and recall periods and analyzed whether they impacted the patient's performance. We hypothesized that IS within MTL subregions would differentially affect both encoding and retrieval.

2 | MATERIALS AND METHODS

2.1 | Patient selection

Patients undergoing iEEG monitoring as part of their presurgical treatment for drug-resistant epilepsy participated in the Restoring Active Memory project of the Defense Advanced Research Projects Agency. See Appendix S1 for additional information on inclusion and exclusion criteria. Data were collected at the following participating hospitals: Columbia University Hospital (New York, NY), Dartmouth-Hitchcock Medical Center (Lebanon, NH), Emory University Hospital (Atlanta, GA), Hospital of the University of Pennsylvania (Philadelphia, PA), Mayo Clinic (Rochester, MN), Thomas Jefferson University Hospital (Philadelphia, PA), and University of Texas Southwestern Medical Center (Dallas, TX). The research protocol was approved by each respective institutional review board, and informed consent was obtained from each participant.

2.2 | Assessment of hemisphere language dominance

At the request of the clinicians at each clinical facility, a subset of patients was further evaluated preoperatively to determine their lateralization of language and memory. The methods used were either the Wada test, also known as the intracarotid sodium amobarbital procedure, or task-based functional magnetic resonance imaging (fMRI).[32]

2.3 | Task description

In the free recall task, participants are instructed to study lists of words, and after a distractor epoch, recall as many words as possible. Participants performed up to 25 lists per session. Each list consisted of 12 common words presented one at a time, on a computer screen. Words were selected from a pool of nouns (http://memory.psych.upenn.edu/WordPools). We employed two different versions of the task. In "categorized free recall," the words were drawn from three different semantic categories per list. In "standard free recall," the 12 words on each list were semantically unrelated. The two versions were otherwise identical. Each word was displayed for 1600 ms, and the interword interval was jittered between 750 and 1000 ms.[29] After 12 words were presented, a distractor epoch followed, with subjects solving simple arithmetic operations for 20 s. Then, subjects had 30 s to recall as many words as possible. Patients participated in between one and six sessions (35 [i.e., 45%] in one session, 36 [46%] in two or three sessions, seven [9%] in four or more sessions).

2.4 | iEEG data

iEEG signal was recorded using depth electrodes (AdTech, PMT), which were implanted to localize epileptic regions. Recordings were collected with DeltaMed XlTek (Natus), Grass Telefactor, and Nihon-Kohden EEG systems, depending on the site of data collection. The iEEG was sampled at either 500, 1000, 1600, or 2000 Hz (varying between hospitals). We converted the iEEG signals recorded at individual electrodes to a bipolar scheme by computing the signal difference between adjacent electrode pairs on each depth electrode.[29]

2.5 | Neuroimaging data and electrode localization

Preimplantation volumetric T1-weighted MRI scans and T2 oblique scans of mesial–temporal structures were normalized and coregistered to postimplantation computed tomography (CT) scans using Advanced Normalization Tools and an in-house pipeline with neuroradiologist supervision (https://github.com/pennmem/neurorad_pipeline).[30,33]

Neuroradiologists determined the precise localization of all depth electrodes in the hippocampus subfields and MTL cortices using postimplantation CT and MRI. In addition, the hippocampal subfields and MTL cortices were segmented on preimplant T2-weighted MRI using the automatic segmentation of hippocampal subfields multiatlas segmentation method[34] used in prior studies.[28,30] The anatomical labels created by the segmentation method were CA1, CA2, CA3, dentate gyrus, subiculum, perirhinal, and parahippocampal cortex. The performance of this method relative to manual segmentation was highest for the dentate gyrus, followed by CA1, perirhinal cortex, and entorhinal cortex labels.[34]

Cortical regions were delineated on preimplant whole-brain volumetric T1-weighted MRI scans according to the Desikan–Killiany atlas.[35]

2.6 | IS annotation

We used the Micromed Brain Quick EEG viewer to annotate all IS. Two trained observers (L.C.-R. and Z.W.) manually identified all IS in the EEG. A board-certified clinical neurophysiologist (M.R.S.) supervised the detection and verified all IS (Figure 1B). We used the definition of the International Federation of Societies for EEG and Clinical Neurophysiology that describes IS as transient, clearly distinguished from background activity with a pointed peak and duration of 20–70 ms.[3] We included only IS but not sharp waves. To distinguish between IS and sharp waves, we measured the wave duration of each event using the EEG viewer's tools.

All IS events were manually detected during the following periods of the task: (1) prestimulus period (−750 ms to 0 ms relative to word onset); (2) word encoding, during which words are displayed for 1600 ms on a monitor screen; and (3) retrieval, during which patients have 30 s to recall freely as many words as they can.

2.7 | Statistical analysis of the effect of IS

2.7.1 | Effect of IS during encoding

We ran two types of analyses: analyses at the word level (when IS occur before the stimulus presentation or during the word encoding epoch) and analyses at the list level (when the IS occur during the retrieval epoch).

To determine whether IS occurrence during the prestimulus and word encoding epoch affected successful memory encoding, we fitted mixed-effects logistic regression models to the data from the 78 patients, collected in 40 668 trials overall (157 sessions and 3389 lists). We conducted separate analyses for the following regions of interest (ROIs):

- Hippocampus;
- Parahippocampal gyrus (PHG);
- Superior temporal gyrus, middle temporal gyrus, and inferior temporal gyrus; and
- MTL subfields: CA1, CA3, dentate gyrus, entorhinal cortex, perirhinal cortex, parahippocampal cortex, and subiculum.

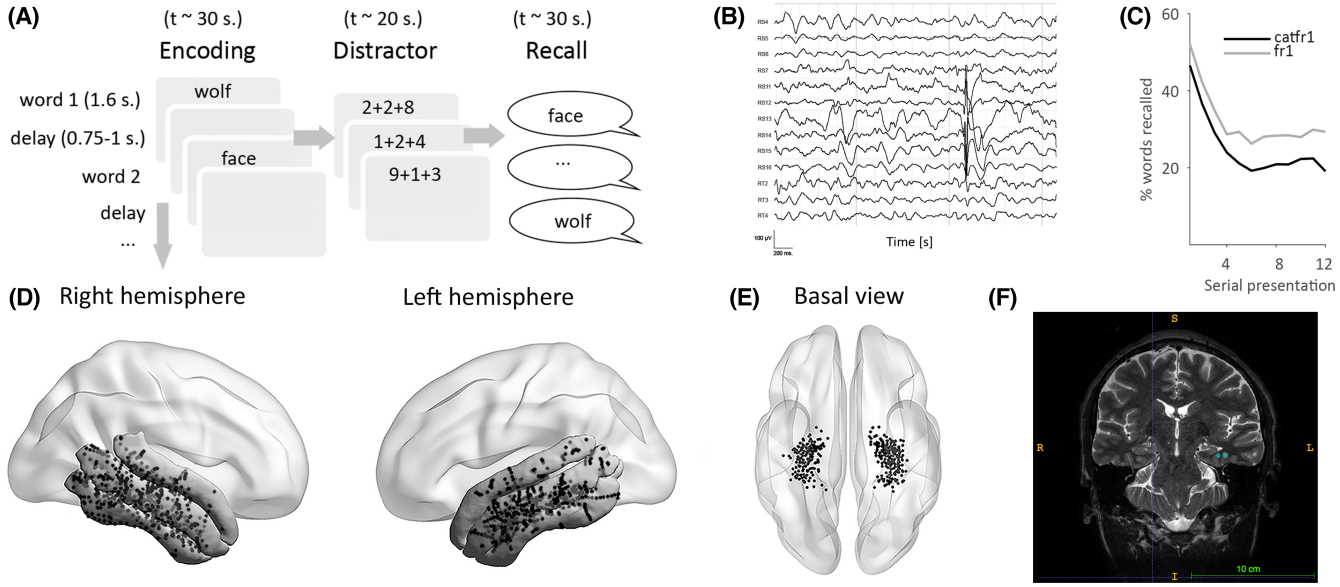


FIGURE 1 Task overview and recording sites. (A) Subjects participated in a verbal free recall task, which has three main components (encoding, distractor, and recall). First, the participant is instructed to remember a list of 12 words that are presented sequentially on a computer screen separated by an interword interval. After 12 words are presented, a distractor epoch follows, with participants solving simple arithmetic operations. Finally, the participant has 30 s to recall as many words as possible. (B) Examples of interictal spikes. The recordings were obtained while the patient was engaged in the task. (C) Percentage of words recalled across all subjects as a function of their serial presentation during a list. catfr1; categorized free recall; fr1, standard free recall. (D) Electrode contacts localized to lateral temporal gyri are shown in a lateral view of the brain. The electrodes are located either at the top of a gyrus or within a sulcus. Each dot shows an electrode contact. (E) Electrode contacts localized to medial temporal lobe are shown in a basal view of the brain. The electrodes are not on the surface but within the limbic cortex. (F) Example T2-weighted magnetic resonance imaging of one participant whose bipolar electrode contacts are in left perirhinal cortex. I, inferior; L, left; R, right; S, superior.

The dependent variable in these analyses was the dichotomous response *Yijkl*, which assumes a value of 1 if patient *i* correctly recalled word *l* of list *k* in session *j*, and 0 otherwise; the independent variables, on the other hand, were:

1. Pos_{ijkl}: the position of word *l* in the 12-word list presented during list *k* in session *j* of patient *i* (as a categorical variable);
2. $Cats_{ij}$: the type of task applied in session *j* of patient *i* (as a binary categorical variable indicating whether the 12 words within each list were unrelated or formed three groups of four categorically related words each); and
3. IS_{ijkl}: the proportion of electrodes located in the brain region under study that registered an interictal spike before the presentation of word *l* (for the prestimulus model) and during the presentation of word *l* (when memory encoding is assumed to take place) of list *k* in session *j* of patient *I*.

Furthermore, we included random effects for the patients, sessions (nested within patients), lists (nested within sessions), and the words used in the trials (which form a crossed random effect that accounts for possible differences among words concerning the difficulty of recall; a total of 528 different words were used in the study).

2.7.2 | Effect of IS during retrieval

We used a binomial regression model to determine whether IS during retrieval had an impact on recall. We fit the model to a subset of 28 patients and ensured that there were enough patients for each anatomical region to have sufficient statistical power. We conducted separate analyses for the following ROIs: (1) hippocampus, (2) PHG, (3) superior temporal gyrus, (4) middle temporal gyrus, and (5) inferior temporal gyrus. Due to sample sizes, we did not fit separate models for the hippocampal subregions.

The dependent variable Y_{ijk} denotes the number of words recalled by patient *i* in list *k* of session *j* and is assumed to follow a binomial distribution Bin(12, π_{ijk}), where π_{ijk} is modeled as a function of IS_{ijk}, which indicates the average IS counts detected in the electrodes of the brain region under study during the recall period of the 12-word list *k* in session *j* of patient *i*. We included random effects for the patients and sessions (nested within patients).

Note that patients differed regarding the number of electrodes placed in the respective brain regions and that, in the analysis for a given brain region, we only included the data from patients with at least one bipolar pair; as a result, the number of observations involved in the analysis varied across each ROI. We used the PROC GLIMMIX procedure in SAS version 9.4[36] for the analyses. We corrected the *p*-values for multiple comparisons using the adaptative Hochberg algorithm.[37]

2.8 | Power analysis of generalized linear mixed model

We used the simr package in R to calculate power and optimal sample sizes to detect IS effects on memory encoding and recall.[38] This algorithm considers data's hierarchical structure (it includes all the levels of the data that were explained in the previous section). Briefly, power estimation starts by fitting a mixed-effects logistic regression model to one portion of the dataset and specifying an effect size. For this analysis, we used the encoding data and required that the behavioral data of each patient have at least one session complete (each session consists of 25 lists). Power was calculated based on Monte Carlo simulations. Considering an effect size of −.2 (odds ratio [OR] = .8), as reported previously in the literature,[5,20,21] we found that 11 patients are needed on each ROI to detect a significant effect with a power of 80% or above.

3 | RESULTS

3.1 | Patient characteristics

Seventy-eight adult patients with medically refractory focal epilepsy due to diverse etiologies and implanted depth intracranial electrodes participated in a delayed verbal free recall task. Of the 78 patients, 36 (46%) were males, 41 (53%) females, and their age ranged from 19 to 65 years (mean age = 37.4, Tables 1 and S2). Among the 78 patients, 29 had a left hemispheric seizure onset zone (SOZ), 28 had a right hemispheric SOZ, and 17 had a bilateral SOZ. Concerning seizure focality, 19 had a mesial–temporal SOZ, 10 had a lateral temporal cortex SOZ, 11 had a mesial and lateral temporal cortex SOZ, 22 had an SOZ that was temporal plus other extratemporal regions, and 12 had an extratemporal SOZ (Tables 1 and S2).

3.2 | Subject performance in the verbal episodic free recall task

Across all subjects, sessions, and lists, the proportion of words recalled in the delayed verbal free recall task (Figure 1A) was 27.1%. Word order influenced the probability of recall, such that the words presented first exhibited a primacy effect of enhanced recall.[39] We did not

TABLE 1 Characteristics of the patients included in the study

Characteristic	Range, *n* (%)
Age, years	19–65, mean = 37.4
Gender	
Male	36/78 (46%)
Female	41/78 (53%)
Missing	1/78 (1%)
Handedness	
Left	11/78 (14%)
Right	61/78 (78%)
Ambidextrous	5/78 (6%)
Missing	1/78 (1%)
Dominant hemisphere	
Left	54/78 (69%)
Right	6/78 (8%)
Bilateral	3/78 (4%)
Missing	15/78 (19%)
iEEG implantation	
Left	16/78 (20.5%)
Right	10/78 (12.8%)
Bilateral	52/78 (66.7%)
Seizure lateralization	
Left	29/78 (37.2%)
Right	28/78 (35.9%)
Bilateral	17/78 (2183%)
Undetermined	4/78 (5.1%)
Seizure focality	
Mesial temporal	19/78 (24.4%)
Lateral temporal cortex	10/78 (12.8%)
Mesial and lateral temporal cortex	11/78 (14.1%)
Temporal plus other extratemporal region(s)	22/78 (28.2%)
Extra temporal	12/78 (15.4%)
Undetermined	4/78 (5.1%)

observe a recency effect, which is expected due to the arithmetic distractor task subjects had to perform between word presentation and recall.

3.3 | Interictal spikes during the encoding trials

First, we examined the effect of IS during word encoding in the hippocampus and PHG by fitting a mixed-effects logistic regression for each anatomical region. An example of an interictal spike is shown in Figure 1B. Of 78 subjects, 74 had electrode contacts in the MTL (Figure 1E,F). In the left hippocampus (n = 49 participants, n = 184 electrode contacts) IS decreased memory encoding from 24% to 18.7% (OR = .73, 95% confidence interval [CI] = .63–.84, $p < .001$, Figures 2A and S1). We found no evidence that successful memory encoding was disrupted by IS in the left PHG (n = 38 participants, n = 85 electrode contacts, OR = .81, 95% CI = .63–1.05; Figure 2A), right hippocampus (n = 41 participants, n = 132 electrode contacts, OR = .94, 95% CI = .8–1.1; Figure 2A), and right PHG (n = 29 participants, n = 69 electrode contacts, OR = .97, 95% CI = .76–1.25; Figure 2A).

Having found that IS disrupted memory encoding in the left hippocampus, we asked whether we would observe this disruption across the hippocampal subfields, such as CA1, CA3, dentate gyrus, and subiculum. The number of participants with electrode contacts in each subregion in shown in Table S1. Similarly, we assessed whether IS disrupted memory encoding across the PHG subfields, which includes the entorhinal cortex, parahippocampal cortex, and perirhinal cortex.

In left MTL, we found that IS decreased the memory encoding from 23.2% to 18.6% in CA1 (OR = .76, 95% CI = .66–.88, $p < .01$; Figures 2C and S1), and in dentate gyrus from 23.1% to 18.1% (OR = .74, 95% CI = .62–.89, $p = .01$; Figures 2C and S1). The occurrence of IS in other subregions of the left MTL, such as entorhinal cortex, parahippocampal cortex, perirhinal cortex, CA3, and subiculum, trended toward decreased odds of memory encoding (Figures 2C and S1). IS that occurred in the right MTL structures did not disrupt encoding ($p > .05$, Figures 2C and S1).

Next, we asked whether IS in the lateral temporal gyri also decrease the probability of successful memory encoding. Table S1 shows the number of participants with electrode contacts in each region.

IS in the left middle temporal gyrus decreased the probability of word encoding from 24.4% to 12.9% (OR = .46, 95% CI = .27–.78, $p < .05$; Figures 2B and S1). IS in the left inferior and superior temporal gyrus did not disrupt encoding ($p > .05$; Figures 2B and S1). In the right lateral temporal gyri, we did not find a significant effect ($p > .05$; Figures 2B and S1).

Having found that the spontaneous occurrence of IS during the encoding epoch affected memory encoding only in the left structures (hippocampus and middle temporal gyrus), we next assessed this effect in the subset of participants with left hemisphere language dominance. Of 78 patients, 54 (69%) had left hemisphere dominance, six (8%) had right dominance, three (4%) had bilateral hemisphere dominance, and in 15 (19%) patients this information was not available.

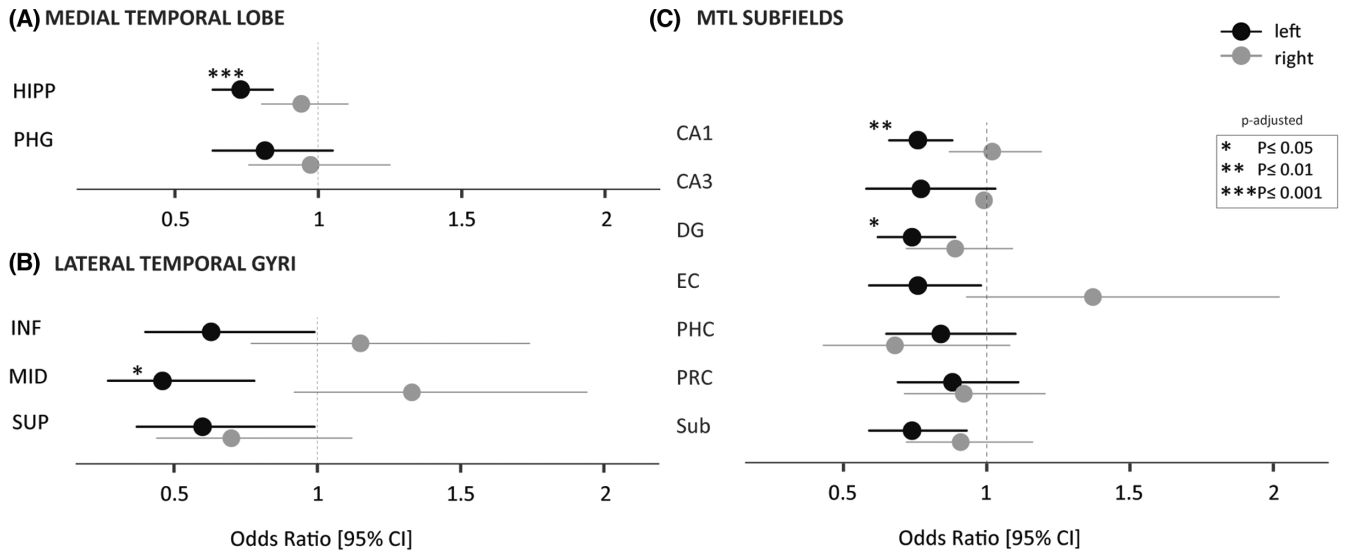
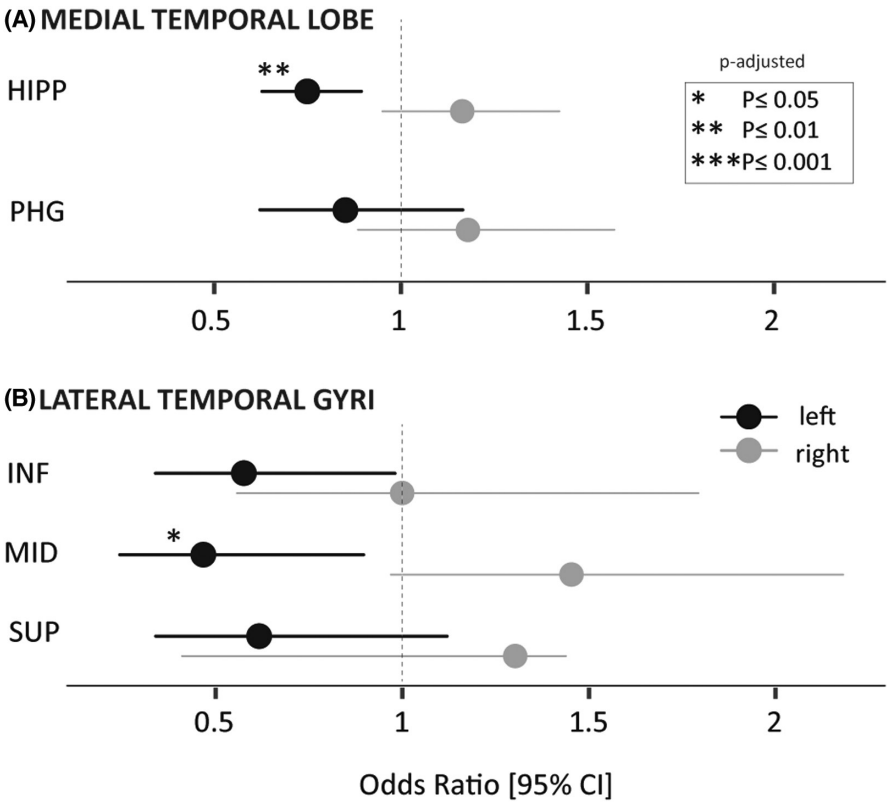


FIGURE 2 Interictal spikes (IS) in the left hippocampus and left lateral temporal cortex during encoding were associated with a decrease in the probability of word recall ($n = 78$). (A) Probability of successful recall for IS detected in the hippocampus (HIPP) and parahippocampal gyrus (PHG) during word encoding. (B) Probability of successful recall for lateral temporal gyri IS. CI, confidence interval; INF, inferior; MID, middle; SUP, superior. (C) Probability of successful recall for IS detected across each medial temporal lobe (MTL) subregion. The *p*-values were corrected using the adaptative Hochberg algorithm for multiple comparisons. CA, cornu ammonis; DG, dentate gyrus; EC, entorhinal cortex; PHC, parahippocampal cortex; PRC, perirhinal cortex; Sub, subiculum.

FIGURE 3 Effect of interictal spikes (IS) in patients with left hemisphere dominance ($n = 54$). (A) Probability of successful recall for IS detected in the hippocampus (HIPP) and parahippocampal gyrus (PHG) during word encoding. (B) Probability of successful recall for lateral temporal gyri interictal spikes. CI, confidence interval; INF, inferior; MID, middle; SUP, superior. The *p*-values were corrected using the adaptative Hochberg algorithm for multiple comparisons.



When restricting the analysis to left hemisphere dominant patients ($n = 54$), we observed that the results were very similar to the entire cohort. IS disrupted encoding when occurring in the left hippocampus (OR = .77, 95% CI = .64–.92, $p < .05$; Figure 3A) but not left PHG ($p > .05$; Figure 3A). We did not find that IS disrupted encoding in the right hippocampus and PHG ($p > .05$; Figure 3A). Due to sample sizes, we did not fit a separate model for each MTL subregion.

As in the previous analysis, IS in the left middle temporal gyrus decreased the odds of memory encoding (OR = .46, 95% CI = .27–.78, $p < .05$; Figure 3B). We did not

find that IS disrupted encoding in the left inferior and superior temporal gyrus and the right lateral–temporal regions ($p > .05$; Figure 3B).

We also examined the effects of lesions on encoding, and whether lesions interacted with IS to influence memory encoding performance, only on the segmented regions that exhibited spike-related encoding disruption (Appendix S1). We found that lesions in the left middle temporal gyrus decreased the odds of memory encoding ($p < .05$; Table S3). In contrast, lesions in the left CA1 or left dentate gyrus did not disrupt performance ($p > .05$; Table S3). We did not observe a significant interaction between the effect of IS during encoding and the presence of a lesion in any of the regions analyzed ($p > .05$; Table S3).

Patients also exhibited a diverse range of verbal scores that could have impacted their performance on the task and influenced the effect of IS on verbal episodic memory encoding (see Appendix S1). To test this hypothesis, we extended the statistical model and estimated the correlation between (1) the baseline recall performance, during our task, in the absence of IS; and (2) the effect of IS on the recall performance. We found that, in regions where IS disrupt encoding, the correlation between baseline performance and the effect of spikes was not significant ($p > .05$; Appendix S1, Table S4).

3.4 | Interictal spikes during the prestimulus period

Previous studies have suggested that IS have the most significant impact on performance when they occur before a cognitive stimulus is presented.[40] To determine whether this is the case, we analyzed the effect of IS on memory encoding during the prestimulus period (−750 ms to 0 ms relative to word onset). The spontaneous occurrence of IS before stimulus presentation did not disrupt memory encoding in any brain region tested ($p > .05$; Figure 4A,B).

3.5 | Interictal spikes during the retrieval epoch

Next, we asked whether the occurrence of IS during retrieval affected free recall. As previous studies have shown that IS affect recall,[5,21,22] we wished to confirm this in our

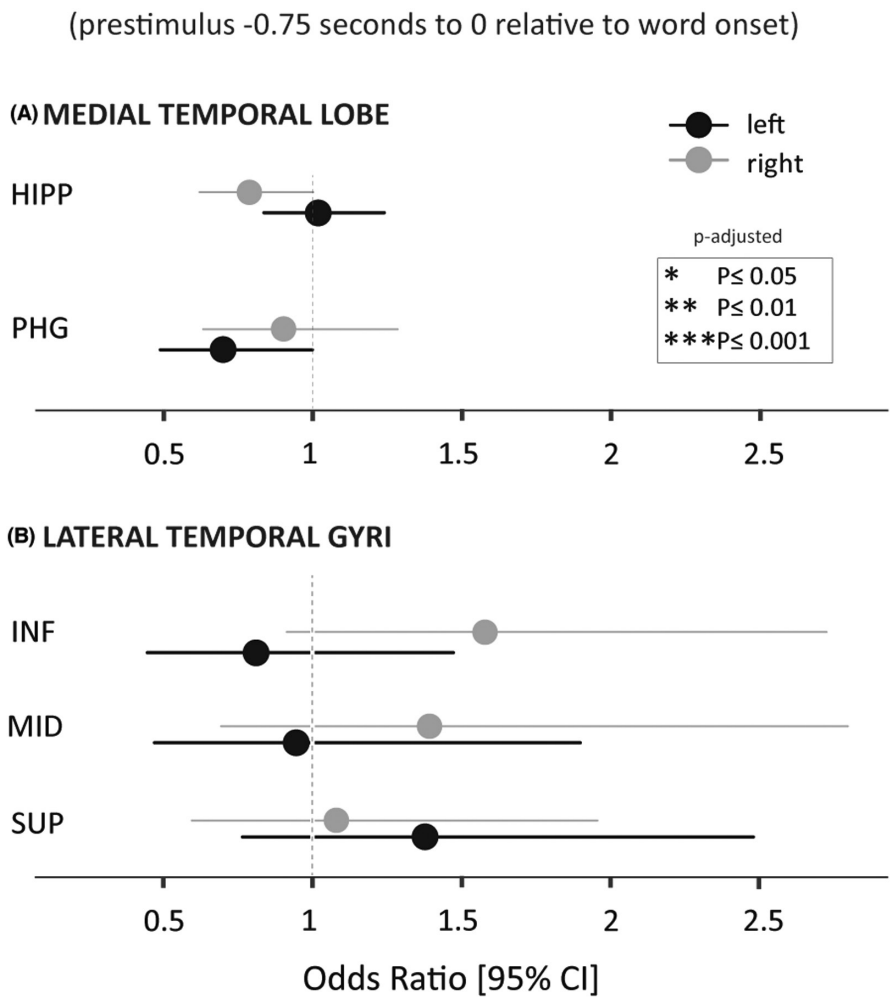


FIGURE 4 Interictal spikes (IS) during the prestimulus window did not affect memory encoding ($n = 78$). Probability of successful memory encoding for IS detected during the prestimulus window in the medial temporal lobe (A) and in the lateral temporal gyri (B) is shown. The p-values were corrected using the adaptative Hochberg algorithm for multiple comparisons. CI, confidence interval; HIPP, hippocampus; INF, inferior; MID, middle; PHG, parahippocampal gyrus; SUP, superior.

dataset and chose a subset of patients ($n = 28$). To ensure that we had enough electrode/patients in the MTL, we selected patients with IS during the retrieval epoch and three or more electrode contacts in any MTL substructure. Due to sample sizes, we did not fit a separate model for each MTL subregion.

We first analyzed this effect in the hippocampus and PHG. In the right hemisphere, IS in hippocampus ($n = 17$ participants, $n = 56$ electrode contacts) decreased the probability of word recall from 32.4% to 18.6% (OR = .22, 95% CI = .08–.63, $p = .004$; Figures 5A and S2) and in PHG ($n = 14$ participants, $n = 32$ electrode contacts) from 30.4% to 19.9% (OR = .24, 95% CI = .07–.8, $p = .02$; Figures 5A and S2). In contrast to results observed during encoding, we found no evidence that recall was disrupted by IS in the left hippocampus ($n = 22$ participants, $n = 97$ electrode contacts) or left PHG ($n = 15$ participants, $n = 39$ electrode contacts, $p > .05$; Figures 5A and S2). IS did not disrupt recall in any of the subregions of the lateral temporal neocortex: left superior temporal gyrus ($n = 19$ participants, $n = 120$ electrode contacts), left middle temporal gyrus ($n = 20$ participants, $n = 182$ electrode contacts), left inferior temporal gyrus ($n = 16$ participants, $n = 76$ electrode contacts), right superior temporal gyrus ($n = 11$ participants, $n = 68$ electrode contacts), right middle temporal gyrus ($n = 18$ participants, $n = 160$ electrode contacts), and right inferior temporal gyrus ($n = 15$ participants, $n = 70$ electrode contacts, $p > .05$; Figures 5B and S2).

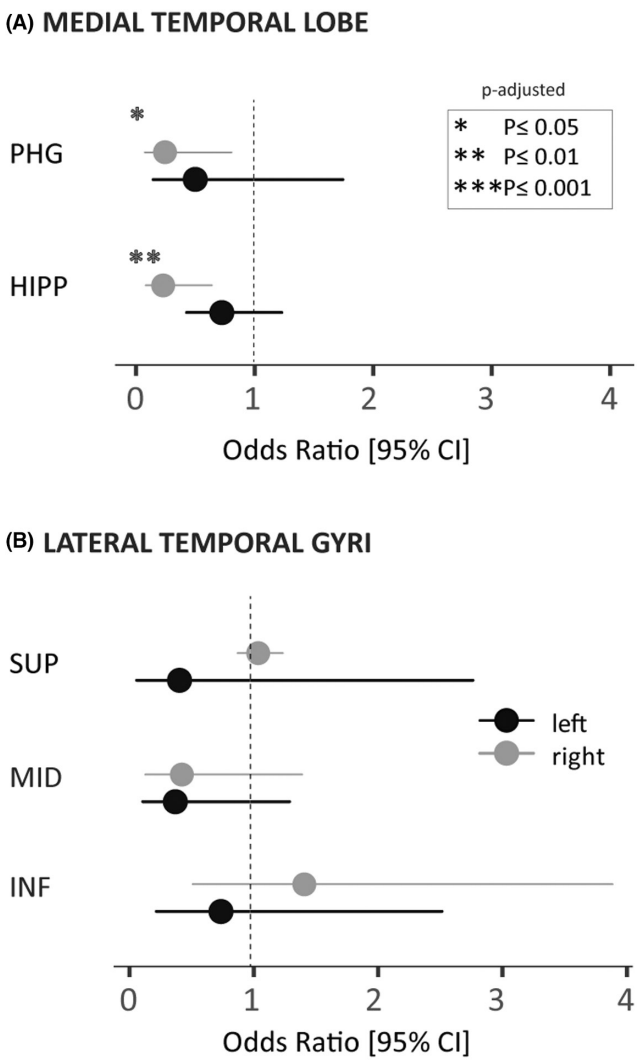


FIGURE 5 Interictal spikes (IS) in the right hippocampus during the retrieval epoch were associated with a decrease in the probability of word recall ($n = 28$). Probability of successful memory encoding for IS detected during the retrieval epoch in the medial temporal lobe (A) and in the lateral temporal gyri (B) is shown. The p-values were corrected using the adaptative Hochberg algorithm for multiple comparisons. CI, confidence interval; HIPP, hippocampus; INF, inferior; MID, middle; PHG, parahippocampal gyrus; SUP, superior.

4 | DISCUSSION

This study investigated the impact of IS on memory encoding and retrieval in the MTL substructures and lateral temporal cortex during a verbal free recall task. We found that the effect of IS during memory encoding was temporally selective. Only IS during word presentation decreased the odds of memory encoding but not IS that happened immediately before word presentation. When assessing the spatial distribution, we found that IS in the left hippocampus and left middle temporal gyrus disrupted word encoding. Within the hippocampus, the effect was restricted to area CA1 and the dentate gyrus. Furthermore, we confirmed that IS occurring during the retrieval epoch in the right hippocampus and right PHG decreased the odds of recall. These results suggest that IS have a complex effect in the MTL on encoding and retrieval in the context of a verbal episodic memory task.

4.1 | IS in the left hippocampus disrupt verbal episodic memory encoding

Consistent with the view that the ability to encode episodic memories depends on the hippocampus,[41,42] we found that IS in left CA1 and left dentate gyrus decreased word encoding. This is in line with fMRI studies showing that episodic memory encoding activates the anterior hippocampus.[41,42]

However, our results are in contrast with other studies that have reported no effect of IS in the MTL on memory encoding,[5,21,22] although one recent study also reported impairment.[13] Likely, our methods account for the discrepancy between those studies and ours. The verbal free

recall task used here may be more sensitive in detecting a TCI/TMI during the encoding period than other tasks.[5,21]

Another important difference in our study was a much larger sample size than previous studies.[43] We selected patients with electrode coverage in the MTL or lateral temporal cortex from a multicenter collaboration project[28,29] to investigate particular ROIs.

Furthermore, a key to addressing the impact of IS on memory encoding is to have reliable events.[6] Most of the investigations that have assessed the effects of IS on memory have relied on IS detection algorithms.[10,25,44] However, these algorithms have many false negative detections.[44,45] In comparison, our investigation's strength is that experts manually performed all the IS annotations independently (i.e., without having information on the patients' performance on the free recall task). Moreover, we included only spikes and did not include sharp waves, as the latter event might reflect a different electrophysiological mechanism or propagation of IS from a distant source.[3]

With respect to timing, we found that IS occurring during stimulus presentation were associated with memory encoding disruption but not IS occurring before stimulus onset. This finding supports the hypothesis that IS-related effects are transient and highly specific.[7,8] Furthermore, this is in accordance with a recent study that found a selective temporal impairment during stimulus presentation using an associative memory task.[13] However, another study reported that IS occurring before or during the presentation of a cognitive stimulus decrease memory performance.[40] More research that takes into consideration IS timing and performance might provide further insights.

Other extrahippocampal regions that have been associated with memory encoding are the perirhinal and lateral entorhinal cortices, which provide input to the anterior portion of the hippocampus and have connections with areas in the lateral anterior temporal lobe.[18,19] In the case of the present research, IS in the perirhinal cortex and entorhinal cortex did not impact memory encoding.

4.2 | Retrieval analysis: IS in the right hippocampus and PHG decrease free recall performance

In contrast with the results observed for the encoding analysis, we found that IS in both the right hippocampus and PHG decreased the probability of recall. Likewise, another study using the same task reported that left-lateralized IS had a larger effect during encoding, whereas either left or right lateralized IS were associated with decreased retrieval, although a regional analysis was not performed for the retrieval epoch.[20] Notably, a small study using a verbal working memory task found a relationship between right hippocampal IS and reduced odds of recall.[21] A novel finding of our research is the involvement of the right PHG in verbal episodic memory recall.

However, our study is at odds with classical reports supporting a material-specific lateralization in the temporal lobe, although more recent studies have presented data that challenge this notion.[46] fMRI evidence indicates that verbal episodic retrieval involves bilateral medial–temporal structures more than encoding.[47] Experiments in humans suggest that the right-sided regions are more active during episodic recall, whereas left-sided regions are more involved during episodic encoding.[48] Future experiments with cued recall paradigms and a larger number of patients may be better suited to resolve the role of IS in specific regions in disrupting recall.

Another interesting topic is that right hippocampal IS had a larger effect on retrieval than left hippocampal IS during encoding. Although it would be interesting to determine whether this difference is significant, the current design of our analysis does not allow us to make a comparison among regions. A single model that considers the simultaneous occurrence of IS among areas and epochs would shed light on this issue.

4.3 | IS in the lateral temporal cortex during encoding and retrieval

Recent investigations have defined the patterns of spectral modulations in the lateral temporal cortex, and other neocortical regions associated with successful verbal episodic memory encoding and retrieval.[28,29] Thus, given these aspects, we analyzed whether IS in the lateral temporal cortex impacted memory encoding and recall. In agreement with previous work,[20] we found that memory encoding was impaired by IS in the left middle temporal gyrus. Notably, temporal lobe epilepsy patients often have deficits in short-term/working memory tasks that are thought to involve the lateral temporal cortex.[46,49] We found that IS in the left hippocampus also disrupt verbal episodic memory encoding. Although the primary structure subserving short-term verbal encoding may be the left middle temporal gyrus, it appears that IS in the left hippocampus can also cause a substantial disruption, which may have important implications in planning surgeries targeting the mesial–temporal lobe.

4.4 | Study limitations

In each participant, electrode placement was primarily dictated by the presumed location of the SOZ, and surgical

technique varied across sites. Thus, spatial sampling and the statistical power to detect a TCI/TMI effect varied across anatomic ROIs.

Another potential limitation of this study lies in our assessment of spike-related effects on memory, while excluding sharp wave events. We made this choice because the temporal dispersion of the latter could be associated with propagation from a distant site. One prior study demonstrated that sharp waves but not IS produce a TCI/TMI[21]; nonetheless, our study clearly shows the potency of IS, suggesting more work is needed to clarify the differences between these epileptiform events. Furthermore, the effect of IS is possibly moderated by other variables at the patient level. As other authors have discussed, the impact of IS likely differs depending on the functionality of the area.[20] Another possibility is that in patients with low baseline performance, IS will not have a further impact (floor effect). A secondary analysis including these variables did not show any evidence for these hypotheses; however, additional research with a larger sample is required to reach robust conclusions in this regard.

Another challenge to our research is that IS propagate, and the propagated events may have different effects than the IS recorded from the initial generator site. A related issue is that IS are often registered from multiple anatomical locations simultaneously. Unfortunately, our statistical methods do not account for the collective effects of IS at different sites.

Finally, we did not examine the impact of IS during the distractor epoch, because prior studies using the same task did not find a significant effect of IS during the distractor epoch in any ROI.[15,22] Because we manually annotated the IS events, we felt including the distractor epoch would be of a low yield.

4.5 | Conclusions and future directions

Our results suggest that IS in the left CA1, dentate gyrus, and left middle temporal gyrus disrupt verbal episodic memory encoding, whereas the occurrence of IS in the right hippocampus and right PHG affects retrieval. However, many questions remain. Although it is possible that local neural hypersynchrony may directly disrupt memory processing, IS may also impact memory processing due to their effect on a more extensive limbic–cortical network.[12,50] Future investigations that characterize network dynamics and single unit activity during interictal periods are needed to shed light on the mechanisms involved.

Our findings have several implications. It might be possible to use our experimental approach to map the functional networks associated with verbal episodic memory. In addition, our findings provide evidence to encourage the development of pharmaceuticals or devices that can combat memory deficits in patients with epilepsy by reducing the number of spontaneous IS, which has not been a focus of pharmaceutical development.[51] Although nearly half of patients with epilepsy exhibit clinical cognitive or memory impairment,[6] a consensus on treatment for IS-related deficits is lacking.[51] Our study provides strong support that IS in the lateral and medial temporal lobe are causally related to a verbal TCI/TMI. Further work is needed to explore the network effects of these discharges.

AUTHOR CONTRIBUTIONS

Liliana Camarillo-Rodriguez, Michael R. Sperling, and Shennan A. Weiss contributed to the study concept and design, and participated in the data acquisition and analysis and drafting of the manuscript. Iwin Leenen participated in the data acquisition and analysis and drafting of the manuscript. Mijail Serruya, Paul A. Wanda, Nora A. Herweg, and Michael J. Kahana contributed to the study concept and design and participated in the data acquisition and analysis. Zachary Waldman, Daniel Rubinstein, Iren Orosz, Bradley Lega, Irina Podkorytova, Robert E. Gross, Gregory Worrell, Kathryn A. Davis, Barbara C. Jobst, and Sameer A. Sheth participated in the data acquisition and analysis.

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CONFLICT OF INTEREST

M.R.S. is a consultant/advisor for Medtronic (fee to institution); has received research support (to institution) from Eisai, Engage Therapeutics, Medtronic, Neurelis, Pfizer, SK Life Science, Takeda, UCB, Cerevel, and Xenon; and has been a speaker for Eisai, Medscape, NeurologyLive, UCB, and Projects in Knowledge. M.J.K. has started a company, Nia Therapeutics ("Nia"), intended to develop and commercialize brain stimulation therapies for memory restoration and has >5% equity interest in Nia. R.E.G. serves as a consultant to Medtronic, which is a subcontractor on the MEMES project. R.E.G. receives compensation for these services. The terms of this arrangement have been reviewed and approved by Emory University in accordance with its conflict-of-interest policies. S.A.S. has consulting agreements with Boston Scientific, Abbott, Zimmer Biomet, and Neuropace. G.W. declares interests in Cadence Neuroscience (licensed technology) and NeuroOne (licensed technology and holds stock). None of the other authors has any conflict of interest to disclose. We

confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Abbreviation: iEEG, intracranial electroencephalographic.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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