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Comparison of fMRI correlates of successful episodic memory encoding in temporal lobe epilepsy patients and healthy controls

Paul F. Hill^{a,b,*}, Danielle R. King^{a,b}, Bradley C. Lega^c, Michael D. Rugg^{a,b,d}

^aCenter for Vital Longevity, University of Texas at Dallas, 1600 Viceroy Dr. #800, Dallas, TX, 75235, USA

^bSchool of Behavioral and Brain Sciences, University of Texas at Dallas, 800 W Campbell Rd, Richardson, TX, 75080, USA

^cDepartment of Neurosurgery, University of Texas Southwestern Medical Center, 5303 Harry Hines Blvd 6th Floor Suite 108, Dallas, TX, 75390, USA

^dDepartment of Psychiatry, University of Texas Southwestern Medical Center, 6363 Forest Park Rd 7th Floor Suite 749, Dallas, TX, 75235, USA

Abstract

Intra-cranial electroencephalographic brain recordings (iEEG) provide a powerful tool for investigating the neural processes supporting episodic memory encoding and form the basis of experimental therapies aimed at improving memory dysfunction. However, given the invasiveness of iEEG, investigations are constrained to patients with drug-resistant epilepsy for whom such recordings are clinically indicated. Particularly in the case of temporal lobe epilepsy (TLE), neuropathology and the possibility of functional reorganization are potential constraints on the generalizability of intra-cerebral findings and pose challenges to the development of therapies for memory disorders stemming from other etiologies. Here, samples of TLE (N = 16; all of whom had undergone iEEG) and age-matched healthy control (N = 19) participants underwent fMRI as they studied lists of concrete nouns. fMRI BOLD responses elicited by the study words were segregated according to subsequent performance on tests of delayed free recall and recognition memory. Subsequent memory effects predictive of both successful recall and recognition memory were evident in several neural regions, most prominently in the left inferior frontal gyrus, and did not demonstrate any group differences. Behaviorally, the groups did not differ in overall recall performance or in the strength of temporal contiguity effects. However, group differences in serial position effects and false alarm rates were evident during the free recall and recognition memory tasks, respectively. Despite these behavioral differences, neuropathology associated with temporal lobe epilepsy was apparently insufficient to give rise to detectable differences in the functional neuroanatomy of episodic memory encoding relative to neurologically healthy controls. The

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*Corresponding author. Center for Vital Longevity, University of Texas at Dallas, 1600 Viceroy Dr. #800, Dallas, TX, 75235, USA. paul.hill@utdallas.edu (P.F. Hill).

Declaration of competing interest

None.

findings provide reassurance that iEEG findings derived from experimental paradigms similar to those employed here generalize to the neurotypical population.

Keywords

Episodic memory; Encoding; Temporal lobe epilepsy

1. Introduction

When coupled with the subsequent memory procedure (Paller and Wagner, 2002), intracerebral recordings of neural activity (iEEG) provide Johnson and Knight, 2015). iEEG has been especially heavily used to identify neural correlates of the encoding operations that support the ability to freely recall studied words following an intervening distractor interval. These studies have consistently linked successful encoding to a number of electrophysiological phenomena - including modulation of gamma and theta power, and increased theta-gamma phase amplitude coupling - in inferior frontal gyrus (IFG), inferior temporal gyrus, posterior parietal cortex, and hippocampus, among other regions (e.g. Burke et al., 2014; Kucewicz et al., 2019; Kragel et al., 2017; Lega et al., 2012, 2014; Long and Kahana, 2015). In a complementary line of research, iEEG has emerged as a powerful tool in the development of experimental therapies and medical devices aimed at treating memory disorders (Ezzyat et al., 2017, 2018; Kucewicz et al., 2018).

Due to the invasive nature of iEEG, experimental applications of the technique are largely limited to patients with drug resistant epilepsy who have undergone surgically guided electrode placement to localize epileptogenic brain regions. Given the well-known dependence of episodic memory on the medial temporal lobes (MTL), much of the iEEG work carried out in the memory domain has been performed on patients with temporal lobe epilepsy (TLE). TLE is frequently associated with structural pathology in the MTL (including hippocampal sclerosis and atrophy) and often presents with comorbid psychopathology and cognitive impairment, particularly in relation to episodic memory and executive function. Moreover, the pathology underlying TLE may promote adaptive neural reorganization and compensation, resulting in altered regional neural function (Bonelli et al., 2013; Powell et al., 2007; Richardson et al., 2003; Sidhu et al., 2015). Together, these factors potentially compromise the generalizability of iEEG findings to the general population.

In a prior study that aimed to compare the neural correlates of successful memory encoding in TLE patients with those in neurologically healthy adults, Long et al. (2014) examined the spectral correlates of successful encoding using iEEG in TLE patients and scalp EEG in healthy control participants. Across both groups and recording modalities, successful encoding elicited similar patterns of activity in the theta and high gamma frequency bands in multiple frontal and temporal ROIs. However, the use of different signal acquisition methodologies and behavioral paradigms (delayed free recall in TLE, immediate free recall in healthy controls) precluded direct comparisons between the two groups.

In a parallel literature, functional magnetic resonance imaging (fMRI) has been used to characterize the neural correlates of encoding operations supporting delayed free recall in

neurologically healthy adults. Results from these studies are largely consistent with those reported in the iEEG literature, revealing a consistent pattern of predominantly left lateralized subsequent memory effects in the IFG, inferior temporal gyrus, posterior parietal cortex, along with effects in the hippocampus bilaterally (Brassen et al., 2006; Dickerson et al., 2007; Long et al., 2010; Staresina and Davachi, 2006; Strange et al., 2002). The noninvasiveness and full-brain coverage afforded by fMRI make it well suited to examine potential reorganization of the neural circuits supporting episodic encoding in TLE.

Prior fMRI investigations have reported encoding effects that differed between TLE patients and healthy controls, primarily within the MTL (Bonelli et al., 2010; Powell et al., 2007; Sidhu et al., 2013). The group differences reported in these studies were highly variable in respect of the location and direction of the differences, and it is unclear from the published reports whether the contrasts necessary to identify any group-invariant subsequent memory effects (e.g., inclusive masking of simple group effects) were performed. Moreover, in each of the aforementioned studies subsequent memory performance was assessed with a post-scan recognition memory test. To our knowledge, there are no published prior fMRI investigations that directly compared subsequent memory effects for delayed free recall in TLE and healthy participants. Finally, and of importance, the majority of the TLE patients examined in these prior studies exhibited evidence of frank hippocampal pathology (hippocampal sclerosis), in contrast to the TLE samples typically employed in iEEG studies, including the sample employed in the present study.

In summary, iEEG has emerged as a powerful tool for studying the neurophysiological basis of successful memory encoding and is being used to develop experimental therapies aimed at improving memory dysfunction. However, for the reasons noted previously, studies using iEEG are limited to patient populations in whom neuropathology, coupled with possible functional reorganization, pose significant threats to the generalizability of the findings. Thus, the primary aim of the current study was to compare fMRI subsequent memory effects in samples of TLE patients and neurologically healthy adults. To advance this aim, TLE and healthy volunteers underwent fMRI as they studied lists of concrete nouns. fMRI BOLD responses elicited by the study words were segregated according to subsequent performance on tests of both free recall and recognition memory. To foreshadow the results, we identified several canonical subsequent memory effects that did not reliably differ in their magnitudes across the two groups.

2. Materials and methods

2.1. Participants

Samples of 16 TLE and 19 age-matched [$t(28.92) = -1.65, p = .110$] healthy control (HC) participants contributed to the data reported here. All participants gave informed consent in accordance with the University of Texas at Dallas and University of Texas Southwestern Institutional Review Boards and were compensated \$30 an hour.

2.1.1. TLE participants—Nineteen adults with medication resistant TLE (defined by ictal activity originating in the temporal lobes) were recruited to participate in this experiment. Each TLE participant had previously undergone iEEG to localize and monitor

epileptogenic activity, during which time they performed a delayed free recall task similar to the one reported here. Enrollment was limited to patients that correctly recalled at least 10% of study items across a full iEEG session. The average delay between iEEG surgery and the fMRI session was 3 months ($SD = 2.12$ months). Three TLE participants were left-handed, and all participants spoke fluent English before the age of five. Three right-handed participants were excluded from subsequent analyses for the following reasons: excessive in-scanner motion ($N = 1$), technical malfunction with the in-scanner microphone ($N = 1$), and structural abnormality resulting in poor normalization of the structural and functional MRI scans ($N = 1$). Data from the remaining 16 TLE participants (20–59 years, $M = 36$ years, $SD = 11.7$ years; 11 females) are reported in the following analyses. None of the patients reported in these analyses showed radiological evidence of hippocampal sclerosis. Additional clinical details for these 16 participants are reported in Table 1.

2.1.2. Healthy control participants—An additional 20 adult volunteers were recruited from the University of Texas at Dallas and surrounding community to serve as a healthy age-matched control group. One participant was excluded from subsequent analyses due to a technical malfunction with the in-scanner microphone. Data from the remaining 19 HC participants (20–60 years; $M = 30.2$ years; $SD = 9.3$ years; 9 females) are reported in the analyses of the free recall task. Data from the recognition memory task were missing for one of these participants. All HC participants were right-handed and spoke fluent English before the age of five. No participant had a history of neurological or psychiatric disease or reported taking any prescription medications affecting the central nervous system.

2.2. Experimental design

Participants underwent fMRI scanning as they performed a verbal delayed free-recall task comprising three phases: encoding, arithmetic distractor, and free recall (Fig. 1). Participants were given instructions and performed practice trials prior to entering the scanner. During the scanning session, the onset of each phase was signaled by a 1 s presentation of the words “STUDY”, “MATH”, and “RECALL”, respectively. Participants completed a total of 18 Encoding-Recall cycles divided equally over six functional runs. Structural T1 MPRAGE scans were collected upon completion of the final Encoding-Recall cycle. The entire scanning session took approximately 65 min.

During encoding, participants studied word lists comprising a unique set of 15 concrete nouns. These words were selected at random, and without replacement, from the same experimental word pool that was used to generate the study lists employed with the TLE participants when they performed the free recall task while undergoing intra-cerebral recordings (see above). Consequently, there was overlap between the study lists employed with the patients in the present study and in the prior iEEG study (on average 57% of the study words employed here were also employed as study items previously). Additionally, 62% of the items employed as lures in the present recognition memory test (see below) were employed as study items in the iEEG sessions. A re-analysis of recognition memory performance after omitting the overlapping study and lure words did not significantly alter the pattern of the results reported below, suggesting that any influence of prior exposure to

experimental items in the TLE sample had dissipated before they undertook the fMRI session.

Each trial began with a red warning fixation cross presented for 500 ms followed by the presentation of a single word in white font for 1800 ms. Each word was followed by the presentation of a white fixation cross for 900 ms. An additional seven null trials (white fixation cross) were pseudo-randomly interspersed throughout each study list under the constraint that no more than three null trials occurred consecutively. This resulted in an inter-stimulus fixation interval that jittered between 900 and 9600 ms (mean ISI = ~1800 ms). Participants were instructed to form a mental image of the object denoted by each word and to refrain from saying the word aloud or rehearsing previously studied words.

After the encoding phase participants completed a 15 s arithmetic distractor task. They viewed math equations in the form of $A + B = C$ and had to indicate whether the expression was correct (e.g., '3 + 1 = 4?') or incorrect (e.g., '4 + 7 = 13?'). Participants indicated their responses via button press using their right index and middle fingers in a counterbalanced fashion. Each equation remained on the screen until a response was made. Participants were instructed to respond as quickly as possible while maintaining accuracy.

Upon completion of the distractor task, participants were prompted to verbally recall as many of the words from the prior list as they could remember, in any order. A green fixation cross was presented in the center of the screen for the entire 30 s duration of the recall phase. Verbal responses during this phase were recorded for later transcription using a scanner-compatible microphone (Optoacoustics) and noise-cancelling software (OptiMRI v. 3.2) to filter out scanner noise. As noted, audio recordings from two participants (one each from the HC and TLE groups) were unusable due to technical issues with the software. Participants were instructed to speak loudly and clearly with their eyes open while minimizing any unnecessary movement. They were also encouraged to avoid repetitions and any non-recall verbalization (e.g., "umm") as well as to avoid recalling words from earlier lists. Participants were encouraged to continue attempting to recall list items for the entire 30s duration.

A surprise recognition memory test was administered approximately 20 min after exiting the scanner. The test was undertaken on a laptop computer in a quiet exam room. The 270 items from the previously studied word lists were intermixed with 135 semantically unrelated new words and presented one at a time. Participants were instructed to judge whether each item had been studied previously or was new, signaling the confidence of their judgment via the following five response options: high confidence old, low confidence old, don't know (DK), low confidence new, high confidence new. Participants entered responses directly onto the laptop keyboard. Response mappings for old and new items were counterbalanced across participants (i.e., 1 = high confidence old/new, 2 = low confidence old/new, 3 = DK, 4 = low confidence new/old, 5 = high confidence new/old). The recognition test was self-paced under the instruction to respond as quickly as possible while maintaining accuracy. An opportunity to take a break was available every 81 trials.

2.3. MRI data acquisition and preprocessing

Functional and anatomical images were acquired with a 3T Philips Achieva MRI scanner (Philips Medical Systems, Andover, MA, USA) equipped with a 32-channel receiver head coil. Functional images were acquired using a T2*-weighted, blood-oxygen level-dependent echoplanar (EPI) sequence (sensitivity encoding [SENSE] factor 2, flip angle 70 deg, 80×78 matrix, field of view [FOV] = 24 cm, repetition time [TR] = 2000 ms, and echo time [TE] = 30 ms). EPI volumes consisted of 34 slices (1-mm interslice gap) with a voxel size of $3 \times 3 \times 3$ mm. slice were acquired in ascending order oriented parallel to the anterior commissure-posterior commissure line. Each functional run included 201 EPI volumes. T1-weighted anatomical images were acquired with a magnetization-prepared rapid gradient echo pulse sequence (FOV = 240×240 , $1 \times 1 \times 1$ mm isotropic voxels, 34 slices, sagittal acquisition). Participants performed a total of 18 study-test cycles split evenly across six scanning runs.

All fMRI preprocessing and analyses were conducted with Statistical Parametric Mapping (SPM12, Wellcome Department of Cognitive Neurology, London, UK), run under Matlab R2017a (MathWorks). Functional images were realigned to the mean EPI image and then slice-time corrected using sinc interpolation to the 17th slice. The images were then reoriented and spatially normalized to a sample-specific EPI template following previously published procedures (de Chastelaine et al., 2011, 2016). Normalized volumes were resampled into 3 mm isotropic voxels and smoothed with an isotropic 8 mm full-width half-maximum Gaussian kernel. Anatomical images were spatially normalized to a sample-specific T1 template following procedures analogous to those applied to the functional images. The data from the six scanning runs were concatenated using the `spm_fmri_concatenate` function.

2.4. Behavioral data analysis

All behavioral analyses were conducted with R software. *t*-tests were performed using the base package `t.test` function. ANOVAs were conducted using the `afex` package (Singmann et al., 2016) and the Greenhouse-Geisser procedure (Greenhouse and Geisser, 1959) was used to correct degrees of freedom for non-sphericity when necessary. Post-hoc tests on significant effects from the ANOVAs were conducted using the `emmeans` package (Lenth et al., 2018) and corrected for multiple comparisons using the Holm-Bonferroni procedure where appropriate. Descriptive statistics for free recall and recognition memory performance are reported in Table 2. Note that when the behavioral analyses were repeated using ANCOVAs to control for any effects of age on performance the results did not differ from those reported below.

2.5. MRI data analysis

The fMRI data were analyzed in two stages. At the first stage, a separate GLM was constructed for each participant. Parameter estimates from events of interest were then carried forward to second-level random effects factorial ANOVAs to test for group level effects. Separate GLMs were employed to identify subsequent memory effects associated with the free recall and recognition memory tasks.

2.5.1. Subsequent recall effects—Two events of interest from the encoding phase were included in the design matrix of the free recall analyses: study items that were subsequently recalled (R) and items that were subsequently forgotten (NR). Each event of interest was modeled with a delta function convolved with SPM's canonical hemodynamic response function (HRF) and its temporal and dispersion derivatives. The three 1s periods during which task cues were presented, the 15s duration arithmetic phase, and the 30s duration recall phase were each modeled as covariates of no interest, along with six regressors representing motion-related variance (three for rigid-body translation and three for rotation). Data from volumes showing a transient displacement of >1 mm or $>1^\circ$ in any direction were eliminated by defining them as covariates of no interest. Parameter estimates from the two events of interest were carried over to a second-level random effects 2×2 factorial mixed effects ANOVA treating group (HC, TLE) as a between subjects factor and subsequent recall status (R, NR) as a within subjects factor (note that in SPM, a pooled error term is estimated. Hence, the two main effects and their interaction were tested using a common error term).

2.5.2. Subsequent recognition effects—A similar approach was used to analyze the post-scan recognition memory task. Encoding trials were categorized into three events of interest: old items recognized with high confidence (HiHits), old items recognized with low confidence (LoHits), and old items that were incorrectly endorsed as 'New' or 'DK' (Miss/DK). Recognition hits were segregated by confidence in order to separately examine the neural correlates of the encoding of 'strong' and 'weak' memories (Squire et al., 2007; Wais et al., 2010). As for the recall analyses, each event of interest was modeled with a delta function convolved with SPM's canonical HRF and temporal and dispersion derivatives. Also as previously, task instructions, arithmetic and recall phases, and motion outliers were modeled as covariates of no interest. Parameter estimates from the events of interest were carried over to a second-level random effects 2×3 factorial ANOVA treating group (HC, TLE) as a between subjects factor and subsequent recognition status (HiHit, LoHit, Miss/DK) as a within subjects factor.

There was considerable overlap between study items that were later recalled and those that were later recognized (see Results 3.1.2.). We performed a follow-up analysis to further examine test-selective effects. For this analysis, encoding trials were sorted into three categories according to subsequent memory status on the two memory tests: study items that were freely recalled, items that were recognized but not recalled, and forgotten study items (neither recalled nor recognized). Note that freely recalled study items were entered into the design matrix collapsed across subsequent recognition memory status. This was necessitated by the limited number of study items that were freely recalled but not recognized during the later recognition memory test ($<10\%$ of trials, see Results 3.1.2.). The resulting three events of interest were specified in the first level design matrices and all other aspects of the models were specified as before. Parameter estimates for these events of interest were carried forward to a mixed effects 3×2 ANOVA.

2.5.3. Common and selective group effects

Whole brain analyses were conducted using F-contrasts derived from the respective ANOVA models. To identify effects common to the two groups, the across-group main effect of memory (height-threshold $p < .001$, uncorrected) was exclusively masked with the group \times subsequent memory interaction (liberally thresholded at $p < .1$). Thus, voxels were identified where a reliable across-group main effect was unmodified by effects due to group. Regions demonstrating subsequent memory effects that differed according to group were identified with the memory \times group interaction contrast (height-threshold $p < .001$, uncorrected). Family-wise error (FWE) corrected cluster-extent thresholds were estimated with the Gaussian random field method implemented in SPM12.

To test *a priori* predictions regarding hippocampal involvement during encoding, we applied small volume corrections (SVC) for each of the aforementioned contrasts within an anatomically defined bilateral hippocampal ROI. The ROI was manually traced on an anatomical T1 template averaged across a large dataset from our lab ($N = 136$) and spatially smoothed to approximate the smoothness of the functional data (de Chastelaine et al., 2017).

For each significant cluster ($p < .05$), we extracted parameter estimates for the BOLD responses elicited by the respective recall (R, NR) and recognition (HiHit, LoHit, Miss/DK) responses, averaged across all voxels falling within a 5 mm radius (3 mm for hippocampus) of the peak voxel. Given the wide range of ages in both groups, along with the known influence of age on memory performance, we submitted the extracted parameter estimates to separate ANCOVA models with factors of group and memory status, controlling for the effects of age. Controlling for the effects of age did not significantly alter any of the neural subsequent memory effects identified for the free recall and recognition memory tests that are reported below in analyses in which age was not employed as a covariate. Results of the ANCOVA models are available from the first author upon request.

3. Results

3.1. Behavioral results

3.1.1. Free recall—As illustrated in Fig. 2A, probability of free recall was numerically higher in HC compared to TLE participants; however, this difference was not statistically significant ($t(31.75) = 1.08$, $p = .287$). Additionally, total number of prior list intrusions did not significantly differ between the two groups ($t(32.67) = 0.20$, $p = .841$). To test for serial position effects on recall performance, we performed a mixed-factorial ANOVA in which group (TLE, HC) was treated as a between-subjects factor and serial position as a within-subjects factor. The ANOVA revealed a significant main effect of serial position on recall performance ($F_{(14, 462)} = 14.47$, $p < .001$) (Fig. 2B). Post-hoc pairwise comparisons between serial positions revealed that both groups demonstrated a significant primacy effect for the initial two words in each list as well as a significant recency effect for the final two words. The ANOVA also identified a significant interaction between group and serial position ($F_{(14, 462)} = 2.98$, $p < .001$). Inspection of Fig. 2B suggests that the interaction was driven by a tendency for TLE participants to recall fewer items from later in the study list. Post-hoc between-group comparisons between recall at each serial position were significant ($p < .05$)

prior to correction for multiple comparisons for study items occurring in the 10th, 11th, and 15th list positions. None of these effects, however, survived correction.

We next computed probability of first recall, a metric that identifies the probability of initiating free recall as a function of serial position in the study list (Howard and Kahana, 1999). As can be seen in Fig. 2C, both groups exhibited a clear tendency to initiate recall with the first studied item (i.e., primacy bias). A mixed-factorial ANOVA with factors of group and serial position identified a significant group \times serial position interaction ($F_{(14, 462)} = 3.58, p < .001$). Post-hoc between-group comparisons confirmed that the primacy bias for the initial study item was stronger in TLE relative to HC participants ($t_{(467)} = -6.16, p < .001$), and this effect remained significant after correcting for multiple comparisons (Note that the emmeans package in R computes a pooled standard error. Each pairwise comparison was therefore tested using a common error term). Probability of first recall for the other serial positions did not significantly vary between the two groups.

In tests of free recall, items studied in neighboring list positions typically have a higher likelihood of being successively recalled, a phenomenon known as the temporal contiguity effect (Kahana, 1996). Here, we computed lag conditional response probabilities (i.e., lag-CRPs; Kahana, 1996) to estimate temporal contiguity effects in HC and TLE participants. In brief, upon recalling an item i , lag-CRPs quantify the probability of next recalling an item that was initially studied in the $i \pm \text{lag}$ list position conditional on the total possible transitions for a given lag. As can be seen in Fig. 2D, both groups demonstrated strong temporal contiguity effects as evidenced by elevated transitional probabilities at shorter lags (illustrated by the peakedness of the lag-CRP curves). Moreover, both groups demonstrate canonical asymmetric lag-CRPs indicating a bias for forward (positive lags) rather than backward (negative lags) recall transitions (Kahana, 1996). To further qualify temporal contiguity effects, we estimated a summary measure of temporal clustering for each participant following the procedure described by Polyn et al. (2009). Scores on this measure can range from 0 to 1, with a score of 1 indicating perfect temporal clustering. The two groups did not significantly differ on this measure ($t_{(25.37)} = -1.24, p = .228$) (Table 2).

3.1.2. Recognition memory

Recognition accuracy was operationalized as $\text{pHit}/(\text{pHit} + \text{pFA})$ for each confidence bin (Wixted et al., 2010) and submitted to a 2 (HC, TLE) \times 2 (high, low confidence) factorial ANOVA. As illustrated in Fig. 3A, this analysis revealed a main effect of group ($F_{(1,32)} = 11.64, p = .002$), reflecting reduced recognition accuracy in TLE compared to HC participants. This analysis also identified a significant main effect of confidence ($F_{(1,32)} = 44.27, p < .001$), which was driven by higher accuracy for high vs. low confidence recognition hits. There was no group by confidence interaction on recognition accuracy.

To unpack the results further, we performed analogous 2 (group) \times 2 (confidence) ANOVAs on false alarm rates (proportion of new items erroneously endorsed as 'old') and hit rates (proportion of old items correctly endorsed as 'old'). For false alarms, the ANOVA revealed a significant main effect of group ($F_{(1,32)} = 11.23, p = .002$), driven by a higher proportion of false alarms in TLE compared to HC participants. There was no effect of confidence, and no group by confidence interaction for false alarm rate. For hit rate, we observed a

significant main effect of confidence ($F_{(1,32)} = 118.65, p < .001$), again reflecting a greater proportion of hits for high vs. low confidence items. There was no effect of group, and no group by confidence interaction for hit rate. One TLE participant demonstrated a particularly exaggerated false alarm rate (95%). Closer inspection revealed that this participant exhibited an exceptionally liberal response criterion, also endorsing 96% of test items as 'old'. Omitting the participant from the analyses did not however modify group differences in recognition accuracy ($F_{(1,31)} = 9.88, p = .004$) or false alarm rate ($F_{(1,31)} = 10.28, p < .001$).

Motivated by the observation of a differential false alarm rate in the two groups, we computed a response bias estimate, Br (Snodgrass and Corwin, 1998) for each participant. Higher values on this index indicate a more liberal bias. As illustrated in Fig. 3D and summarized in Table 2, this analysis identified a significant main effect of group ($F_{(1,32)} = 5.43, p = .026$) which reflected a more liberal response bias in TLE compared to HC participants. The group effect was no longer significant, however, after omitting data from the aforementioned outlying TLE participant ($F_{(1,31)} = 4.07, p = .052$). This result should therefore be interpreted cautiously. This analysis also identified a main effect of confidence ($F_{(1,32)} = 16.42, p < .001$), such that participants adopted a more liberal response criterion for items recognized with high confidence. This effect was unmodified by the inclusion of the outlying TLE participant. The interaction between group and recognition confidence was not significant.

Recognition memory response times (RTs) were categorized according to recognition status (hit, miss, correct rejection, false alarm) and confidence (high, low) and submitted to a 4 (recognition status) \times 2 (confidence) \times 2 (group) factorial ANOVA. The ANOVA revealed a significant recognition status \times confidence interaction ($F_{(3,84)} = 12.09, p < .001$). Post hoc analyses revealed faster RTs for hits compared to misses, correct rejections and false alarms, and slower RTs for misses compared to correct rejections and false alarms, although only for those items receiving a high confidence endorsement. Additionally, recognition RTs were faster for high than low confidence recognition judgments ($F_{(1,28)} = 53.13, p < .001$). We did not identify any significant effects of group.

The majority of successfully recalled study items went on to be recognized on the subsequent recognition memory test (90% for both groups). Moreover, recognition confidence for a given study item varied according to the item's prior recall status (Fig. 3E). Among HC participants, 48% of study items recognized with high confidence were also classified as free-recall hits, while only 24% of low confidence recognition hits had been previously recalled. Of the forgotten study items (i.e., old items incorrectly endorsed as 'New' or 'DK'), 10% had been previously recalled. The results were strikingly similar for the TLE participants: of those study items that were freely recalled, 45% were later recognized with high confidence, 24% were recognized with low confidence, and 10% were incorrectly classified as 'New' or 'DK'.

3.2. fMRI results

3.2.1. Subsequent recall effects—The results of the whole brain analyses identifying subsequent recall effects common to the two groups are illustrated in Fig. 4A and summarized in Table 3. Positive effects - regions demonstrating greater BOLD signal for

later recalled than later forgotten items - were identified in the left IFG and right cerebellum. Negative effects - regions where later recalled items elicited lower BOLD signals than did forgotten items - were evident in the left superior temporal gyrus and right anterior hippocampus (after SVC). Performing separate 2 (group) \times 2 (subsequent recall) ANOVAs of parameter estimates extracted from each of the clusters yielded non-significant main effects of group in the left IFG ($F_{(1,33)} = 0.33, p = .567$), left superior temporal gyrus ($F_{(1,33)} = 1.29, p = .265$), and right cerebellum ($F_{(1,33)} = 3.12, p = .087$). We did, however, identify a significant main effect of group in the right hippocampus ($F_{(1,33)} = 5.85, p = .021$) which was driven by greater hippocampal activity overall in HC relative to TLE participants. Consistent with the impression given by Fig. 5A, the interactions between group and subsequent recall were far from significant in all regions (all $ps > .1$). We thus found no evidence that positive or negative subsequent recall effects significantly differed between groups.

3.2.2. Subsequent recognition effects—We identified a main effect of subsequent recognition in the left IFG, which was evident for both high and low confidence recognition hits (Fig. 4B and Table 3). Negative effects were evident in several regions, again common to the two groups. These regions included right angular gyrus, medial prefrontal cortex, and posterior cingulate. Each of these negative effects was limited to study items recognized with high confidence. Submitting parameter estimates extracted from each of the regions to separate 2 (group) \times 3 (subsequent recognition status) ANOVAs failed to identify either a significant main effect of group (all $ps > .2$) or an interaction between group and subsequent recognition (all $ps > .3$) in any of the foregoing regions (see Fig. 5B). As for the recall task, therefore, we found no evidence that the magnitude of subsequent recognition effects were significantly moderated by group.

As already noted and illustrated in Fig. 3E, successfully recalled study items were highly likely to also be recognized on the subsequent recognition memory test. Motivated by these behavioral findings, we performed a follow-up analysis to identify subsequent memory effects that varied between the free recall and recognition memory tests (see Methods 2.5.2.). This analysis demonstrated that, in both groups, increased left IFG activity at encoding was predictive of subsequent memory for items that were freely recalled as well as those that were later recognized without recall. The magnitude of the left IFG effect was graded as a function of subsequent memory success (recalled $>$ recognized without recall $>$ forgotten; see Fig. 6).

This analysis also revealed that the aforementioned negative recognition memory effects identified in right lateralized posterior cingulate, medial prefrontal cortex, and angular gyrus were also evident for the free recall task, but only when contrasting later recalled study items with items that failed to be recalled or recognized. There was also evidence for a graded negative subsequent memory effect in the left superior temporal gyrus (recall $>$ recognition without recall $>$ forgotten; see Fig. 6). By contrast, the negative subsequent recall effect identified in the right anterior hippocampus was unique to the free recall task, that is, it was unmodified by whether or not non-recalled items were later recognized.

3.3. Hemisphere of ictal onset

The TLE sample examined in the present study was heterogeneous with respect to the hemisphere of epileptogenic origin. Because verbal memory deficits tend to be more pronounced in left relative to right TLE patients (e.g. Bonelli et al., 2010), we performed a follow-up analysis comparing behavioral and neural subsequent memory effects in TLE participants with left/bilateral vs. right ictal onset. Combining left and bilateral participants was necessitated by the small sample size of each respective subgroup. For each of the regions listed in Table 3, we submitted the extracted parameter estimates to a mixed-factorial ANOVA with factors of memory status (R, NR or HiHit, LoHit, Miss/DK) and hemisphere of ictal onset (Left/Bilateral, Right). Consistent with the impression given by Fig. 5, these analyses did not identify any regions where neural subsequent memory effects were significantly moderated by hemisphere of ictal onset (all $ps > .1$). In addition, side of ictal onset did not significantly moderate probability of free recall ($t_{(11,99)} = -1.01, p = .331$) or recognition accuracy ($F_{(1, 14)} = 0.72, p = .410$).

At the request of a reviewer, we performed an identical analysis, but with patients segregated according to whether ictal onset was of hippocampal ($N = 8$) or non-hippocampal ($N = 8$) origin (see Table 1). This analysis did not identify any regions where subsequent free recall effects were significantly moderated by site of ictal origin (all $ps > .1$). We did, however, identify a significant effect of ictal origin on the negative subsequent recognition effect in posterior cingulate ($F_{(1,14)} = 6.28, p = .025$), the magnitude of which was stronger in non-hippocampal compared to hippocampal TLE patients. All other subsequent recognition effects were unmoderated by ictal origin (all $ps > .08$). Nor did the two patient groups differ on behavioral measures of probability of free recall ($t_{(13,99)} = 0.23, p = .863$) or recognition accuracy ($F_{(1,14)} = 0.03, p = .823$).

4. Discussion

The present study used fMRI to compare the neural correlates of successful encoding in samples of TLE and HC participants. Subsequent memory effects predictive of successful free recall and recognition memory were evident in several neural regions in both groups of participants, most prominently in left inferior frontal gyrus. Importantly, we were unable to identify any subsequent memory effects that differed across the two groups. Behaviorally, the groups did not differ in overall recall performance or in the strength of temporal contiguity effects. However, group differences in serial position effects and false alarm rates were present in the free recall and recognition memory tasks, respectively.

4.1. Behavioral results

As just noted, recall probability did not significantly differ between groups. Both groups demonstrated clear primacy and recency effects (though see below regarding group differences in the magnitude of these effects) as well as strikingly similar temporal contiguity effects. The latter results suggest that the ability to form associations between study items and their temporal context (Howard and Kahana, 2002) was largely preserved in this selective sample of TLE patients. On their surface, these null effects of recall and temporal context may appear surprising given the consistently reported memory

impairments in ostensibly similar patient populations (Butler and Zeman, 2008). However, as previously noted (see Methods 2.1.1.), our TLE cohort was selected partly on the basis of prior success on a similar version of the free recall task and, in addition, did not show radiological evidence of hippocampal sclerosis.

Despite the null findings for overall recall performance and temporal contiguity, group differences in memory performance were present. Although both groups demonstrated clear primacy and recency effects, recall of items occurring in later list positions tended to be lower in the TLE participants. Notably, this drop-off in recall performance was evident from midway through the study list, negating the possibility that it merely reflected a smaller recency effect. Differential serial position effects were also evident for the probability of first recall. Although both groups demonstrated a significant tendency to initiate recall with the first-presented study item (i.e., primacy bias), the effect was markedly stronger among the TLE participants. One possibility is that the attentional resources directed towards each item belonging to a study list declined more quickly in the TLE participants, allowing more rehearsal of items occurring in the initial list positions at the expense of those occurring later in the list. Though speculative, this interpretation would account for the higher probability of first recall for initial list items in the TLE group compared to HC, as well as the relative decline of recall performance for study items occurring in later list positions.

In contrast to the null findings for free recall, recognition accuracy was markedly lower in the TLE relative to HC participants. This difference between the groups was driven by an elevated false alarm rate in the TLE participants; hit rates did not significantly differ between the groups. This pattern of results is consistent with the notion that TLE participants not only demonstrated lower discriminability than HC but also adopted a more liberal response criterion. This account is undermined however by the marginal group effect in response bias, at least as this was indexed by the Br metric. A second possibility is that the elevated false-alarm rate reflects impaired engagement of control processes supporting monitoring and evaluation of the outcome of a retrieval attempt (Burgess and Shallice, 1996; Rugg, 2004). Although this latter interpretation is speculative, it is consistent with prior findings of executive dysfunction in patients with epilepsy (Stretton and Thompson, 2012). By this interpretation, the recognition memory impairment we observed in our TLE participants is a consequence of a deficit in post-retrieval processing (Rugg, 2004) rather than in encoding, storage or the generation of retrieval cues in the test phase.

4.2. Neural subsequent memory effects

We did not identify any neural subsequent memory effects that differed in magnitude or location between the TLE and HC groups. The similarity of the effects across the two groups suggests that the functional neuroanatomy of successful episodic memory encoding was largely unaltered in our (highly selected) sample of TLE patients relative to the controls.

The most prominent subsequent memory effect - evident for both recall and recognition - was observed in the left IFG. Subsequent memory effects in the left IFG have been reported across a wide variety of study materials and paradigms, and especially in paradigms requiring or encouraging semantically oriented study processing (for reviews, see Kim, 2011; Spaniol et al., 2009). As has been previously reported (Staresina and Davachi, 2006),

activity in this region was graded with respect to subsequent memory performance (recall > recognized without recall > forgotten). On the assumption that items needed more effective encoding to go on to be successfully recalled than to be later recognized, this finding is consistent with the proposal that the magnitude of the left IFG subsequent memory effect co-varies with subsequent memory strength.

We also identified several regions where a relative attenuation of neural activity was predictive of later memory performance (so-called negative subsequent memory effects). As with the ‘positive’ left IFG effect just discussed, these effects were also invariant across the TLE and HC groups. In the case of recognition memory, we observed negative subsequent memory effects in several regions held to belong to the ‘default mode network’ (Buckner et al., 2008; Raichle et al., 2001), including the posterior cingulate, medial prefrontal cortex, and right angular gyrus. These findings replicate numerous prior reports of similar effects (e.g. Daselaar et al., 2004; Huijbers et al., 2011; Otten and Rugg, 2001; for review, see Kim, 2011), and likely reflect the benefit to encoding resulting from the allocation of attentional processes away from internal representations and toward external study events (Rugg et al., 2015).

Equivalently-sized negative subsequent memory effects in each of the aforementioned regions were also evident for the free recall task, but only when contrasting study items that went on to be successfully recalled with what might be considered ‘truly’ forgotten items, that is, items that failed to be either recalled or recognized (see Fig. 6). Thus, unlike the positive subsequent memory effects identified in the left IFG, these negative effects did not scale with memory strength, at least when strength is operationalized in terms of successful recall vs. successful recognition. One possible explanation for these findings is that the neural activity reflected by the negative effects contributed to encoding processes that specifically supported subsequent recognition memory and played no role in the encoding processes that supported subsequent recall. An alternate explanation is that the neural processing reflected by the negative effects contributed to the encoding of later recalled items, but that this required supplementation – perhaps from the left IFG – to confer the additional memory strength necessary for the items to be accessible to recall. The present data do not permit adjudication between these alternative accounts.

We also observed a negative subsequent memory effect in the right anterior hippocampus that was unique to the free recall task. As illustrated in Fig. 4A, the effect was driven by an increase in hippocampal activity (relative to baseline) for later non-recalled study items. This finding is seemingly at odds with prior fMRI studies reporting positive hippocampal effects for both subsequent free recall (Brassen et al., 2006; Dickerson et al., 2007; Staresina and Davachi, 2006; Strange et al., 2002) and subsequent recollection more generally (Kim, 2011; Spaniol et al., 2009). While the present result is surprising, it is not altogether without precedent (de Chastelaine and Rugg, 2015; Davachi et al., 2003; Shrager et al., 2008; Staresina and Davachi, 2008). One potential explanation (originally proposed by Shrager et al., 2008) is that negative hippocampal subsequent memory *effects reflect negative transfer appropriate processing*. By this account, increased hippocampal activity elicited by subsequently non-recalled study items reflects encoding of extraneous details of the study episode at the expense of item-specific information necessary for later free recall (de

Chastelaine and Rugg, 2015; Shrager et al., 2008; Staresina and Davachi, 2008). Thus, the increased hippocampal activity identified here for unrecalled items may indeed have reflected successful encoding, but of task-irrelevant details that were insufficient to support recall in the absence of an explicit retrieval cue. Intriguingly, a prior report of iEEG hippocampal subsequent recall effects described power decreases in the 9–28 Hz frequency range (Sederberg et al., 2003). It is conceivable that this finding is an electrophysiological correlate of the present fMRI findings. We caution however that this interpretation is purely speculative and requires further investigation.

In addition to the aforementioned negative subsequent memory effects identified in default mode regions, we also observed a negative effect in the left superior temporal gyrus in the vicinity of auditory cortex. The magnitude of the effect was graded with respect to subsequent memory status (free recall > recognition without recall > forgotten), suggesting that activity in this region covaried negatively with subsequent memory strength. The location of this effect in auditory cortex raises the possibility that successful encoding was more likely on trials on which there was suppression of auditory processing and, perhaps, a suppression of the otherwise distracting influence of scanner noise. This account is of course speculative, but it is consistent with a prior report that a relative enhancement of auditory cortex activity was predictive of encoding failure in older adults, a finding that, as here, was taken to reflect the deleterious effects of failing to suppress task-irrelevant, distracting sensory input (Stevens et al., 2008).

A potential caveat to interpretation of the current results is the small size and heterogeneity of the TLE cohort. Although heterogeneity has not generally precluded identification of reproducible subsequent memory effects in TLE patients who perform memory tasks during iEEG recordings, future studies controlling for factors such as hemisphere of ictal onset may be more sensitive to potential epilepsy-related changes in the neural circuitry supporting memory encoding. Another potential limitation stems from the relatively short study-test delays that were employed here (<1 min for recall, and <30min for recognition). Further research with TLE patients is required to characterize encoding-related activity that is predictive of memories that survive over longer study-test durations (see Uncapher and Rugg, 2005, for evidence of a dissociation between subsequent memory effects predictive of memory after short and longer delays), and to determine whether this activity differentiates TLE patients from healthy controls. Lastly, we reiterate that the sample of TLE participants reported here were free from hippocampal sclerosis and were selected on the basis of their ability to perform the free recall task. It is therefore premature to conclude that the null behavioral and neural findings reported here will generalize to a broader and even more heterogeneous TLE patient population. However, the characteristics of the present TLE sample are consistent with those of samples that typically contribute data to iEEG studies. Future studies will be necessary to establish whether similar behavioral and neural effects are evident in other forms of focal epilepsy.

5. Summary

Using fMRI, we identified several subsequent memory effects that were common to TLE and HC participants. Crucially, we did not identify any differences in encoding-related

activity between the two groups. These results help to bridge a critical gap in an emerging literature that describes findings from analogous subsequent memory procedures in the context of intracranial recordings employed to functionally map (Burke et al., 2014; Kucewicz et al., 2019; Kragel et al., 2017; Lega et al., 2012, Lega et al., 2016; Long and Kahana, 2015) or augment (Ezzyat et al., 2017, 2018; Kucewicz et al., 2018) memory encoding in patients with TLE. The present findings provide reassurance that the functional neuroanatomy supporting successful episodic memory encoding is largely unaltered in a selective sample TLE patients. Consequently, strategies initially developed to treat memory dysfunction in TLE patients may be transferable to individuals suffering memory disorders as a consequence of other etiologies.

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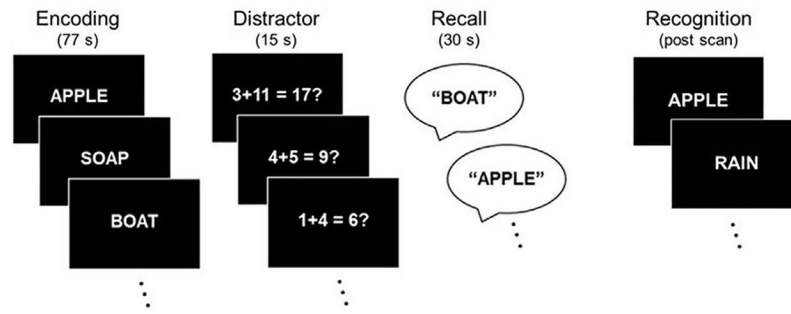


Fig. 1. Schematic of the free recall and recognition memory tasks. Participants performed 18 study-test cycles divided evenly over six functional scanner runs. During each cycle, participants first studied lists of 15 concrete nouns followed by a 15s arithmetic distractor task. Participants were then given 30s to freely recall items from the previously studied list in any order. After the scanning session, participants performed a recognition memory task requiring old/new judgments and confidence ratings.

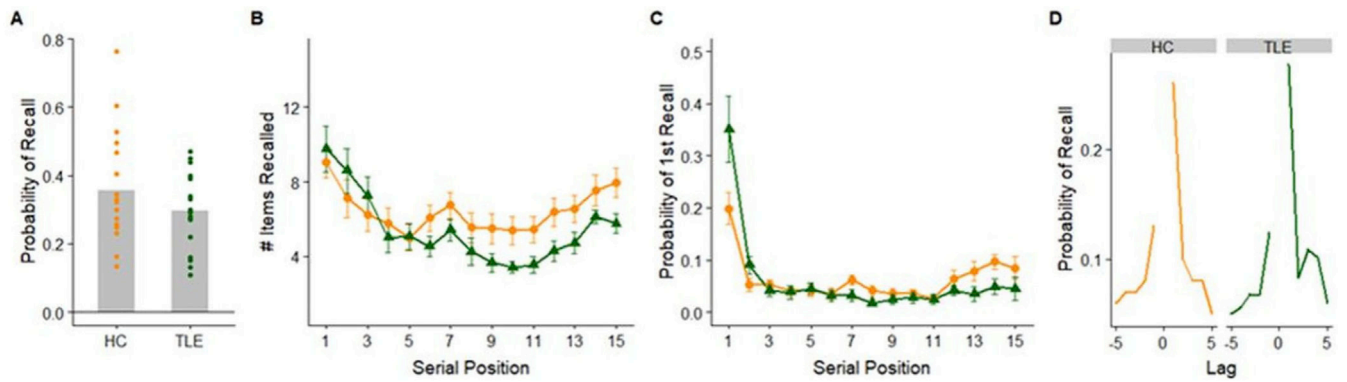
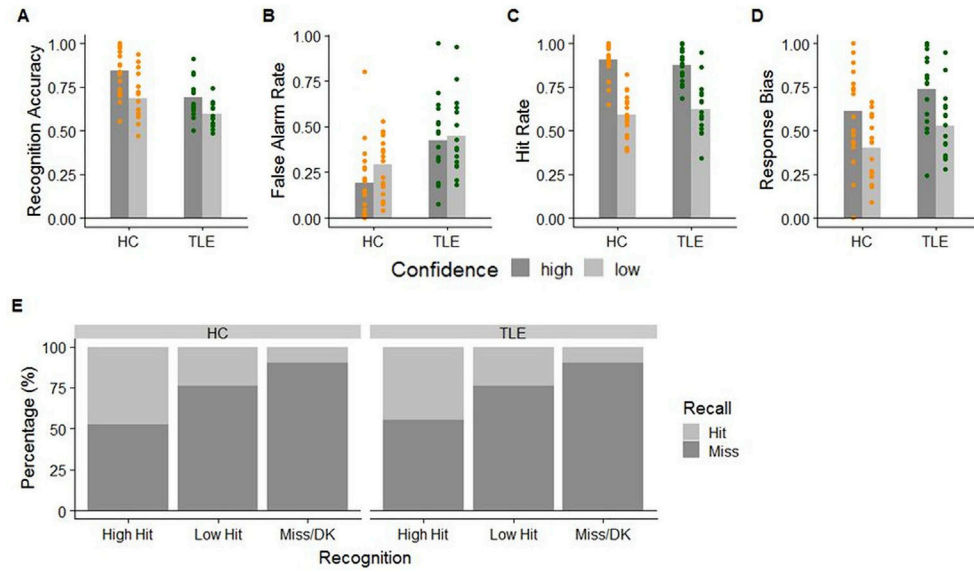


Fig. 2.

Behavioral performance on the free recall task. For display purposes, data are collapsed across sessions for each subject and then averaged across subjects within each group. Error bars represent 1 SE. (A) Probability of freely recalling a study item. (B) Serial position curves showing recall performance as a function of list position demonstrate primacy and recency effects in each group. (C) Probability of first recall curves indicate a tendency to initiate recall with the initial item from the study list. (D) Lag-CRP curves demonstrating temporal contiguity effects in each group. Both groups show canonical asymmetric peaks around zero indicating a tendency to recall items studied in adjacent positions, but with a more pronounced tendency for forward transitions. For (B) and (C), orange circles = HC, green triangles = TLE.

**Fig. 3.**

Behavioral performance on the post-scan recognition memory task collapsed across confidence ratings. For display purposes, data are collapsed across sessions for each subject and then averaged across subjects within each group. (A) Recognition accuracy was calculated as the proportion of old and new items endorsed as old. (B) The false alarm rate was computed as the probability of erroneously endorsing a new item as old. (C) The hit rate was computed as the probability of correctly endorsing an old item as old. (D) An estimate of response bias. Higher values reflect a more liberal response bias. (E) Stacked bar plots showing item recognition as a function of prior recall status.

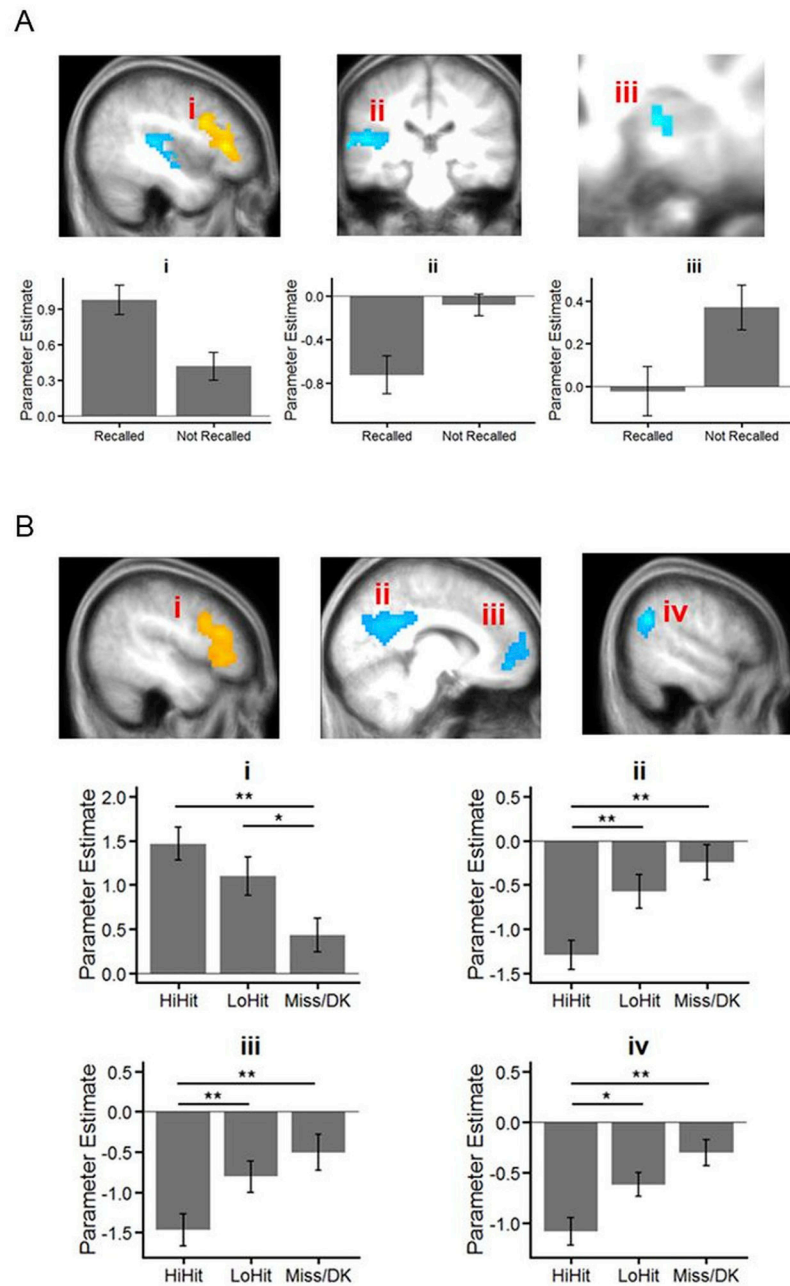


Fig. 4. Clusters demonstrating cross-group subsequent memory effects displayed on sections of the across-group mean T1-weighted structural image. Warm and cool colors correspond to positive and negative subsequent memory effects, respectively. (A) Subsequent recall effects. Mean parameter estimates and standard errors for subsequently recalled (R) and forgotten (NR) study items are plotted for left inferior frontal gyrus (i), left superior temporal gyrus (ii), and right anterior hippocampus (iii). (B) Subsequent recognition effects. Mean parameter estimates and standard errors for study items recognized with high (HiHit) and low (LoHit) confidence as well as recognition misses (Miss/DK) are plotted for left inferior

frontal gyrus (i), posterior cingulate (ii), medial prefrontal cortex (iii), and right angular gyrus (iv). $*p < .01$, $**p < .001$.

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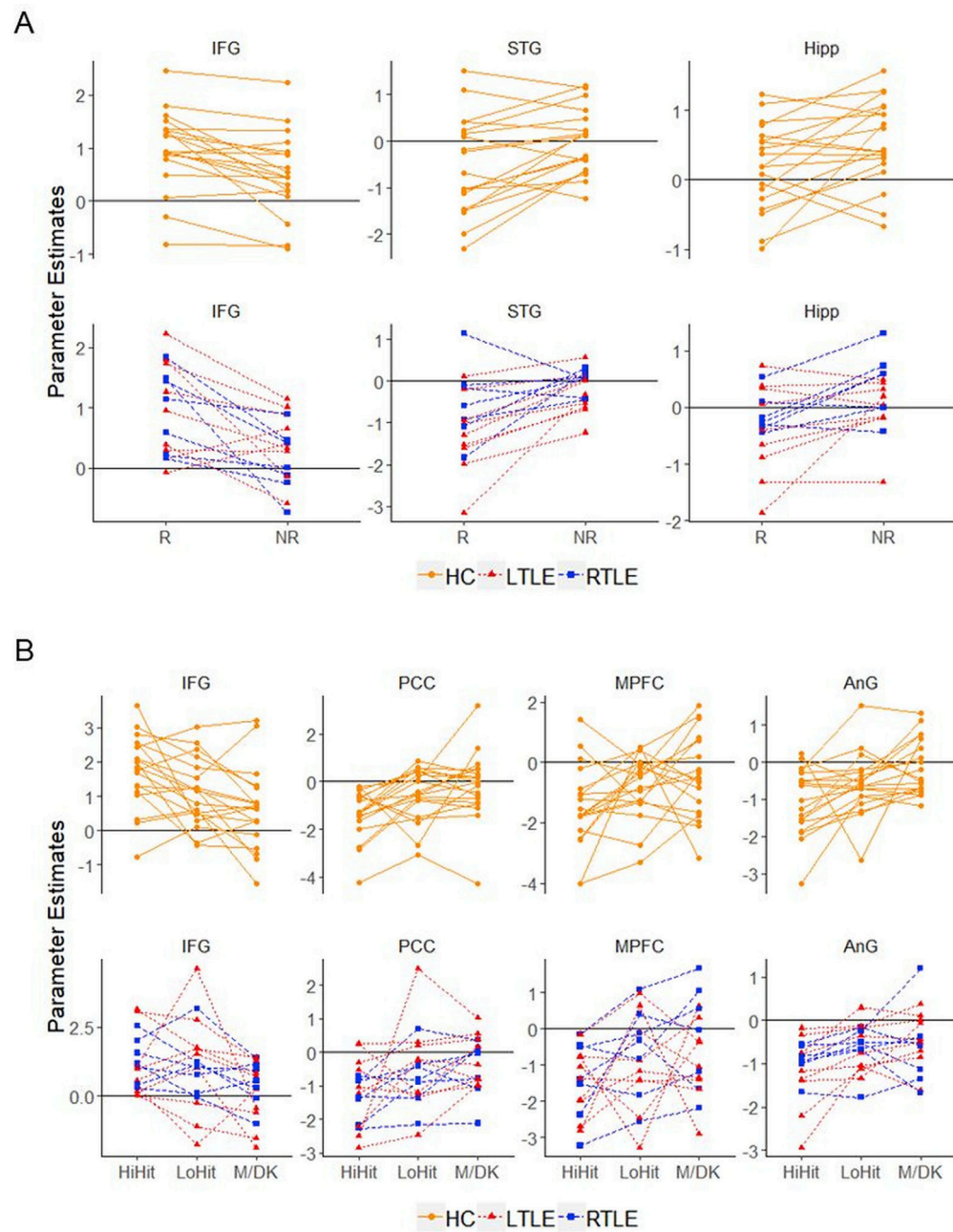


Fig. 5. Parameter estimates for each participant corresponding to events of interest from the (A) free recall and (B) recognition memory tests are plotted separately for HC (top panels) and TLE (bottom panels) participants. TLE participants were further segregated into subgroups according to the hemisphere of ictal onset. Left/bilateral TLE participants (LTLE) are plotted in red. Right TLE participants (RTLE) are plotted in blue.

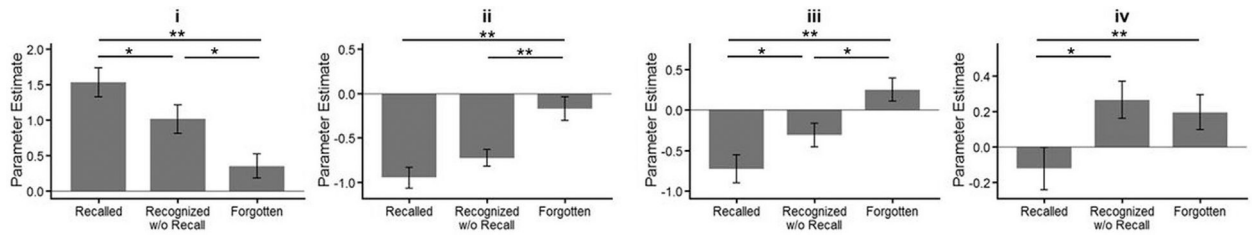


Fig. 6.

Mean parameter estimates and standard errors for study items that were recalled, recognized without recall, and forgotten (neither recalled nor recognized). Parameter estimates are plotted for the left inferior frontal gyrus (i), averaged across right posterior cingulate, medial prefrontal cortex, and angular gyrus (ii), left superior temporal gyrus (iii), and right anterior hippocampus (iv).

Table 1

TLE characteristics.

ID	Age	Ictal Duration (yrs)	Hemisphere of Ictal Onset	Ictal Onset	Post-scan Surgery	Handedness	Antiepileptic Medications (#)
UT011	59	26	Bilateral	B. temporal lobe	None	R	3
UT014	47	2	Right	R. anterior hipp, temporal cortex	R. temporal lobectomy	R	3
UT019	48	5	Right	R. hipp, amyg	R. temporal lobectomy	L	1
UT028	24	18	Right	R. MTG, anterior temporal lobe	R. MTG resection	R	2
UT034	26	22	Left	L. hipp, amyg	L. anterior temporal resection	R	2
UT035	37	35	Bilateral	L. hipp	RNS bilateral hipp	R	3
UT039	39	12	Bilateral	L. hipp, R. fusiform gyrus	RNS bilateral hipp & fusiform gyrus	R	4
UT041	46	11	Right	R. hipp, amyg	R. anterior temporal lobectomy	L	2
UT044	33	25	Right	R. anterior MTG	R. anterior temporal lobectomy	R	4
UT050	43	20	Left	L. hipp	RNS bilateral hipp	R	4
UT060	20	2	Bilateral	B. temporal lobe	R. anterior temporal lobectomy	R	3
UT068	44	19	Left	L. posterior MTG	L. temporal pole resection	R	3
UT080	23	8	Left	L. fusiform gyrus	RNS L. fusiform gyrus	R	1
UT096	21	1	Right	R. operculo-insular	R. insula resection	L	2
UT104	26	2	Right	R. hipp, temporal lobe	R. anterior temporal lobectomy	R	2
UT114	42	8	Left	L. operculo-insular	L. insula LiTT & RNS	R	2

Notes: hipp = hippocampus, amyg = amygdala, MTG = middle temporal gyrus, B = bilateral, R = right, L = left, RNS = responsive neurostimulation device, LiTT = laser interstitial thermal therapy

Table 2

Means (standard deviations) of recall and recognition memory estimates.

			High Confidence		Low Confidence	
	HC	TLE	HC	TLE	HC	TLE
Recall Probability	.36 (.16)	.30 (.11)	–	–	–	–
Intrusions (Total #)	5.47 (6.24)	4.92 (5.62)	–	–	–	–
Temporal Clustering Factor	.61 (.06)	.64 (.09)	–	–	–	–
Recognition Accuracy	.78 (.10)	.67 (.08)	.84 (.13)	.69 (.11)	.68 (.13)	.59 (.08)
Hit Rate	.79 (.12)	.78 (.11)	.90 (.10)	.88 (.09)	.58 (.12)	.62 (.15)
False Alarm Rate	.23 (.12)	.41 (.19)	.18 (.20)	.43 (.23)	.29 (.15)	.45 (.21)
Response Bias	.53 (.16)	.63 (.17)	.64 (.30)	.74 (.21)	.40 (.18)	.53 (.19)

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Table 3

Loci of subsequent memory effects.

Contrast	MNI			Peak z	Cluster Size	Region
	x	y	z			
Recalled > Not Recalled	-45	29	8	4.61	335	L. Inferior Frontal Gyrus
	33	-67	-28	4.38	104	R. Cerebellum
Not Recalled > Recalled	-54	-28	11	4.63	307	L. Superior Temporal Gyrus
	24	-16	-19	3.69	13	R. Anterior Hippocampus ^t
HiHit + LoHit > Miss/DK	-48	26	20	4.83	452	L. Inferior Frontal Gyrus
Miss/DK > HiHit	57	-55	29	5.81	148	R. Angular Gyrus
	9	-49	29	5.22	641	R. Posterior Cingulate
	9	50	-7	4.42	202	R. Medial Prefrontal Cortex

Notes: height threshold $p < .001$ (uncorrected), cluster-extent threshold $p < .05$ (FWER corrected).

^tSignificant after a *priori* small volume correction.

R = right, L = left, B = bilateral.