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Brief Communication

Effects of hippocampal interictal discharge timing, duration, and spatial extent on list learning

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ABSTRACT

Interictal epileptiform discharges (IEDs) can impair memory. The properties of IEDs most detrimental to memory, however, are undefined. We studied the impact of temporal and spatial characteristics of IEDs on list learning. Subjects completed a memory task during intracranial EEG recordings including hippocampal depth and temporal neocortical subdural electrodes. Subjects viewed a series of objects, and after a distracting task, recalled the objects from the list. The impacts of IED presence, duration, and propagation to neocortex during encoding of individual stimuli were assessed. The effects of IED total number and duration during maintenance and recall periods on delayed recall performance were also determined. The influence of IEDs during recall was further investigated by comparing the likelihood of IEDs preceding correctly recalled items vs. periods of no verbal response. Across 6 subjects, we analyzed 28 hippocampal and 139 lateral temporal contacts. Recall performance was poor, with a median of 17.2% correct responses (range 10.4–21.9%). Interictal epileptiform discharges during encoding, maintenance, and recall did not significantly impact task performance, and there was no significant difference between the likelihood of IEDs during correct recall vs. periods of no response. No significant effects of discharge duration during encoding, maintenance, or recall were observed. Interictal epileptiform discharges with spread to lateral temporal cortex during encoding did not adversely impact recall. A post hoc analysis refining model assumptions indicated a negative impact of IED count during the maintenance period, but otherwise confirmed the above results. Our findings suggest no major effect of hippocampal IEDs on list learning, but study limitations, such as baseline hippocampal dysfunction, should be considered. The impact of IEDs during the maintenance period may be a focus of future research.

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1. Introduction

Interictal epileptiform discharges (IEDs) are electrophysiological abnormalities on EEG in individuals with epilepsy or a propensity for epilepsy. Interictal epileptiform discharges can disrupt cognitive task performance in animal models and humans, with memory processes particularly vulnerable to IED effects in the temporal lobes [1]. In humans, IEDs impaired verbal and nonverbal working [2], short-term [3], and long-term [4] memory and correlated with accelerated rates of long-term forgetting [4,5].

Abbreviations: B, bilateral; iEEG, intracranial electroencephalogram; IQR, interquartile range; L, left; MRI, magnetic resonance imaging; NA, not available; QIC, quasi-likelihood under independence model criterion; QICC, corrected quasi-likelihood under independence model criterion; R, right.

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Studies of IED timing in relation to memory performance suggest no effect of hippocampal or mesial temporal IEDs during encoding, but a negative impact during maintenance [6] and retrieval [6–8]. A reduced mesial temporal IED rate from baseline during encoding of images correctly recognized after a 24-h delay may suggest a negative effect of greater IED burden on encoding, although the study was not designed to address this issue [9]. Whether specific IED characteristics, such as duration or spatial extent, determine effects on encoding is unclear.

In this study, patients with intractable focal-onset epilepsy completed a list learning task during iEEG monitoring with hippocampal depth and neocortical subdural electrodes. The properties of hippocampal IEDs during encoding were characterized and their relationships to delayed free recall performance were determined, with the hypothesis that IEDs with longer duration or greater spatial extent were more likely to impair memory. The effects of discharges during maintenance and recall periods were also assessed, with the expectation that a greater burden of IEDs would correlate with impaired performance.

2. Methods

2.1. Subjects

Subjects were six adults with medically refractory focal-onset seizures, admitted to New York University Langone Health for iEEG implantation for epilepsy surgery evaluation (Table 1). Participants had hippocampal IEDs and suspected temporal lobe seizures, with implanted mesial depth and neocortical subdural temporal electrodes. The local institutional review board approved the study, and written informed consent was obtained from each subject.

2.2. Intracranial EEG (iEEG) recordings

A total of 31 hippocampal and 142 lateral temporal electrodes, covering inferior, middle, and/or superior temporal gyri, were placed. Hippocampal depth electrodes were placed on the right ($n = 4$), on the left ($n = 1$), or bilaterally ($n = 1$), with an orthogonal ($n = 5$) or posterior to anterior approach ($n = 1$). Electrode placement was determined by clinical indications. Intracranial EEG recordings were acquired using a NicoletOne C64 clinical amplifier (Natus Neurologics, Middleton, WI), digitized at 512 Hz. Hippocampal recordings were obtained from depth electrodes (Ad-Tech Medical Instrument Corp., Racine, WI), containing 8–12 platinum contacts spaced 5 mm apart. Lateral temporal contacts consisted of subdural platinum-iridium electrodes embedded in silastic sheets (2.3-mm diameter contacts, 10-mm center-to-center spacing), arranged as grid arrays (8×8 contacts) and/or linear strips (4–8 contacts). One subject (S1) was also implanted with a 12-contact lateral temporal depth electrode. Intracranial EEG signals were referenced to a two-contact subdural strip facing toward the skull. Electrode coordinates were determined by aligning pre- and postoperative brain MRI scans using previously published methods [10]. Hippocampal localization was also confirmed by visual inspection of post-implantation MRIs (LL, LD).

2.3. Memory task

Subjects performed a list learning task during the intracranial recordings. Participants were asked to remember a series of individual pictures of objects on a computer screen (“encoding trials”). Subjects also made a simple determination regarding each item (e.g., whether it could fit inside of a shoebox, whether it was used indoors or outdoors), to ensure attention to the task. Each object was shown for 3 s, and responses were indicated by button press. Participants were not required to name the objects out loud during encoding. Between each image, a blank screen was displayed for 0.8–1.2 s. The stimulus list contained 16 objects. The list was followed by an 18-s duration distracting task, in which subjects classified a series of faces as male or female.

Subjects were then given 45 s for free recall of the object list. The task was repeated, using up to 12 different stimulus lists per subject. Stimulus images were compiled from existing data sets [11–15] and are available upon request.

2.4. Artifact rejection

To assess for artifacts, recordings were visually inspected and power spectra for each channel were viewed with respect to the mean power spectrum of all channels in that subject. Channels

Table 1
Demographic and clinical information. F = female, M = male, R = right, L = left, B = bilateral, NA = not available.

Subject	Age (years)	Sex	Handedness	Language Dominance on Wada	Memory Dominance on Wada	Lateralization Dominance Electrodes	Seizure Onset Zone	Structural MRI
S1	24	F	R	L	B	L	Left hippocampal and peri-opercular cortex	Nonspecific T2 hyperintensity in the left anterior insular WM
S2	34	F	R	L	L > R	R	No seizures recorded	Small right parasagittal falx calcification vs. meningioma
S3	57	M	R	NA	NA	R	Right posterior temporal neocortex	Mid-aqueduct atresia with hydrocephalus and anterior third ventriculostomy, diffuse volume loss, right orbitofrontal encephalomalacia
S4	22	M	R	NA	NA	B	Left parieto- occipital lobe (subsequent to cortical stimulation)	Possible subtle periventricular gray matter heterotopia of the right lateral frontal horn
S5	47	F	L	L	L	R	Broad electrographic onset over the right temporal (neocortical and mesial) and occipital lobes	Bi-parietal cortical atrophy
S6	51	F	R	L	L>R	R	Multifocal: right posterior quadrant, temporal, and frontal	Right frontal-temporal-parietal craniotomy, left frontal ventricular catheter, third and lateral ventriculomegaly (R > L), encephalomalacia of bilateral frontal lobes, right anterior temporal lobe, and bilateral cerebellar hemispheres, right hippocampal sclerosis, periventricular white matter hypodensities

with artifacts that may lead to false IED detections were removed. Three hippocampal and three lateral temporal electrodes were removed from the analyses due to artifacts.

2.5. Interictal discharge detection

Interictal epileptiform discharges were identified by an automated algorithm [16], to provide an objective method for detection. Recordings were downsampled to 200 Hz, followed by 10-Hz high pass, 60-Hz low pass, and 60-Hz notch filters. The amplitude envelope was then calculated by taking the absolute value of the Hilbert transform. For each 5-s sliding window (with 4-s overlap), the amplitude envelope was modeled as a skewed log-normal distribution, and each time point was assigned an "IED activity value" calculated as the sum of the mean and median of the modeled distribution [16]. Interictal epileptiform discharges were defined as excursions above a set threshold ($k = 3$, as this value was optimal in our dataset), with the duration of an IED being the amount of time that the IED activity value was above the threshold. Interictal epileptiform discharges with less than 120-ms separation between them within a channel and less than 125-ms separation between them across channels were merged as single events, assigned to the channel of maximum IED activity value and aggregated across all hippocampal depth electrodes. The duration of an IED was counted across all involved hippocampal contacts. Hippocampal IEDs were also identified by manual review (BLM), to confirm results from automated detection, while blinded to timing and memory task performance. The manually detected IEDs were identified independently from the automated detections, prior to running the automated detection algorithm.

2.6. Data analysis

2.6.1. Presence of IEDs during encoding

Whether an IED was present during the 3-s encoding period was determined for each image. All stimulus lists were combined for each subject. The percentage of images recalled when an IED was present vs. absent was compared using a two-tailed Wilcoxon signed-rank test across all subjects.

2.6.2. Spatial extent

Encoding trials with hippocampal IEDs were categorized as (1) without temporal neocortical spread or (2) containing at least one IED with spread to, or co-occurring with IEDs in, temporal neocortex. Interictal epileptiform discharge-containing trials across all stimulus lists for each subject were entered into the analysis. Univariate logistic regression was performed using a generalized estimating equation (GEE), with spatial extent during the encoding image (without vs. with lateral temporal involvement) as the predictor of interest and delayed recall of the item (remembered vs. forgotten) as the outcome measure.

2.6.3. Duration

The total duration of hippocampal IED activity during each encoding trial was calculated by summing durations in the channels of maximum IED activity value to which the IEDs had been assigned. Encoding images presented during IED activity were entered into the analysis, across all stimulus lists for each subject. A univariate logistic regression was conducted using a GEE, with the total duration of spiking during the encoding image as the predictor of interest and delayed recall of the item (remembered vs. forgotten) as the outcome measure.

2.6.4. Secondary analyses

In secondary analyses, the number and duration of IEDs were calculated during each 18-s maintenance and 45-s recall period, separately for each list. Univariate linear GEE analyses modeled the relationships between IED number and duration during maintenance and recall periods and the number of items correctly recalled for each list across subjects.

Additionally, the 45-s audio recordings of subjects' verbal responses were time-locked to the EEG. The initial second of the EEG was discarded to allow for a preparatory period before free recall. Data were analyzed up to 3 s after the last utterance, as subjects may have stopped attempts at recall after this point. The likelihood of an IED occurring ([duration of period with IEDs/duration of period] $\times$ 100) in the one-second periods prior to correctly recalled items ("recall periods") was compared to the likelihood of an IED occurring during times without verbal response ("non-recall periods"). The epochs without verbal response represented a presumed failure of correct recall, and were defined as occurring at least 3 s from any vocalization. The likelihoods of IED occurrence were calculated using recall and non-recall periods aggregated across all stimulus lists for each subject and compared using a Wilcoxon signed-rank test. This approach was based on previous studies of IED effects on free recall [7,17].

The analyses of IED presence and duration during encoding, as well as IED number during maintenance and recall, were repeated using manual hippocampal IED detection.

The GEE models had an exchangeable working correlation matrix structure, which assumed homogenous correlations between elements. This model may not best represent the data, however, as IED frequency and task performance can fluctuate over time. In a post hoc analysis, we repeated the GEE analyses, assuming an autoregressive relationship, which allowed for this variation.

We used non-parametric testing given the small sample sizes common in electrocorticography studies. A p-value <0.05 was the threshold for statistical significance. Statistics were calculated using SPSS software.

3. Results

3.1. Task performance

EEG was recorded over 1120 trials (objects) of the list learning task. Median percent correct recall was 17.2% (range 10.4–21.9%) (Table 2).

3.2. Presence of IEDs during encoding

No statistically significant relationship was evident between the presence or absence of hippocampal IEDs during encoding and percentage of items correctly recalled ($p > 0.1$).

3.3. Spatial extent

No statistically significant relationship between spatial extent of discharges during encoding and free recall performance was evident ($p > 0.1$). The majority of hippocampal IEDs had spread to or co-occurrence with IEDs in lateral temporal cortex (7 encoding trials with discharges restricted to the hippocampus, 358 encoding trials with discharges also involving lateral temporal cortex).

3.4. Duration

No significant relationship between hippocampal IED duration during encoding and free recall performance was evident ($p > 0.1$).

Table 2
Discharge count and task performance data. Columns indicate the total number of hippocampal interictal epileptiform discharges (IEDs) during encoding image presentation ("Total IEDs - Encoding"), maintenance ("Total IEDs – Maintenance"), and recall ("Total IEDs – Recall") periods, summed across lists for each subject. The percentage of encoding trials containing IEDs is listed ("Encoding Trials with IEDS"). "Median Duration" signifies the median duration of hippocampal IEDs during encoding and the median total duration of IEDs per list during maintenance and recall periods. Data are based on automated detection. "HP Contacts" denote the number of hippocampal electrodes analyzed for each subject. Task performance data ("Recalled Trials", "Forgotten Trials") are also listed, including the percentage of items recalled when discharges were present ("Percent Recall – IEDs Present During Encoding") vs. absent ("Percent Recall – IEDs Absent During Encoding"). HP = hippocampal, IQR = interquartile range.

Subject	HP Contacts	Total IEDs-Encoding	Encoding Trials with IEDs	Percent Recall-IEDs Present During Encoding	Percent Recall-IEDs Absent During Encoding	Median IED Duration in ms-Encoding (IQR)	Total IEDs-Maintenance	Median Total IED Duration per list in ms -Maintenance (IQR)	Total IEDs-Recall	Median Total IED Duration per list in ms-Recall (IQR)	Recalled Trials	Forgotten Trials
S1	1	8	4.2%	0%	19.6%	11.7 (27.3)	4	0 (0)	4	0 (3.9)	36	156
S2	6	68	29.2%	14.3%	25%	37.1 (44.9)	29	80.1 (310.5)	47	64.4 (74.2)	42	150
S3	7	137	50.5%	9.3%	11.6%	37.1 (72.3)	56	158.2 (212.9)	111	359.4 (201.2)	20	172
S4	8	46	19.8%	21.1%	18.8%	17.6 (29.3)	13	9.8 (15.6)	47	50.8 (74.2)	37	155
S5	3	164	52.6%	10.9%	12.1%	105.5 (142.6)	50	254.9 (357.4)	119	847.6 (1277.3)	22	170
S6	3	82	40.6%	18.5%	13.7%	31.2 (39.1)	29	68.4 (185.5)	87	437.5 (250)	25	135

3.5. IEDs during maintenance and recall periods

No significant associations were seen between hippocampal IED counts or duration during the maintenance or recall periods and the number of items recalled (p-values >0.1). The likelihood of an IED occurring during recall periods did not significantly differ from non-recall periods ($p > 0.1$).

3.6. Manual IED detection

Results were similar when based on manual IED detection, with no significant relationships between performance and the presence of hippocampal IEDs during encoding, duration of IEDs during encoding, or IED counts during maintenance or recall periods (p-values >0.1).

3.7. Autoregressive GEE analyses

The autoregressive GEE approach improved the goodness-of-fit measures (quasi-likelihood under independence model criterion [QIC] and corrected quasi-likelihood under independence model criterion [QICC] values) of the models. Duration and propagation of IEDs during encoding were non-significant factors ($p > 0.1$). Interictal epileptiform discharge counts and duration during recall were also non-significant predictors of memory performance ($p > 0.1$). During the maintenance period, however, a greater number of IEDs was associated with poorer recall ($\beta = -0.07$, $p = 0.012$), although duration of IEDs during maintenance did not have a significant impact ($p > 0.1$).

4. Discussion

The primary analysis failed to support that hippocampal IEDs disrupt list learning. No significant effects of hippocampal IED presence, duration, or propagation to lateral temporal cortex were seen during list encoding. Further, there was no relationship between performance and IED number or duration during maintenance or recall periods, although a post hoc analysis suggested a possible negative impact of greater IED counts during maintenance. Our findings contrast with earlier work indicating that scalp-recorded IEDs impair memory [3,18]. The majority of IEDs in the present analysis, however, were right-sided, within and/or ipsilateral to the seizure onset zone. The results are consistent with prior hippocampal or medial temporal iEEG-recorded data suggesting that right-sided IEDs have less impact on memory tasks with a verbal component [7] and that IEDs within [17] or ipsilateral to [6] the seizure onset zone have little effect on memory. Two factors likely explain our results: dysfunctional hippocampi and task design with relatively prolonged encoding, maintenance, and retrieval periods.

Interictal epileptiform discharges may have little influence if hippocampal function is impaired at baseline. Data from a prior list learning task support this, as left-sided discharges during encoding outside of the seizure onset zone (presumably healthy tissue) impaired recall, while discharges within the seizure onset zone (presumably dysfunctional) had no effect [17]. Baseline hippocampal function was likely impaired in our cohort, as 4/5 patients with clinical neuropsychological testing had memory deficits and one subject had mesial temporal sclerosis. Five subjects were implanted unilaterally in the hemisphere of suspected seizure onset; four were implanted on the right, opposite to the side dominant for language and memory in those with Wada testing. The lack of left-sided coverage outside of the seizure onset zone may have contributed to the present results; additional data from subjects with bilateral implantations would be necessary to address this issue.

Longer encoding, maintenance, or retrieval intervals may offset IED effects, allowing enough time to perform the task despite IED interruptions. Matsumoto et al. [9], for example, allowed six seconds for encoding, but the significant relationship between hippocampal IEDs and delayed recall was evident only during the initial two seconds. The three-second encoding period in our trial may have obscured IED effects.

Our study had several limitations, including the small subject number and limited number of hippocampal discharges during each task phase. Electrodes were placed for clinical indications, with some degree of variability in location across subjects. Further, few discharges were restricted to the hippocampus, limiting our analysis of spatial extent. Our patients' poor task performance, similar to other series [17], may also create floor effects that reduce the impact of IEDs. Future studies should address factors we did not explore, such as pathological frequencies embedded within the discharges, type of memory task, timing within the encoding period, and extra-temporal IED effects (i.e., frontal spindles). Studies may be best suited to a task in which each trial contains encoding, delay, and retrieval periods, to evaluate the impact of IEDs during each phase on individual stimuli. Comparing IED rates preceding correctly recalled items to periods of no verbal response during free recall is suboptimal in that memory processes may be ongoing, even in the absence of verbal response. Future studies should also clarify the effects of IEDs during the maintenance period. Results may be highly dependent upon model assumptions, however, such that results should be interpreted cautiously. Whether discharges with certain properties may be detrimental

during particular tasks deserves further investigation, as this may have treatment implications.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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