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Authors

Silva, Alexander
Leonard, Matthew
Oganian, Yulia
et al.

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Interictal epileptiform discharges contribute to word-finding difficulty in epilepsy through multiple cognitive mechanisms

Alexander B. Silva[1,2,3], **Matthew K. Leonard**[1], **Yulia Oganian**[4], **Emma D'Esopo**[5], **Devon Krish**[5], **Brandon Kopald**[5], **Edwina B. Tran**[5], **Edward F. Chang**[1,3], **Jonathan K. Kleen**[5]

[1]Department of Neurosurgery, Weill Institute of Neurosciences, University of California San Francisco, San Francisco, CA, USA.

[2]Medical Scientist Training Program, University of California, San Francisco, CA, USA

[3]University of California, Berkeley - University of California, San Francisco Graduate Program in Bioengineering, Berkeley, CA, USA

[4]University of Tübingen, Tübingen, Germany

[5]Department of Neurology, Weill Institute of Neurosciences, University of California San Francisco, San Francisco, CA, USA.

Abstract

Objective: Cognitive impairment often impacts quality of life in epilepsy even if seizures are controlled. Word-finding difficulty is particularly prevalent and often attributed to etiological (static, baseline) circuit alterations. We sought to determine whether interictal discharges convey significant superimposed contributions to word-finding difficulty in patients, and if so, through which cognitive mechanism(s).

Methods: Twenty-three patients undergoing intracranial monitoring for drug-resistant epilepsy participated in multiple tasks involving word-production (auditory naming, short-term verbal free recall, repetition) to probe word-finding difficulty across different cognitive domains. We compared behavioral performance between trials with vs. without interictal discharges across six major brain areas and adjusted for inter-subject differences using mixed-effects models. We also evaluated for subjective word finding difficulties through retrospective chart review.

Results: Subjective word-finding difficulty was reported by the majority (79%) of studied patients pre-operatively. During intracranial recordings, IEDs in the medial temporal lobe were associated with long-term lexico-semantic memory impairments as indexed by auditory naming (p=0.009), in addition to their established impact on short-term verbal memory as indexed by

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Corresponding author: Jonathan K. Kleen, Assistant Professor, Dept. of Neurology, 400 Parnassus Avenue, 8th Floor, UCSF Epilepsy Center, San Francisco, CA 94143, T: 415-353-9051, F: 415-353-2837, jon.kleen@ucsf.edu.
Author contributions
Jonathan Kleen, Matthew Leonard, and Edward Chang conceived of and designed the study. Alexander Silva and Jonathan Kleen performed analysis, conducted statistical testing, and wrote the manuscript. All authors edited the manuscript, contributed to data-collection, and provided insight regarding the analyses performed.

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free recall (p=0.004). Interictal discharges involving the lateral temporal cortex and lateral frontal cortex were associated with delayed reaction time in the auditory naming task (p=0.016 and p=0.018), as well as phonological working memory impairments as indexed by repetition reaction time (p=0.002). Effects of IEDs across anatomical regions were strongly dependent on their precise timing within the task.

Significance: IEDs appear to act through multiple cognitive mechanisms to form a convergent basis for the debilitating clinical word-finding difficulty reported by patients with epilepsy. This was particularly notable for medial temporal spikes which are quite common in adult focal epilepsy. In parallel with the treatment of seizures, the modulation of interictal discharges through emerging pharmacological means and neurostimulation approaches may be an opportunity to help address devastating memory and language impairments in epilepsy.

Introduction

Cognitive impairments negatively impact quality of life in patients with epilepsy in addition to the burden of seizures.[1–4] Language and memory impairments such as word finding difficulty (WFD) are particularly prevalent in temporal lobe epilepsy (TLE), and the burden on patients and society is amplified as TLE represents the majority of adult focal epilepsy.[5] An improved understanding of WFD and other cognitive impairment mechanisms, as well as new targeted therapies to directly address these comorbidities, are desperately needed.

Cognitive impairments in focal epilepsy are partly driven by lesioned, sclerotic, or otherwise reorganized circuits that are part of a patient's enduring epilepsy etiology.[4] In addition, these abnormal circuits often give rise to bursts of pathophysiological activity called interictal epileptiform discharges (IEDs) which can produce superimposed transient cognitive impairment (TCI).[6,7] TCI is an established phenomenon in which focal IEDs briefly commandeer local neuronal populations into a pathological discharge, disrupting neural information processing locally in the anatomic region in which they occur.[8–17] This is believed to result in a temporary impairment in the cognitive function attributed to that region (eg., occipital spikes are related to brief impairments in visual sensory processing[18,19]).

The true cognitive impact of IEDs themselves may not be apparent through simple means (such as correlating spike rates to test scores) due to multiple confounding factors, such as influences of underlying pathologies and different cognitive baselines.[10,11,15] However, TCI may be dissociated from these factors by evaluating behavioral task trials with vs. without IEDs in the same patient, helping to adjust for inter-subject differences.

In the past decade multiple intracranial human studies have demonstrated TCI using short-term episodic memory processing tasks and artificial novel stimuli[11–16]. However, whether TCI generalizes to natural language settings and forms a basis for WFD, perhaps the most commonly reported subjective cognitive symptom in epilepsy[1,2], remains an open question. Such a finding would further necessitate and inform the design of future clinical trials to evaluate the question of whether modulation of IED burden in parallel with new pharmacological[20,21] and neuromodulatory[22] seizure treatment approaches can alleviate severe cognitive impairments in epilepsy.[6,13]

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In this study, we directly investigated whether IEDs were associated with WFD in patients with both temporal and non-temporal lobe focal epilepsy. Since clinical symptoms of WFD can occur through multiple cognitive mechanisms,[23,24] we investigated the effects of IEDs on performance across multiple behavioral tasks that engaged word production through different means. We found that IEDs appear to impact cognitive functions involved in auditory naming, verbal word recall, and word repetition, and these effects were highly dependent on anatomic region and precise timing of IEDs within the tasks. IEDs in mesial temporal structures showed particular impact during long-term lexico-semantic processing, and we confirmed that the strength of this effect rivaled their established impact on short-term verbal memory processing.[14–16] Our study highlights that IED-related impairments extend to multiple language-related brain functions, forming a convergent basis for pervasive WFD symptoms in epilepsy.

Materials and methods

Participants

Twenty-three patients with medication-resistant epilepsy participated in the study. Eligible patients were adults 18–65 undergoing intracranial monitoring for drug-resistant epilepsy who were able to perform the cognitive tasks described below. All patients had cortical and/or subcortical intracranial electrodes implanted in the brain using grid, strip, and/or depth electrode components. Written informed consent was obtained for each participant and this work was approved by the UCSF Institutional Review Board.

Neuropsychological Testing

Pre-operative reports of word-finding difficulty and neuropsychological testing scores were obtained retrospectively from clinical records. In brief, we searched each patient's chart, including outpatient clinic notes and neuropsychological reports for pre-operative documentation of subjective WFD. We evaluated auditory naming, Boston naming, and Delis-Kaplan Executive Function System (DKEFS) neuropsychological tests because of their relevance for word finding difficulty as determined by a neuropsychologist (B.K.). We applied nonparametric Wilcoxon rank tests to compare percentile distributions of pre-operative neuropsychological test scores to normative distribution percentiles.

Neural data acquisition and processing:

Intracranial EEG (ICEEG) was recorded from deep brain and superficial cortical structures. Neural data was recorded from the implanted intracranial electrodes using a multichannel amplifier optically connected to a digital signal processor (Tucker-Davis Technologies). The voltage at each electrode contact was amplified and recorded at a sampling rate of 3052 Hz. The local field potential was then visually examined and channels containing low signal, noise, or substantial artifacts were excluded from future analysis. Neural signals were then downsampled to 512 Hz after application of an anti-aliasing filter and notch-filtered (60 Hz and harmonics) to remove line noise.

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Electrode localization:

To localize implanted electrodes anatomically, we co-registered each patient's preoperative T1 MRI with the electrode coordinates obtained from their postoperative CT scan using the SPM12 software package.[25] Electrodes were then classified to an anatomical region based on the automated anatomical labeling brain atlas and cortical parcellation. To visualize electrode coverage across patients, we performed patient-specific nonlinear surface registration using a spherical sulcal based alignment in Freesurfer to an average brain volume template (CVS atlas in MNI152 space).[26–28]

Cognitive behavioral tasks

Cognitive testing with simultaneous ICEEG began 2–3 days following the implantation of electrodes when pain was significantly controlled, and antiepileptic medications had been reduced for clinical purposes. Participants performed the three tasks in order (Figure 2A) during each session (1–7 sessions per patient). All tasks required speaking the same target words, enabling an efficient interrogation of multiple cognitive faculties underlying diverse means of word production. Any trials occurring during or within 2 hours after seizure events were excluded from our analysis.

The first task in each session was an adapted auditory naming task (AAN) to assess long term memory recall of semantic associations and lexical word memory.[2,23,29] AAN was similar to the classic auditory naming task[23] including natural language format similar to WFD contexts in real life, but we tailored it so that all trials had consistent syntax (always noun-verb-noun order) and so that the semantic context was increasingly constrained as the sentence unfolded - for example, "A *person* that *flies* to the *moon*." We implemented this structure for behavioral timing precision so that the participant could not infer the correct answer (the "target word") until the last word of a given sentence stimulus. Each participant performed blocks of 40–50 unique trials of AAN per session, in which an audio recording of each stimulus was played to the participant, and they were instructed to respond as soon as they came up with the answer. If the participant indicated they could not come up with an answer or roughly 10 seconds without a response elapsed, this was considered a missed or "incorrect" trial and the task progressed to the next trial stimulus.

The second task in each session was verbal free recall to assess short-term verbal episodic memory encoding and retrieval.[14–16] Approximately 3–5 minutes following each block of AAN, participants were asked instructed to remember and say aloud as many of the AAN trial target words that they could recall.

The third task in each session was a single word repetition task to assess phonological working memory as well as auditory speech processing.[30–32] Audio recordings of the same preceding AAN target words (40–50 trials) were played to the participant and they were asked to immediately repeat each word aloud. In sum, to help control for speech-motor influences, all three tasks required production of the same words yet through different cognitive modalities.

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Detection of IEDs and trial labeling

As in prior studies,[13–15] IEDs and their durations were detected from the preprocessed ICEEG waveform using a linelength-based algorithm described previously[33] applying a 40ms transform window with manual percentile-based thresholding (average positive predictive value across patients 88%, median 100%; false-positives were in general related to either artifact or normal physiological variants such as delta oscillations with arciform morphology). This was followed by manual verification by an epileptologist (J.K.K.) who subsequently screened all detections to improve the dataset to a clinical standard, all while blinded to task events. IEDs included single interictal spikes, sharp waves, or bursts of epileptiform activity.[11] A given channel was considered involved in an IED if it featured significant waveform deflection from baseline in the form of spikes/sharp waves and related slow waves, with or without overlying pathological fast frequency activity. We avoided artifact and subtle field deflections that appeared due to volume conduction only. The anatomical location (field) of the IED was determined by the Freesurfer-based parcellation labels[26] for each individual electrode which allowed automated labeling of the regions of interest (ROIs) in which each IED occurred. Multiple channels (and thus multiple ROIs, if the channels spanned multiple) marked with an IED were considered involved in the same marked IED event if they overlapped in time (for example due to broad fields, repetitive spike complexes, rapid propagation within or between ROIs, etc).

IEDs were labeled according to whether involved electrodes fell in six major brain regions (ROIs): medial temporal lobe including hippocampus (MT/Hipp), superior and middle temporal gyri (STG/MTG), inferior temporal gyrus (ITG), precentral gyrus, and inferior and middle frontal gyri (lateral frontal lobe; LFL).[13–15] A subset of IEDs spanned multiple ROIs (Supplementary Figure 1).

The timestamps/duration of IEDs and the specific electrodes involved were labeled as to when they occurred in task trials. For the AAN task, we labeled trials with IEDs as those in which an IED occurred in or overlapped with the interval between stimulus onset and 2 seconds after stimulus offset. Importantly, these periods were therefore defined by stimuli timing only, not behavior such as the time between stimulus offset and speech onset (“reaction time”; relatedly, see Results regarding lack of relation between sentence stimuli length and reaction time). For the repetition task, trials in which an IED occurred 1 second before stimulus onset through 1 second after stimulus offset were labeled as an IED trial. For the analysis of short-term verbal memory encoding, AAN trials labeled as with vs. without IED were also labeled as “remembered” if the target word was among those spoken by the patient in the subsequent free recall task, or “not remembered” if not. For the analysis of short-term verbal memory retrieval, following the procedure of Ung et al[14] we labeled the 1-second window preceding each word’s speech onset as a “recall occurred” trial window that contained IEDs or not, and for comparison labeled randomly drawn 1-second windows as trial windows that contained IEDs or not (required to be at least 3 seconds away from a recall speech utterance).

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Statistical modeling IED effects on task behavior

We used generalized linear mixed-effects models comparing trials with vs. without IEDs in each anatomical region to evaluate the influence of IEDs. Mixed-effects models were used to capture the variance present across patients, and all anatomic regions were incorporated into each model to minimize the number of statistical tests and adjust for IEDs that involved multiple structures (for example, an IED involving both MTL/Hipp and STG/MTG simultaneously).[34] More specifically, we fit a single model per hypothesis (AAN accuracy, AAN reaction time, Repetition, Recall encoding, Recall retrieval) that included a term for IEDs in each anatomic region to capture covariance between regions. This technique produces coefficients that measure the unique contribution and effect of IEDs in each ROI, importantly controlling for the lack of independence for IEDs spanning multiple regions.[34,35] We then used Wald statistics when testing multiple parameters to assess significance of IEDs in each region based on model coefficients, similar to prior work.[14] We used a significance level of 0.05 and performed Bonferroni corrections for multiple comparisons (models).

Dependent variables for AAN and repetition were whether responses were correct (non-missed) or not as a binary outcome, and reaction time as a continuous outcome (for correct trials only to control for the influence of accuracy). Dependent variables for short-term verbal memory were binary outcomes of remembered vs. not remembered for encoding, and recalled occurred vs. not for retrieval.[14] To ensure that any measured effect of IEDs was not confounded by the varying difficulty of AAN trials, we created an index of trial difficulty as a covariate by also delivering sentence stimuli to 100 Amazon Mechanical Turk workers (USA-based, HIT>95%). We used the resultant number of unique answers for each sentence stimulus as a surrogate for trial ambiguity (more unique answers = more ambiguous = higher difficulty). To investigate whether timing of IEDs within a task impacted effects on behavior, we slid models in 100ms steps using a 1000ms window of interest time-locked to stimuli or behavior. Additionally, we annotated whether each IED occurred in the left hemisphere and/or the language dominant hemisphere (defined in each patient for clinical purposes). We used these annotations to assess whether the effect of IEDs was modulated by hemispheric laterality. For detailed methodology including full model variables please see the Supplementary Materials.

Results

WFD and neuropsychological testing scores

We first sought to quantify the prevalence of subjective and objective WFD in our patient cohort. Subjective word finding difficulties were reported in retrospective chart review among 79% of participants (Figure 1A; Table 1). This was roughly similar between those with TLE (83%) and extratemporal (non-TLE) focal epilepsy. More objectively, pre-operative neuropsychological testing percentile scores (Figure 1B; compared to a normative median of 50) revealed significant impairments after Bonferroni correction in the Boston naming task (median=11; range=0.5–63; $p=1.6\times10^{-4}$) and the clinical version of the auditory naming task[23] (median=21; range=0.1–84; p=0.002). Delis-Kaplan Executive

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Function System (DKEFS) semantic fluency (median=16; range=1–99.9; p=0.15) and letter fluency (median=37; range=0.4–99.9; p=0.09) were not significantly affected.

IEDs and auditory naming

Implanted intracranial electrode contacts (Figure 2C, Supplementary Table 2; 60–468 electrode contacts per patient) provided wide coverage of the six anatomical ROIs. We computed an IED rate for each patient, finding an interquartile range of 0.51–7.29 spikes/min per patient (Figure 2B). Similar to prior work,[11,15] when looking broadly here at the overall rate of spikes there was no significant correlation with percent accuracy or average reaction time across patients in the AAN task (P>0.05, Spearman correlation; Supplementary Figure 2). We excluded patient regions that did not have at least 5 IED trials in the trial-based analyses below.

The median reaction time, averaged across patients, was 1.16 sec for AAN trials. IEDs involving the MT/Hipp during AAN trials reduced the likelihood of a correct answer relative to trials without IEDs (OR 0.47; 95% CI 0.26–0.83; p=0.009; Figure 3A). In addition, IEDs in the STG/MTG (95% CI, 0.039–0.37; P=0.016) and LFL (95% CI, 0.068–0.72; P=0.018) were associated with increased AAN reaction time (Figure 3B) however these latter effects were reduced to a trend after Bonferroni correction and IEDs in these regions did not significantly affect accuracy (P>0.05).

The effect of MT/Hipp IEDs on AAN accuracy was strongest immediately after the stimulus offset (ie., while participants attempted to find the most likely word; Figure 3C). We tested whether the effect of MT/Hipp IEDs on AAN accuracy was driven by MT/Hipp IEDs that involved multiple anatomic regions by limiting a secondary analysis to IEDs that only involved the MT/Hipp region, finding a similarly significant effect on AAN accuracy compared with the full complement of MT/Hipp IEDs above (OR 0.47; 95% CI 0.26–0.87; P=0.015). Post-stimulus MT/Hipp IEDs decreased mean AAN accuracy across patients from 93.3% to 79.3%. To test this effect in a model-agnostic manner, we compared the mean AAN accuracy between trials with and without MT IEDs, across patients. By randomly shuffling MT/Hipp IED trial labels over 10,000 iterations to create a null distribution, we confirmed MT/Hipp IEDs significantly decreased AAN accuracy (P=0.0012 for post-stimulus MT/Hipp IEDs; P=0.0038 for all MT/Hipp IEDs; Supplementary Figure 3).

IEDs and verbal short-term memory

For validation of our approaches and to compare to prior studies, we also assessed the influence of IEDs on verbal episodic memory,[13–15] using the target words from auditory naming. The median number of AAN words recalled across patients was 15 (IQR: [8.25,24.75]). IEDs involving the MT/Hipp during AAN trials (encoding period) decreased the likelihood of remembering target words from those trials later during free recall (OR, 0.597; 95% CI, 0.357–0.996; P = 0.048, reduced to a trend after Bonferroni correction), while IEDs involving other regions did not (Figure 4A; Supplementary Table 1). This effect was strongest for IEDs occurring around 2 sec into the stimulus (roughly at the end of the sentence stimulus; Supplementary Figure 4A). During dynamic free recall of the target words (retrieval period) the odds of memory retrieval were reduced by IEDs involving the

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MT/Hipp (OR, 0.32; 95% CI, 0.15–0.70; p=0.004) but not other regions (Figure 4B). This effect was largely specific to MT/Hipp IEDs that occurred within 1.25s before a recall, showing precise temporal specificity (Supplementary Figure 4B).

IEDs and repetition

The median reaction time, averaged across patients, was 0.58 sec for repetition trials. There was no significant relation between stimuli length and reaction time in AAN or repetition (p>0.05). IEDs involving the STG/MTG, but no other regions, increased repetition reaction time (95% CI, 0.081–0.36; p=0.002) relative to trials without IEDs (Figure 4C). IEDs immediately before or around the time of stimulus offset had the strongest effect (Figure 4D). Full statistical metrics across cognitive tasks and anatomical regions are provided in Supplementary Table 1.

Effects of IED laterality and additional covariates on model performance

Across all tasks and behavioral measures, incorporating binary variables of whether IEDs were in the left hemisphere did significantly improve model fits across cognitive domains (p>0.05, log likelihood ratio tests). We further tested if incorporating whether an IED occurred in the language dominant hemisphere (defined by clinical neuropsychological testing and magnetoencephalography) improved model fits. Again, we found no improvement in model fits across cognitive domains (p>0.05, log likelihood ratio test). We also tested whether, in general, longer durations or more widespread distributions of IEDs have a larger increased impact of cognition by adding these two terms (the duration of the IED, and the number of anatomic regions impacted by an IED) to our models to test temporal and spatial factors. Neither term, nor inclusion of patients' pre-operative neuropsychological auditory naming testing scores, improved AAN model fit (p>0.05, log likelihood ratio test), underscoring the precise temporal and spatial specificity of IED-related effects.

Discussion

Similar to reports in the literature[1,2,24] and in the clinic, the majority of the patients in our cohort reported subjective WFD and showed neuropsychological testing evidence of the same (Figure 1). Clinical difficulty producing a word could arise through multiple cognitive mechanisms,[2,23] which we demonstrated here using tasks that indexed different cognitive domains, revealing multiple novel findings summarized in Figure 5. Any impact of IEDs would likely be superimposed on baseline cognitive impairments related to static circuit changes and/or lesions and potentially medications, though our behavioral analysis adjusted for such individual differences through mixed-effect models (ie., assessing trials with vs. without IEDs in the same patient). WFD was associated with IEDs involving the LFL, STG/MTG, and MT/Hipp through distinct functional-anatomic mechanisms considering the specific task(s) affected. The MT/Hipp is a common source of seizures in adults,[5] underscoring the potential impact of IEDs in the prominent memory and language symptoms in epilepsy.

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Intracranial studies of human TCI generally use short-term memory behavioral tasks and novel artificial stimuli (such as word lists or a series of pictures)[13–16,36] as opposed to the natural language context in which WFD is usually encountered for patients. Clinical WFD can be rooted in diverse faculties, so we instead approached this problem with mixed behavioral tasks that all involve language and word production, yet require different cognitive functions and anatomic substrates.[2,11] While we cannot isolate all possible neural processes involved, the mechanisms observed here most likely include IED-related interference of semantic, lexical, acoustic-phonological and mnemonic processing depending on task and IED region (see Methods).[14,29,30]

Importantly, IEDs in the MT/Hipp appeared to impact long-term semantic knowledge retrieval (AAN), not only short-term verbal episodic memory as shown previously.[13–15] These findings may reflect the mixed role of the hippocampus, amygdala, temporal pole, and entorhinal cortex structures in declarative memory domains (episodic, semantic) of verbal memory.[2,15,37]

We used AAN trials flexibly here by assessing short-term verbal memory as another perspective into WFD, since the participants presumably encoded some of the target words into short-term memory as evidenced by successfully recalling them minutes later. While we confirmed known associations of MT/Hipp IEDs on recall (memory retrieval),[10–13,15,16] the literature is relatively mixed for the effects of MT/Hipp IEDs on encoding in this experimental context, with some positive[13,16] and others negative[11,12,14,15] depending on certain conditions. It is therefore unsurprising that the MT/Hipp IED encoding effect was marginal in our study (and did not survive correction for multiple comparisons). This may be due to the longer duration of stimulus presentation (2–3 sec) as opposed to prior studies using brief presentations of images, as underscored by the timing-dependent effects (Figure 3C). Future analysis with more participants could help parse out the nuances of this,[16] yet regardless, the demonstration of short-term working memory effects here in a novel manner using natural language stimuli is relevant to clinical WFD in its various forms.

The lack of association of STG/MTG IEDs with short-term verbal memory encoding is notable since some studies found an effect of IEDs in ROIs including the MTG on encoding[14,16] (though not all[15]). While those studies used a task in which words were briefly on screen for 1.6 seconds, we used audio sentence stimuli with longer durations (2–3 seconds), and thus shorter proportions of our stimuli may have overlapped with IEDs. Audio-verbal information may also be more robustly buffered between acoustic-linguistic and memory networks in the distributed temporal lobe circuits subserving encoding, in contrast to the immediate requirement for short (single-word) stimuli in the repetition task in which we observed STG/MTG IED-associated impairments (Figure 4B,D).

Anatomic region-specific TCI was first reported decades ago using scalp EEG.[7,9] More recent studies of TCI utilizing ICEEG[13–16] underscore that IEDs may disrupt local function precisely when and where they occur. Mechanisms are thought to be temporary local suppression and disorganization of neural activity, and perhaps propagation to downstream structures.[12,13,33,38,39] Preventing IEDs could shield normal neural activity for uninterrupted cognitive processing.

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The prospect of reducing IEDs to improve cognition regardless of seizure burden ("treating the EEG") was historically controversial due to risks of medication side effects.[6,7] These risks are increasingly mitigated with individually-tailored therapy and newer agents and formulations that help reduce side effect profiles.[40] Moreover, neurostimulation could provide a new means of therapeutically decreasing IED burden while treating seizures,[22] with quantitative monitoring and rare side effects.[20] While seizure reduction remains the primary goal of neuromodulation therapy, future studies could attempt to delineate any independent contributions of reducing both IEDs and seizures on cognition through careful statistical modeling.

Our study was limited similar to others in IED-related effects herein are correlational and that any IED-related impacts would likely be superimposed on baseline cognitive impairments related to static circuit changes and/or lesions.[4] Delineating the specific relative contributions of IEDs versus other factors including baseline impairments due to etiology-related circuit alterations is an important future direction. Relatedly, probing other specific mechanisms by which IEDs impact cognitive performance, for example via disruption of comprehension, attention, or motor coordination, is an important area of future study. Future studies should also examine the potential influences of relative doses of anti-seizure medications and how this impacts associations of IEDs and behavior, as we were underpowered to assess this here.

Importantly, another limitation of this study was that our electrode coverage across participants was heavier in the left hemisphere, in which language-related functional influences of IEDs might be more noticeable. Adjusting by laterality did not improve our statistical modeling, but the language-related effects observed here may nonetheless be most relevant toward patients with IEDs in the left hemisphere. Studies with larger sample sizes may better define the effects of laterality and leverage finer-grained anatomical IED parcellations, such as defining multiple ROIs within the temporal lobe.[16]

We demonstrate that IEDs have distinct impacts relevant to WFD based on their anatomical region of origin, including that IEDs in the mesial temporal lobe appear to disrupt long-term lexico-semantic retrieval to a degree rivaling their established[15,16] impact on short-term verbal episodic memory. IEDs in the lateral temporal and frontal cortices further contribute to impairments in lexico-semantic retrieval and, additionally, phonological working memory. By studying the effects of multiple anatomical regions across different cognitive-behavioral tasks, we conclude that IEDs have potential to decrease of quality of life not only through memory[11–17] and perception[9,18,19] but through the highly prevalent language-associated symptom of WFD as well. Together, these studies provide justification for future clinical studies and/or clinical trials assessing the therapeutic effect of IED reduction on pervasive and devastating cognitive impairments in epilepsy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability:

Data will be made available to investigators upon reasonable request to the corresponding author.

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Key points:

1. Word finding difficulty (WFD) is prominent among patients with epilepsy and significantly impacts quality of life.
2. Interictal epileptiform discharges (IEDs) were associated with WFD in three different tasks involving word production (auditory naming, short-term verbal recall, and repetition) depending on their timing and the temporal and frontal lobe subregions in which they occurred.
3. IEDs in the medial temporal lobe were strongly associated with long-term lexico-semantic memory impairments in addition to their established connection with short-term verbal memory disruption.
4. Neuromodulation and pharmacological therapies that reduce IED burden may indirectly help address prominent cognitive impairments such as WFD in epilepsy.

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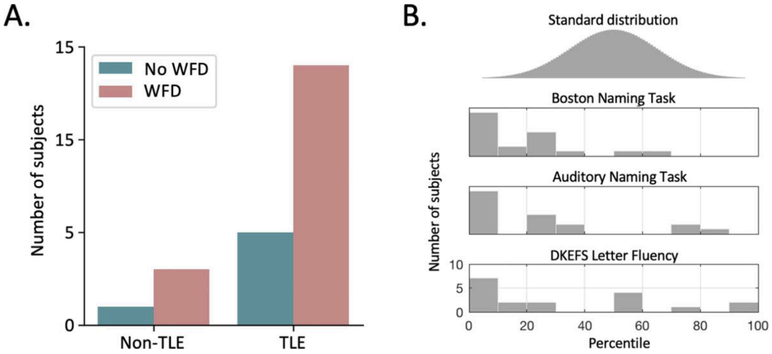

Figure 1. Subjective and objective word finding difficulty in participant cohort.

(A) Number of patients reporting WFD among those with or without TLE. **(B)** Percentile scores for pre-surgical neuropsychological tests reflecting WFD and a standard distribution for comparison.

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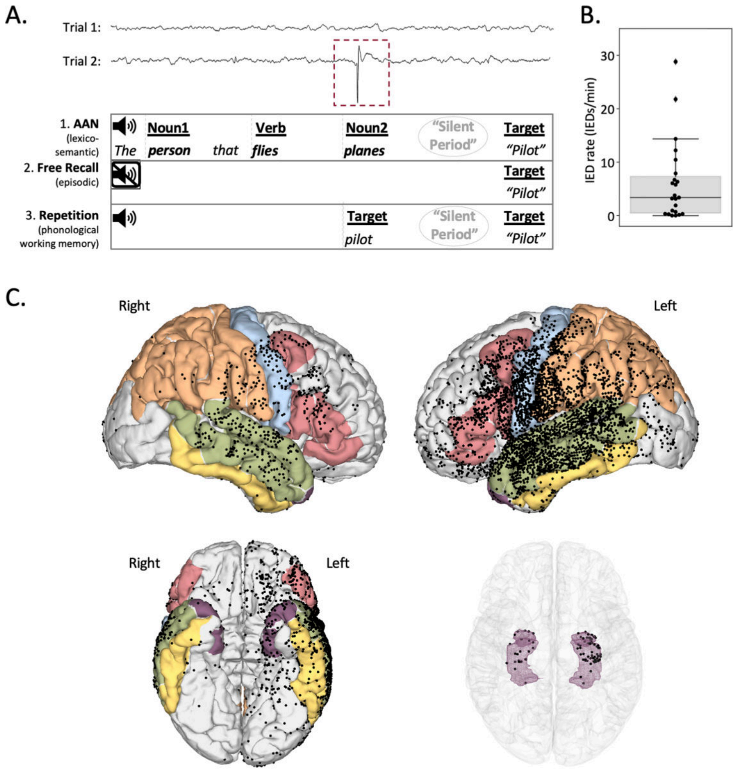

Figure 2. ICEEG and task paradigms.

(A) Examples of 10 second ICEEG recorded from a single channel during one example trial without (top) and one with (bottom) an IED (red outline). Content and order of behavioral task blocks including example trials are shown below. Tasks span three cognitive domains that all require production of the same target words. **(B)** Distribution of IED rate during behavioral testing periods across patients (each dot reflects the rate of IEDs per minute for a single patient) **(C)** Electrode locations across patients and regions analyzed, projected onto average brain reconstruction views; lower right panel shows inferior view of all hippocampus and amygdala electrodes on average reconstructions of these structures within a semi-transparent brain. Blue: precentral gyrus, pink: LFL (lateral frontal lobe including inferior frontal gyri and caudal middle frontal gyrus), orange: parietal cortex, green: STG/MTG (superior and middle temporal gyri), yellow: ITG (inferior temporal gyrus), purple: MT/Hipp (hippocampus, amygdala, temporal pole, and entorhinal cortex).

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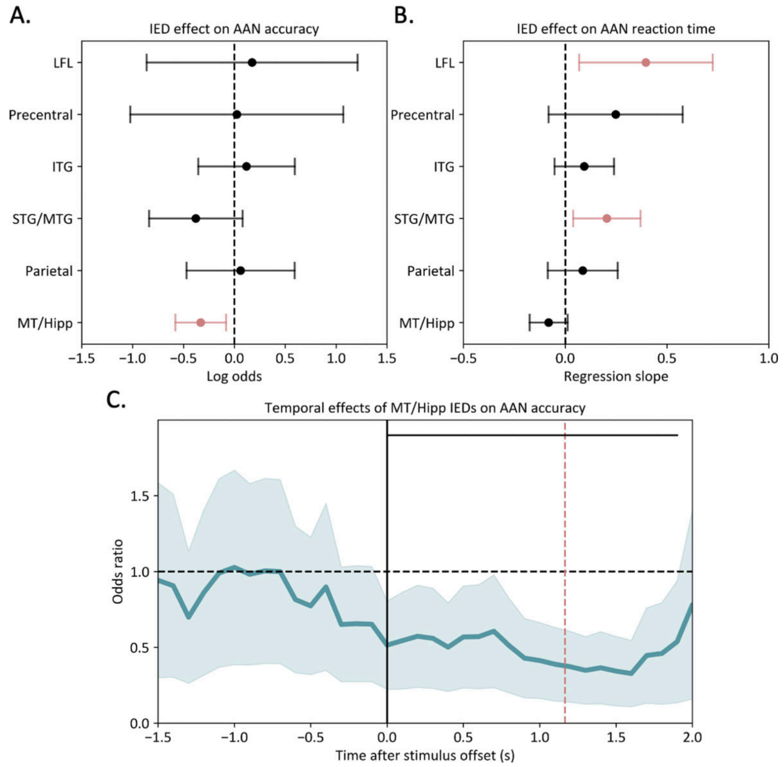

Figure 3. Effects of IEDs on word-finding during AAN.

Effect of IEDs on long-term lexico-semantic memory processing tested by AAN trial accuracy **(A)** and reaction time **(B)**. Bars indicate 95% confidence intervals. Log odds and slope are the computed effects (outcomes) from mixed effects logistic models (on accuracy) and linear regression models (on natural log-transformed reaction time), respectively. **(C)** IEDs in the MT/Hipp region timed immediately after AAN sentence stimuli had the strongest statistical effect on accuracy using a sliding 1-second window of analysis. Shaded error indicates the 95% confidence interval. The red dotted line indicates the median reaction time, and the solid black horizontal line indicates statistically significant timepoints of the sliding model.

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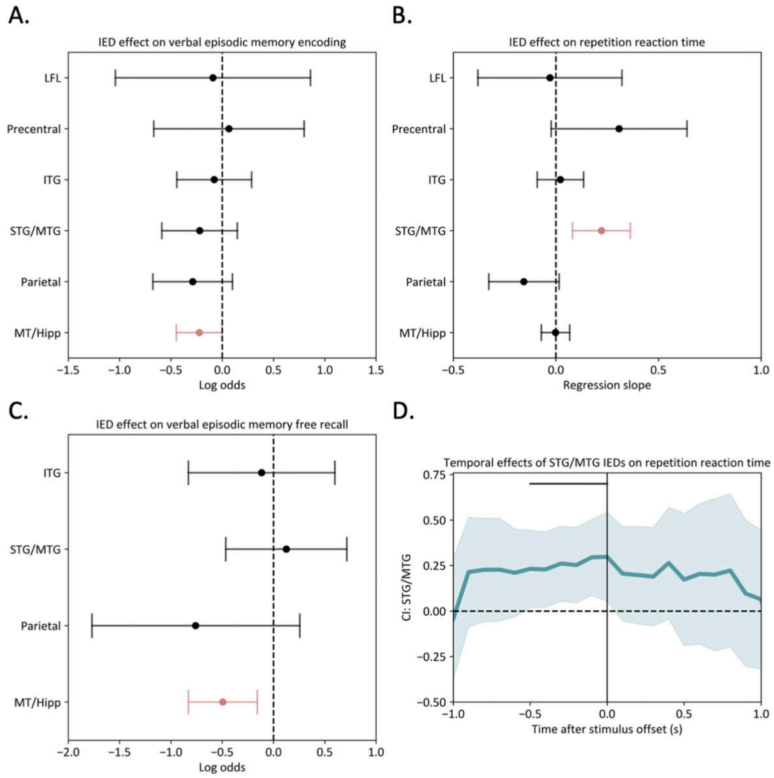

Figure 4. Effects of IEDs on word finding during verbal episodic memory and repetition.

(A) Effect of IEDs occurring during the encoding of AAN target words on the likelihood of later recalling those same words (verbal episodic memory encoding). Red color indicates statistically significant regions (see Supplementary Table 1), and bars indicate 95% confidence intervals. **(B)** The effect of IEDs occurring during attempted retrieval of those words (verbal episodic memory recall). **(C)** IEDs in the STG/MTG, but not other regions, prolonged reaction time during repetition, and **(D)** IEDs immediately before stimulus offset had the strongest effect using a sliding 1-second window of analysis for the model (shaded error indicates the 95% confidence interval, and the solid black horizontal line indicates statistically significant timepoints of the sliding model).

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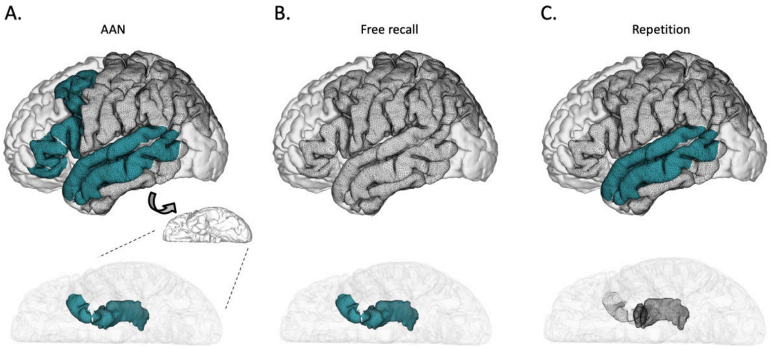

Figure 5. Functional-anatomical IED-related impairments in word-production tasks.
(A) IEDs influenced the AAN task in terms of prolonging reaction time (lateral view in upper panel; dark mesh overlay shows regions evaluated; LFL and STG/MTG significance represented in blue) and missed responses (MT/Hipp, rotated inferior view with glass brain in lower panel). Left and right laterality is combined on left for visualization. **(B)** IEDs impacted the free recall task in terms of encoding and retrieval (MT/Hipp only). **(C)** IEDs impacted the repetition task in terms of prolonging reaction time (STG/MTG only).

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Table 1.

Patient Characteristics and Pre-operative Neuropsychological Testing Results. Abbreviations: Subj, subjective; BNT, Boston Naming Test; ANT, Auditory Naming Test; DKEFS, Delis-Kaplan Executive Function System; SOZ, seizure onset zone; Lat., Laterality of implant.

Patient	Age	Subj. WFD	BNT (%tile)	ANT (%tile)	DKEFS letter fluency (%tile)	DKEFS semantic fluency (%tile)	SOZ	Lat.
1	33	Yes	9	0.1	9	37	Non-TLE	R
2	24	Yes	2	0.1	5	5	TLE	L
3	28	Yes	25	0.1	5	50	TLE	L
4	36	Yes	21		37	25	TLE	L
5	21	No	5	0.1	25	25	TLE	L
6	23	Yes	16	2	2	50	TLE	L
7	20	No	2	0.1	16	37	TLE	R
8	21	Yes	25	21		63	TLE	L
9	19	Yes		0.1	16	5	TLE	L
10	43	Yes	25	25	1	0.4	Non-TLE	L
11	35	No	2	22	50	16	TLE	L
12	38	Yes	0.5	22	5	0.5	TLE	L
13	30	Yes					TLE	L
14	49	No	50	75		37	TLE	L
15	37	Yes	7	75	50	91	TLE	L
16	33	No	63	32	99.9	99.9	Non-TLE	L
17	38	Yes					TLE	B
18	24	No	25	32	98	84	TLE	L
19	51	Yes	25	0.1	75	91	TLE	L
20	22	Yes	1		50	25	TLE	L
21	36	Yes	0.5		8	0.5	TLE	B
22	37	Yes	37	84	50	50	TLE	L
23	47	Yes	13	4	25	16	Non-TLE	L