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RESEARCH ARTICLE

Statistical learning in epilepsy: Behavioral and anatomical mechanisms in the human brain

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Abstract

Objective: Statistical learning, the fundamental cognitive ability of humans to extract regularities across experiences over time, engages the medial temporal lobe (MTL) in the healthy brain. This leads to the hypothesis that statistical learning (SL) may be impaired in patients with epilepsy (PWE) involving the temporal lobe, and that this impairment could contribute to their varied memory deficits. In turn, studies done in collaboration with PWE, that evaluate the necessity of MTL circuitry through disease and causal perturbations, provide an opportunity to advance basic understanding of SL.

Methods: We implemented behavioral testing, volumetric analysis of the MTL substructures, and direct electrical brain stimulation to examine SL across a cohort of 61 PWE and 28 healthy controls.

Results: We found that behavioral performance in an SL task was negatively associated with seizure frequency irrespective of seizure origin. The volume of hippocampal subfields CA1 and CA2/3 correlated with SL performance, suggesting a more specific role of the hippocampus. Transient direct electrical stimulation of the hippocampus disrupted SL. Furthermore, the relationship between SL and seizure frequency was selective, as behavioral performance in an episodic memory task was not impacted by seizure frequency.

Significance: Overall, these results suggest that SL may be hippocampally dependent and that the SL task could serve as a clinically useful behavioral assay of seizure frequency that may complement existing approaches such as seizure diaries. Simple and short SL tasks may thus provide patient-centered endpoints for evaluating the efficacy of novel treatments in epilepsy.

KEYWORDS

direct electrical stimulation, episodic memory, hippocampus, medial temporal lobe, seizure frequency, temporal lobe epilepsy

1 | INTRODUCTION

Memory loss is a comorbidity in epilepsy, especially temporal lobe epilepsy (TLE), and has devastating consequences for quality of life.[1–3] More than 50% of TLE patients exhibit deficits in episodic memory (EM),[3–5] which refers to the ability to encode or retrieve individual autobiographical events.[6] TLE is associated with dysfunction of medial temporal lobe (MTL) structures such as the hippocampus,[4,5,7] which is critical for EM processing.[8,9] Thus, EM deficits in TLE patients may be partially explained by underlying MTL dysfunction. Numerous studies have linked EM deficits to MTL pathology.[5,7,10]

Patients with epilepsy (PWE) often complain of substantially greater memory disturbances in their day-to-day life than is identified with standard neuropsychological evaluations.[11,12] Although EM deficits play a role in such complaints, antiseizure medications (ASMs) also negatively impact memory,[13] complicating the attribution of these deficits to epilepsy. Moreover, other memory-related functions such as spatial navigation and semantic cognition can be impaired in epilepsy.[14,15]

Here, we explore another cognitive ability, statistical learning (SL), in PWE. SL refers to the ubiquitous human ability to extract repeating patterns (or regularities) across space and time.[16,17] It occurs automatically, allowing for predictions of future events and adaptive behavior in new situations based on patterns learned from past experiences. SL is thought to be fundamental to the development and healthy functioning of the mind and is crucial for general human cognition, including language acquisition, object perception, spatial navigation, and conceptual knowledge.[16]

Imaging studies have posited a role of MTL and hippocampus in SL.[17–20] This is also supported by behavioral studies in patients with MTL lesions who showed SL impairment.[21,22] However, these were case studies with one or a small number of patients with varying etiologies other than epilepsy and damage often beyond MTL. Nevertheless, these findings suggest the novel hypothesis that SL may be impaired by epilepsy, given that it is associated with deficits in other forms of memory supported by the MTL.

We implemented behavioral testing methodologies to examine SL behavior in PWE and combined these methodologies with volumetric quantification of manually segmented MTL substructures. The surgical treatment of intractable epilepsy further allowed for direct electrical brain stimulation (DES), a targeted and reversible causal test of the MTL necessity for SL.

Key Points

- Statistical learning is impaired in patients with poorly controlled epilepsy
- The hippocampus is necessary for statistical learning
- A statistical learning task can reliably predict seizure burden in patients with epilepsy

2 | MATERIALS AND METHODS

2.1 | Participants

Eighty-nine participants were recruited to complete the SL task from the Yale Comprehensive Epilepsy Center. Participants were divided into an initial PWE cohort ($n=41$), a matched healthy control (HC) cohort ($n=28$; based on age, sex, and education), and an additional PWE cohort for use in prediction ($n=20$). Patients without a definitive diagnosis of epilepsy or who had severe cognitive deficits were excluded from the analysis ($n=3$). The initial PWE cohort ($n=38$ after exclusion) was classified based on seizure onset zone (SOZ) into TLE ($n=23$) and extratemporal lobe epilepsy (ETLE; $n=15$) by two board-certified epileptologists based on electroencephalographic (EEG) findings. As a positive control, 16 TLE and 15 ETLE patients completed an additional EM task. In PWE, all ASMs, including their ability to impact memory, were documented (Table S1). For the HCs, 28 completed the SL task and 15 completed the EM task. The predictive cohort ($n=20$) was collected to internally validate the ability of SL to predict seizure control. Seizure control was defined as the binary classification of seizure frequency. Subjects with more than three seizure days per year (International League Against Epilepsy [ILAE] post-surgical class 4–6) were classified as uncontrolled epilepsy (UE). Subjects having fewer than four seizure days per year were classified as controlled epilepsy (CE).[23] The DES cohort ($n=5$) was recruited after undergoing intracranial EEG (iEEG) monitoring for seizure localization.

2.2 | Behavioral tasks

The SL behavioral task (followed by the EM behavioral task when applicable) was presented on a laptop running a custom MATLAB script (R2019a, MathWorks) with Psychtoolbox 3.0.16.[24] SL task stimuli consisted of glyphs, which have been previously validated for use in SL tasks.[17] EM task stimuli consisted of faces obtained from the Chicago Face Database.[25]

The SL task was divided into an exposure phase followed by a test phase (see Figure 1A; Supplementary Methods for task design). During the exposure phase, participants were not instructed to learn the pairs but only to pay attention to the glyphs on the screen. Thus, participants had to exclusively rely on the transition probabilities between glyphs to learn the pairs. The test phase contained two parts: an item test, assessing baseline recognition memory, and an association test, assessing SL, where participants had to rely on learned transition probabilities to respond correctly.

The EM task was divided into study and test phases separated by a distractor task (Figure 1B; Supplementary Methods). During the study phase, participants were instructed to memorize face–occupation pairs. The test phase for the EM task consisted of an item test and an association test, which mirrors the SL task. The association test differed from the SL task in that EM performance depended on one-shot learning of pairs presented discretely, as opposed to gradual learning of pairs embedded in a continuous sequence and extracted across multiple exposures.[26]

2.3 | Magnetic resonance imaging acquisition and MTL segmentation

For a subset of participants with epilepsy ($n = 27$), we manually segmented the subfields of the hippocampus (subiculum, CA1, CA2/3, dentate gyrus) and the subregions of the MTL cortex (perirhinal cortex, entorhinal cortex, parahippocampal cortex) into regions of interest (ROIs) using structural magnetic resonance imaging (MRI) scans. Patients with lesions that impacted MTL segmentation were excluded from further analyses ($n = 2$). Segmentation was performed by a single individual following structural landmarks of the MTL and cross-checked by a content expert.[27–29] Details of the acquisition and segmentation process are provided in the Supplementary Methods.

2.4 | Direct electrical brain stimulation

Five PWE undergoing iEEG for clinical localization of their SOZ were recruited for DES based on the location of implanted electrodes (Supplementary Methods).

The SL task presented to the DES cohort had a reduced number of test trials to ease participant burden; each glyph was probed once (rather than twice) in the association test. We first performed the SL task with frontal pole stimulation[30,31] to determine whether patients showed behavioral evidence of baseline SL impairment that would confound analysis. In other words, without performing above chance at baseline, the effects of MTL stimulation would not be interpretable. Given this concern and the risk of DES-induced seizures in the MTL, we excluded two participants who did not show adequate behavioral evidence of SL during frontal pole stimulation. The remaining three participants who showed SL during frontal pole stimulation received DES to the hippocampus ($n = 3$). A different set of glyphs was used for each region (frontal pole and hippocampus) to avoid interference between task repetitions.

2.5 | Statistical analyses

We analyzed the behavioral performance of participants on the SL and EM tasks using one-sample *t*-tests compared to chance within the HC and epilepsy groups. This was to test whether a group showed reliable (above chance) SL or EM. Association test scores were computed as the proportion of correct responses (chance = .5), and item test scores were computed using *d*-prime, which is the difference between the *z*-transform of the hit rate and false alarm rate (chance = 0). To test for group effects, we then compared performance across groups, stratified by SOZ (TLE vs. ETLE) for PWE, and compared them with HCs using analysis of variance (ANOVA) tests followed by post hoc tests using Tukey multiple comparisons correction. The Shapiro–Wilk test was used to assess normality; for nonnormally distributed data, a Kruskal–Wallis test was used instead of ANOVA, and the post hoc test used Dunn multiple comparisons correction. These tests were performed using Prism version 9 (GraphPad Software). Significance level was set at $p \leq .05$.

To test whether variables other than SOZ influenced performance, two linear regressions were used to predict SL and EM association test scores, respectively (Supplementary Methods).

A follow-up comparative analysis was performed to assess the ability of SL and EM association test scores to sort patients based on epilepsy control status. First, to perform a power test for sample size determination, we computed the receiver operator characteristic (ROC) curves and compared the area under the curve (AUC) for SL and EM.[32] The results from these tests were then used to calculate the sample size for a new validation epilepsy cohort (power analysis with 80% confidence).[33] This new cohort of 20 PWE performed the SL task (19 performed the EM task), and new AUC values were calculated, assessing the ability of the tasks to predict seizure control.

To evaluate relationships between behavioral performance and MTL ROI volumes, linear regression was employed to predict performance in SL and EM association tests (Supplementary Methods). All regression

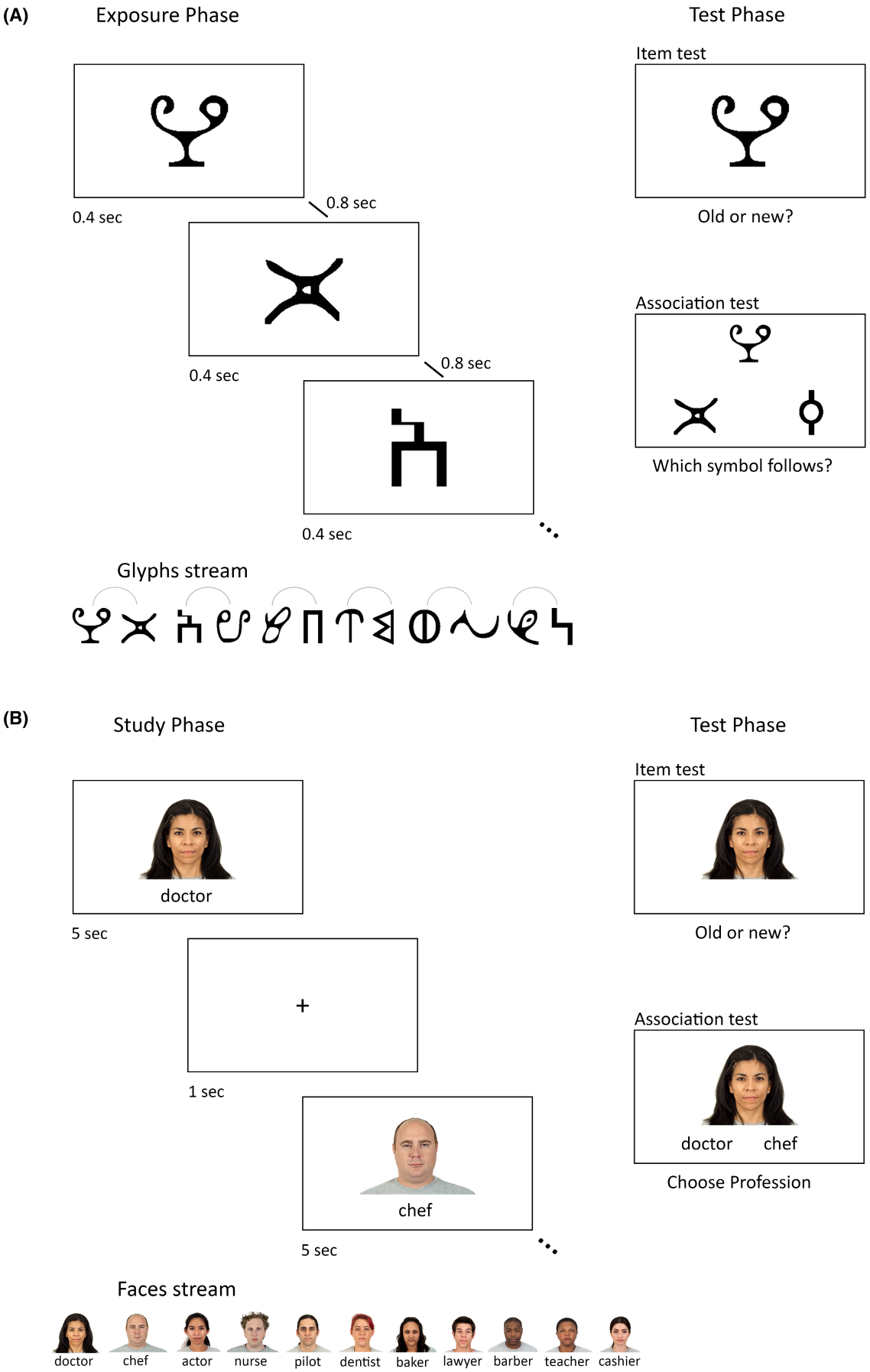

FIGURE 1 Behavioral task designs for statistical learning and episodic memory. (A) Statistical learning task. In the exposure phase, 12 glyphs were randomly assigned to pairs and presented 10 times (one glyph at a time) in random order. The test phase had two parts: an item test and an association test. The association test presented the first glyph of each pair on the top of the screen, and participants chose which glyph completed the pair. (B) Episodic memory task. In the study phase, face–occupation pairs were presented one pair at a time and participants were instructed to memorize each pair. In the test phase, an item test (identifying faces as old or new) was followed by an association test (identifying the occupation previously associated with a given face).

models were implemented with Stata 17 software (Stata Corporation). For DES, given the small sample size of the cohort, descriptive statistics were used to report the behavioral data and the effect of stimulation.

3 | RESULTS

3.1 | Participant demographics and clinical characteristics

Tables S2–S4 summarize the demographics and clinical profiles for participants. There were no significant differences in age (PWE mean = 40.92, HC mean = 35.93, $U = 451.5$, $p = .299$, Mann–Whitney test), sex ($\chi^2_{1,\,66} = .330$, $p = .566$), or education level ($\chi^2_{1,\,61} = .863$, $p = .353$, chi-squared test) between HCs and PWE.

3.2 | Behavioral results

3.2.1 | Statistical learning performance

We observed reliable above chance SL (Figure 2A) in HCs ($n = 28$, mean = .64, SEM = .03, $t_{27} = 4.816$, $p < .0001$) and PWE ($n = 38$, mean = .57, SEM = .03, $t_{37} = 2.20$, $p = .034$), with no statistically significant difference between groups ($t_{64} = 1.77$, $p = .082$). Next, to better understand variance in PWE, we divided patients based on SOZ into TLE and ETLE subgroups and compared each subgroup to chance (Figure 2B). The TLE subgroup performed above chance ($n = 23$, mean = .60, SEM = .04, $t_{22} = 2.502$, $p = .030$), whereas the ETLE subgroup did not ($n = 15$, mean = .52, SEM = .05, $t_{14} = .358$, $p = .726$). However, subgroup differences were not due to group effects when compared across HC, TLE, and ETLE ($H_2 = 4.276$, $p = .118$). Next, given that we did not observe a group effect in the case of SOZ division, we divided the PWE group based on seizure control into CE and UE subgroups (Figure 2C).[23] CE patients performed reliably above chance (CE: $n = 18$, mean = .71, SEM = .03, $t_{17} = 6.876$, $p < .0001$), whereas UE patients performed slightly below chance on average (UE: $n = 20$, mean = .44, SEM = .03). Furthermore, there was a significant effect of HC, CE, and UE group on SL performance ($F_{2,\,63} = 20.81$, $p < .0001$). The UE subgroup performed worse than the CE subgroup ($p < .0001$; Figure 2C) and the HC group ($p < .0001$). Item memory in HCs and PWE divided either into TLE versus ETLE or CE versus UE showed above chance performance with no effect of group on performance (Figure S1).

We then built a linear regression model to investigate how these and other variables jointly predicted SL performance in the PWE group. Specifically, we evaluated SL performance relative to age, sex, ASM, SOZ, MTL lesion, item memory, SOZ dominance, and seizure control. Seizure control was the only reliable predictor of SL performance ($p = .0001$, partial regression coefficient = .291; Figure 2D), with SOZ not reaching significance ($p = .288$, partial regression coefficient = .061). Including the interaction term between seizure control and SOZ in the model did not yield different results. Overall, these data show that SL is impaired in patients with poorly CE, irrespective of SOZ.

3.2.2 | Episodic memory

We next sought to ask whether SOZ predicts EM performance.[3–5] As with SL, HC ($n = 15$, mean = .97, SEM = .02, $t_{14} = 32.39$, $p < .0001$) and PWE ($n = 31$, mean = .84, SEM = .03, $t_{30} = 11.82$, $p < .0001$) groups performed above chance in the association test of the EM task (Figure 3A). However, PWE performed worse than the HC group ($U = 115$, $p = .0032$).

The PWE group was then divided based on SOZ into TLE ($n = 16$, mean = .82, SEM = .05, $t_{15} = 7.065$, $p < .0001$) and ETLE ($n = 15$, mean = .86, SEM = .04, $t_{14} = 10.20$, $p < .0001$) subgroups (Figure 3B). A three-way comparison of HC, TLE, and ETLE revealed a group effect ($H_2 = 8.509$, $p = .014$). Post hoc tests revealed significant differences between HC and TLE ($p = .028$) and HC and ETLE ($p = .042$), but no difference between TLE and ETLE ($p > .99$).

When the PWE group was divided into CE ($n = 15$, mean = .86, SEM = .04, $t_{14} = 8.414$, $p < .0001$) and UE ($n = 16$, mean = .82, SEM = .05, $t_{15} = 8.148$, $p < .0001$) subgroups irrespective of SOZ (Figure 3C), we observed a group effect compared with HC ($H_2 = 9.262$, $p = .0097$). Post hoc tests revealed significant differences between HC and UE ($p = .009$), but not between HC and CE ($p = .1163$) or between CE and UE ($p > .99$).

To evaluate predictors of EM performance in PWE, we used a linear regression with the same variables as the SL model (Figure 3D; variance inflation factor diagnostic did not indicate multicollinearity in either model; Table S5).

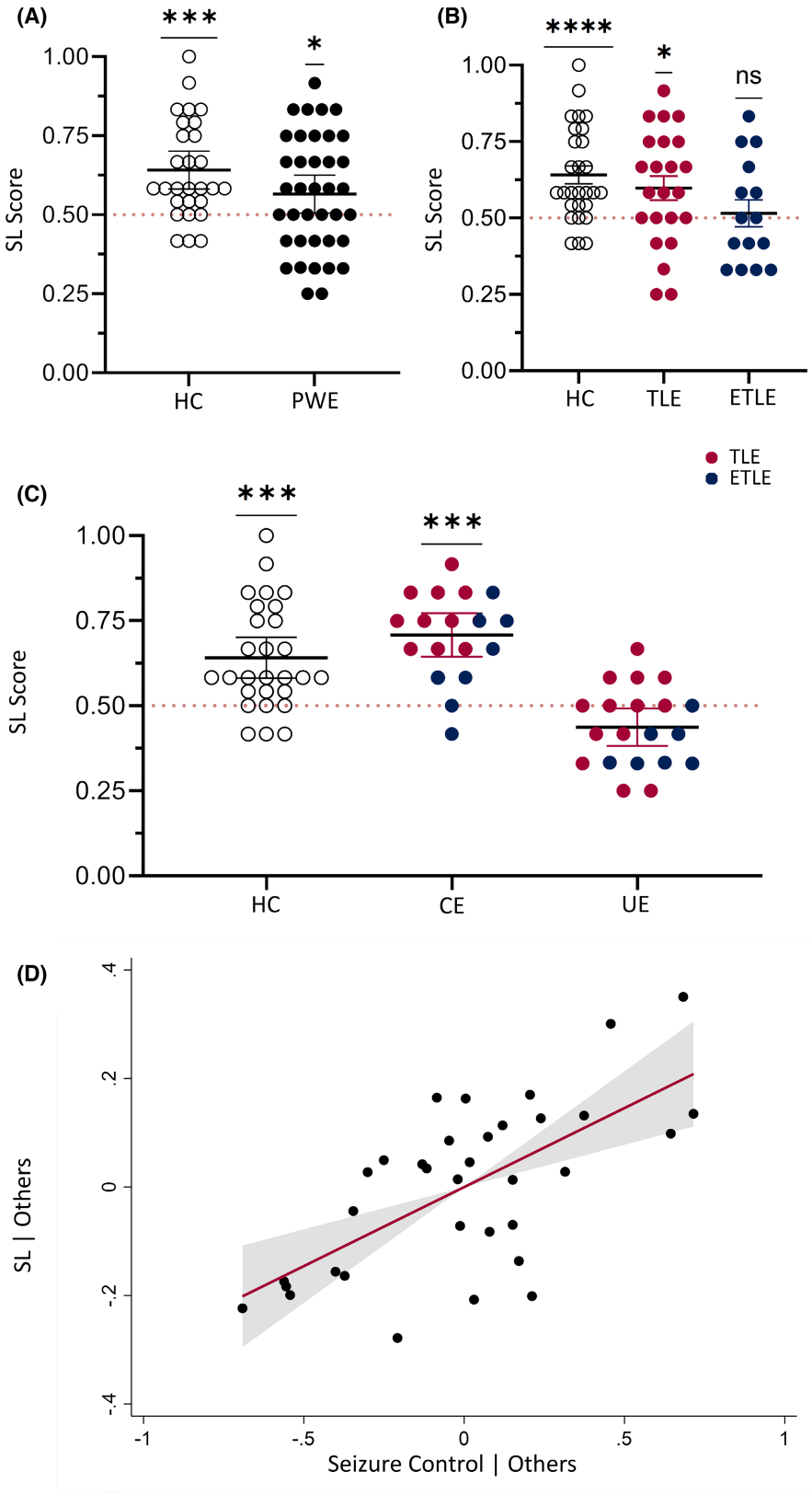

FIGURE 2 Seizure frequency predicts statistical learning performance. (A) Behavioral performance on the statistical learning (SL) task in healthy controls (HC) and patients with epilepsy (PWE). Each dot represents an individual's average association test score relative to chance (dotted line, .5). The black lines reflect the mean and the error bars reflect the 95% confidence interval. (B) Stratifying PWE participants by seizure onset zone (temporal lobe epilepsy [TLE] vs. extratemporal lobe epilepsy [ETLE]). (C) Stratifying PWE participants by seizure control (controlled epilepsy [CE] vs. uncontrolled epilepsy [UE]). (D) Partial relationship between seizure control and SL performance, controlling for all other independent variables. The plot shows residuals of regressing SL by all variables except seizure control versus the residuals of regressing seizure control by all other independent variables. The slope of the dark red line represents the partial regression coefficient from the multivariate regression. Shading around the line of best fit reflects 95% confidence interval. Asterisks denote *p*-values for the one-sample *t*-tests: $^{*}p < .05$, $^{***}p < .001$, $^{****}p < .0001$. ns, not significant.

Poor EM performance was associated with ASMs that impact memory ($p = .009$; partial regression coefficient = −.132), whereas EM item test score was associated with better EM associative performance ($p = .046$, partial regression coefficient = .055). In summary, whereas seizure control was the only predictor of SL, ASM and item memory predicted EM. Critically, EM did not significantly vary by seizure frequency/control ($p = .666$, partial regression coefficient = −.025). Item recognition test scores for the EM task are summarized in Figure S2.

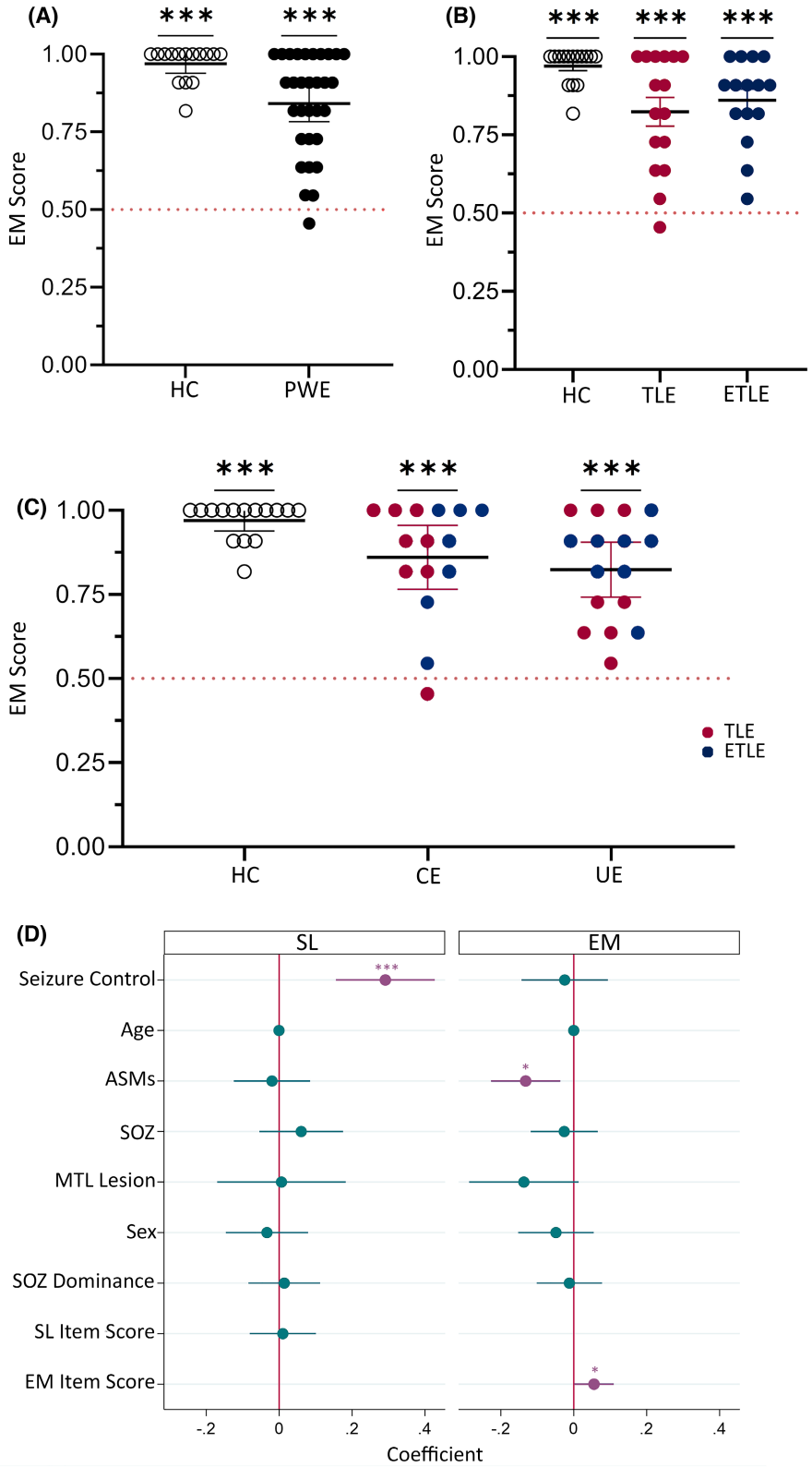

FIGURE 3 Antiseizure medications (ASMs) predict episodic memory (EM) performance. (A) Behavioral performance on the EM task in healthy control (HC) and patients with epilepsy (PWE) groups. Each dot represents an individual's average association test score relative to chance (dotted line, .5). The black lines reflect the mean, and the error bars reflect the 95% confidence interval. (B) Stratifying PWE participants by seizure onset zone (SOZ; temporal lobe epilepsy [TLE] vs. extratemporal lobe epilepsy [ETLE]). (C) Stratifying PWE participants by seizure control (controlled epilepsy [CE] vs. uncontrolled epilepsy [UE]). (D) Summary of predictors of statistical learning (SL) and EM behavioral performance. The dot for each predictor and task reflects the partial regression coefficient, and the surrounding band reflects the 95% confidence interval. Asterisks denote *p*-values for the one-sample *t*-tests in A–C, and they denote *p*-values for the multivariate regression in D. *$p < .05$, ***$p < .001$. MTL, medial temporal lobe.

3.3 | SL as a predictor of seizure control

Given that seizure control was the strongest predictor of SL performance, we asked whether the short behavioral SL task could be used in reverse to predict seizure frequency and epilepsy control in a new cohort of PWE. We performed an AUC analysis of the ROC curves generated from SL and EM scores in a new cohort of patients (Figure 4; Figure S3 shows the results of the initial cohort). The association test scores were used as independent variables to predict seizure control as an outcome variable. SL task performance was a stronger predictor of seizure

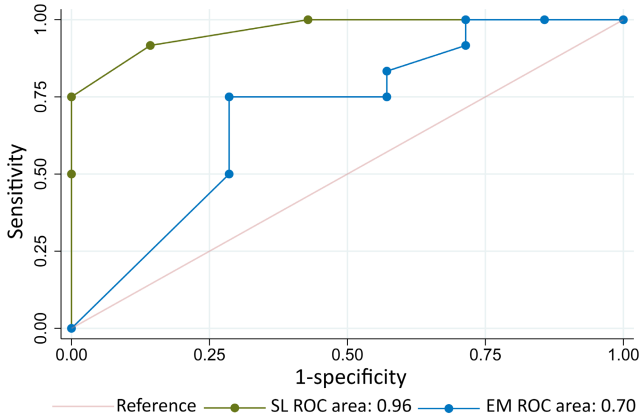

FIGURE 4 Statistical learning (SL) predicts seizure frequency better than episodic memory (EM). The ability to predict seizure control differed by task. The areas under the curve from a receiver operator characteristic (ROC) analysis of the SL and EM association test performance were .96 (95% confidence interval [CI] = .90–1.00, SEM = .03) and .70 (95% CI = .43–.96, SEM = .14), respectively.

control in the new cohort (AUC = .96) than EM task performance (AUC = .70, $\chi^2_{1,19} = 3.94$, $p = .047$). Including the item recognition scores in the model produced similar results (Figure S4).

3.4 | Relationship to MTL substructure volumes

We next built three linear regression models to analyze the relationship between MTL structural volumes and behavioral performance on the SL and EM association tests. This method was adopted to examine MTL structures at different levels of granularity (each with covariates for age and sex). Model A included total hippocampal volume and total MTL cortical volume; Model B considered the anterior and posterior volumes of MTL cortex, and anterior and posterior hippocampal volumes; and Model C included the volumes of hippocampal subfields subiculum, CA1, CA2/3, and dentate gyrus, and MTL subregions perirhinal cortex, entorhinal cortex, and parahippocampal gyrus (Figure 5A). Here, we report the results for the most detailed model, Model C (other models are reported in Table S6).

The fit of Model C for SL associative performance was highly reliable overall ($n = 25$, $R^2 = .46$, $F_{9,15} = 5.34$, $p = .0023$). The volume of hippocampal subfields CA1 ($p = .0001$, coefficient = −.718) and CA2/3 ($p = .002$, coefficient = .757) reliably predicted SL performance (Figure 5B); that is, SL performance was negatively correlated with CA1 volume and positively correlated with CA2/3 volume.

A similar pattern was observed for EM overall ($n = 18$, $R^2 = .77$, $F_{9,8} = 9.07$, $p = .0025$) and in CA1 ($p = .001$, coefficient = −1.105) and CA2/3 ($p = .002$, coefficient = 2.022) hippocampal subfields. Additionally, subiculum volume ($p = .029$, coefficient = −.502), dentate gyrus volume ($p = .012$, coefficient = .171), and patient age ($p = .001$, coefficient = −.009) were associated with EM performance (Figure 5B). Variance inflation factor of independent variables were below 5 (Table S7).

3.5 | Stimulation experiment

Given that the volumes of MTL subregions were associated with SL performance, we next asked whether the MTL is causally necessary for SL.[21,22] We used transient DES in a new cohort of patients to disrupt hippocampal function during the exposure phase of the SL task (Figure 6A). We performed MTL stimulation in the three patients who had adequate baseline SL during stimulation of the frontal pole as a positive control (scores = .67, .83, .67). In contrast, when we stimulated the hippocampus in these patients (Figure 6B), they no longer showed learning (scores = .50, .59, .50, respectively; Figure 6C, Table S8).

4 | DISCUSSION

We investigated how SL—a fundamental form of human learning used to acquire the structure of our environment, make predictions, and behave efficiently—is impacted by epilepsy. We were motivated by studies showing that epilepsy may impact MTL structures leading to memory deficits[4,5,7] and by more recent demonstrations that SL may rely on the MTL.[21,22] We found that SL is impaired in patients with poorly controlled epilepsy irrespective of where their seizures originated. Using a new cohort, we validated that the SL task can reliably predict seizure frequency and control. Furthermore, manual segmentation and quantification of MTL volumes in PWE showed that SL performance was associated with hippocampal subfield CA1 and CA2/3 volumes. Finally, in a subset of intracranial patients with normal SL during baseline frontal pole stimulation, DES of the hippocampus during the exposure phase of the SL task impaired SL performance. Taken together, our results suggest that poorly CE may impair SL via disruption of the hippocampal circuitry. In addition, SL task performance may be a clinically relevant tool to evaluate seizure frequency and control in PWE. The findings in our EM task are concordant with cumulative evidence suggesting that the MTL is critical for EM.[8,9]

Given prior findings that SL may rely on the MTL,[21] we hypothesized that SL would be impaired in TLE. However, SOZ (i.e., TLE vs. ETLE) did not impact SL performance. Rather, seizure control—number of seizure days per

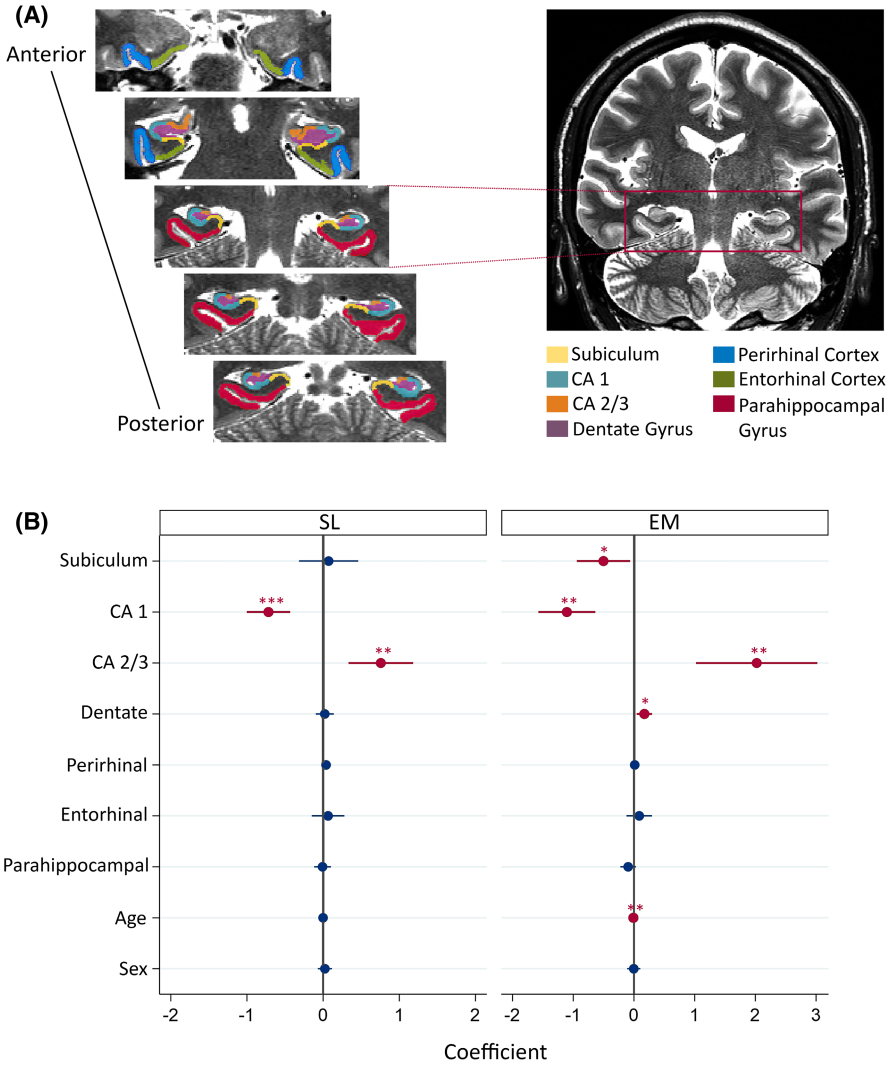

FIGURE 5 Relationship between behavioral performance and medial temporal lobe substructure volumes. (A) Manual segmentation method. Anterior slices include the perirhinal cortex (blue) and entorhinal cortex (olive green). Hippocampal head subfields appear along with these two cortical regions. The disappearance of the uncal apex marks the transition point between the hippocampal head and body. The parahippocampal gyrus formation (red) begins with the hippocampal body. (B) Regression coefficient plots for robust multivariate regression models to predict performance in statistical learning (SL; left) and episodic memory (EM; right) association tests. Asterisks denote *p*-values for the multivariate regression: **p* < .05, ***p* < .01, ****p* < .001.

year—reliably predicted SL performance (and vice versa in the validation cohort) for PWE. One possible reason is that repetitive seizures (regardless of onset) may lead to structural or functional impairment in the MTL and other brain regions relevant for SL.[34,35] Our findings may thus be consistent with a previous report of impairments in auditory SL in a cohort of patients with multilobar brain damage from stroke.[36] In addition, patients with uncontrolled seizures had seizure types that were predominantly (90%) bilateral tonic–clonic or focal impaired-awareness (Table S4), potentially indicating more pronounced global dysfunction. Although there have been conflicting results on the relationship between seizure frequency and declarative memory,[37–40] we did not find the same relationship between seizure control and EM. Some patients who exhibited normal EM performance had a chance level performance on the SL test. This raises the question as to whether the differential effect of seizure frequency on these two behaviors depends on the networks disrupted by seizures, and whether these broad networks differentially support SL and EM.

After manually segmenting and quantifying MTL substructure volumes, we found positive relationships between hippocampal subfield CA2/3 volume and performance on both the SL and EM tasks. The volume–EM relationship observed here is in line with prior work on cell counts and histopathology analysis of resected hippocampal tissue in PWE showing that neuronal loss in hippocampal subfields (excluding CA1) correlates with declarative memory performance.[41] SL performance was also positively correlated with CA2/3 volumes, suggesting involvement of the hippocampus in SL. However, the positive correlation of CA2/3 volume with SL performance observed here is inconsistent with a previous study that found a negative correlation between CA2/3 volume (in the hippocampal head) and SL.[42] A potential explanation for this discrepancy could be the difference in age between the two samples (our sample was older) and, more important, the pathology (we only considered PWE for the volumetric analysis).[42] Epilepsy (especially TLE) is often associated with structural disease.[43] The negative correlation we observed between CA1 volume and performance

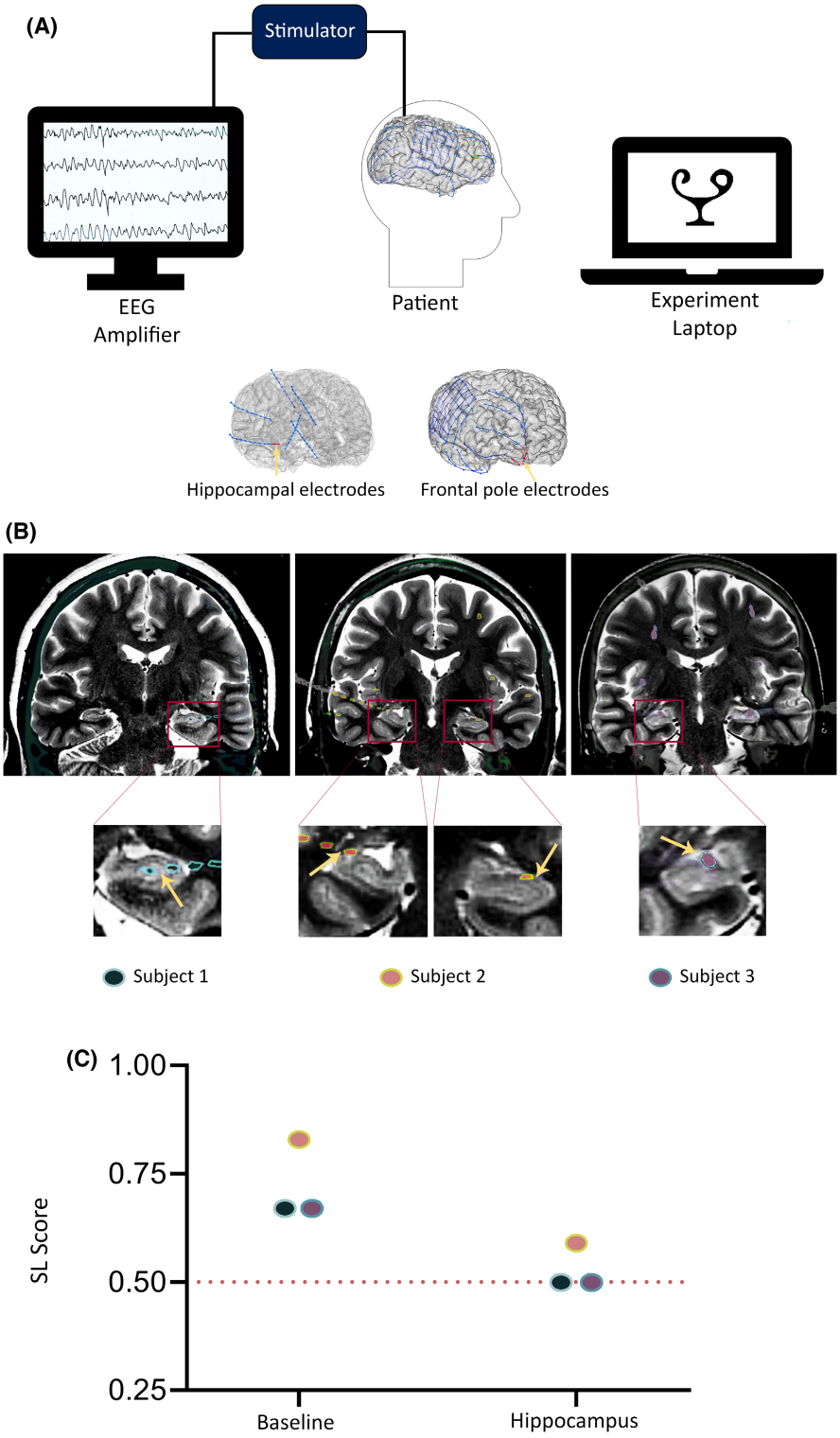

FIGURE 6 Necessity of the hippocampus for statistical learning (SL). (A) Schematic of the stimulation experiment. Three patients performed the SL task twice. One-hertz direct electrical brain stimulation was administered during the exposure phase of the task (Figure 1A; the only change from prior experiments was that each glyph was tested once rather than twice in the association test) through a cortical stimulator. Example electrode localization for the hippocampal and frontal pole contacts (generated using FreeSurfer and iElectrodes software with preoperative magnetic resonance imaging [MRI] and postoperative computed tomography [CT] scans) is shown at the bottom. (B) Electrode localization for each subject included in the stimulation experiment (electrodes shown on CT scan overlaid on T2-weighted MRI). Distinct colors are applied for each patient's contacts. Yellow arrows indicate site of bipolar stimulation. (C) SL scores for three patients in the SL association test when the control region (frontal pole) versus hippocampus was stimulated. The red dotted line represents chance performance (.5). Stimulation of the hippocampus eliminated SL observed during the baseline stimulation of the control region. Colors correspond to patients as indicated in B. EEG, electroencephalographic.

in SL and EM is consistent with histological studies of patients with ILAE type 2 hippocampal sclerosis (patients with predominantly CA1 neuronal cell loss who do not exhibit declarative memory impairment).[41,44,45]

Finally, in a preliminary experiment, we performed transient DES to test for a functional role of the MTL in SL. We found that hippocampal stimulation during the exposure phase of the SL task disrupted performance relative to baseline frontal stimulation. This finding suggests that the MTL may be causally involved in SL, and it supports previous functional MRI and lesion-based studies that implicated the MTL in SL.[17–22] However, given our limited sample size and number of trials, our results cannot be generalized. Notably, whereas our DES protocol allows us to test whether the MTL is necessary for SL, it does not evaluate whether frontal pole or any other neocortical

region is necessary for SL (we excluded patients who did not learn during frontal pole stimulation, because this was our non-MTL positive control). We were also unable to randomize stimulation order of anatomic regions because of the highly epileptogenic nature of the hippocampus (which was stimulated last).[46] This is particularly relevant because SL can be affected by order; exposure to one set of regularities may block or interfere with the subsequent learning of a second set.[47,48] Despite these compromises in experimental design, this cohort represented a rare window of opportunity to perform reversible causal perturbation of the human brain. Although future work is needed to verify and expand upon these findings, we believe that they provide initial support for a causal link between the MTL, specifically the hippocampus, and SL.

Beyond providing a novel assessment of cognition in PWE, a potentially impactful conclusion of our study is that the SL task can be used to stratify PWE by seizure frequency. Notably, the EM task lacked this predictive power. This is clinically relevant, as most neuropsychological testing batteries rely on EM tasks for memory assessment and thus may not capture the full range of memory decline or MTL dysfunction in epilepsy.[3,49] We believe that a short but powerful task such as the SL task may provide added value in classifying seizure frequency, as it may surpass the current methodology of seizure diaries, which have been shown to be unreliable.[50] Thus, the SL task has potential for both seizure control assessment and comprehensive cognitive assessment. Our finding that patients can perform well in EM and poorly in SL is notable, as it highlights a novel aspect of learning dysfunction in some PWE that is not reliant on declarative memory.[11,14,15] Adding SL-based tasks to clinical neuropsychological assessment protocols may thus lead to a more comprehensive understanding of the neurocognitive deficits seen in PWE. We believe that our findings motivate a role for SL as an important aspect in the neurocognitive evaluation of PWE (regardless of epilepsy type).

Our study provides a comprehensive initial investigation of how SL is affected by epilepsy by combining behavior, neuroimaging, and direct electrical stimulation; and in demonstrating a novel link between SL deficits and seizure frequency, we highlight the potential clinical utility of studying SL in epilepsy. In conclusion, characterizing SL deficits in epilepsy may lead to a more comprehensive understanding of the memory problems associated with epilepsy. Moreover, SL tasks have potential as a clinically relevant tool for assessing epilepsy control.

AUTHOR CONTRIBUTIONS

Ayman Aljishi: Writing–original draft (lead); formal analysis (lead); methodology (lead); visualization (lead); conceptualization. **Brynn E. Sherman:** Writing–review and editing; methodology; conceptualization; formal analysis. **David M. Huberdeau:** Conceptualization; writing–review and editing. **Sami Obaid:** Writing–review and editing; methodology; conceptualization. **Kamren Khan:** Writing–review and editing; methodology; conceptualization. **Layton Lamsam:** Writing–review and editing; methodology; conceptualization. **Zion Zibly:** Writing–review and editing; conceptualization. **Adithya Sivaraju:** Writing–review and editing; methodology; formal analysis; conceptualization. **Nicholas B. Turk-Browne:** Writing–review and editing; methodology; conceptualization; funding acquisition; validation. **Eyiyemisi C. Damisah:** Supervision; writing–review and editing; methodology; conceptualization; funding acquisition; validation; formal analysis.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. 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

All data used in this study are available upon reasonable request to the corresponding author.

PATIENT CONSENT AND ETHICS APPROVAL

Informed consent was given by all participants. This study was approved by the institutional review board at Yale University.

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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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