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Extent of single-neuron activity modulation by hippocampal interictal discharges predicts declarative memory disruption in humans

Abbreviated title: Disruption of human declarative memory by IEDs

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Abstract

Memory deficits are common in epilepsy patients. In these patients, the interictal electroencephalography commonly shows interictal epileptiform discharges (IEDs). While IEDs are associated with transient cognitive impairments, it remains poorly understood why this is. We investigated the effects of human (male and female) hippocampal IEDs on single-neuron activity during a memory task in patients with medically-refractory epilepsy undergoing depth electrode monitoring. We quantified the effects of hippocampal IEDs on single-neuron activity and the impact of this modulation on subjectively declared memory strength. Across all recorded neurons, the activity of 50/728 neurons were significantly modulated by IEDs, with the strongest modulation in the MTL (33/416) and in particular the right hippocampus (12/58). Putative inhibitory neurons, as identified by their extracellular signature, where more likely to be modulated by IEDs than putative excitatory neurons (19/157 vs. 31/571). Behaviorally, the occurrence of hippocampal IEDs was accompanied by a disruption of recognition of familiar images only if they occurred up to 2s before stimulus onset. In contrast, IEDs did not impair encoding or recognition of novel images, indicating high temporal and task specificity of the effects of IEDs. The degree of modulation of individual neurons by an IED correlated with the declared confidence of a retrieval trial, with higher firing rates indicative of reduced confidence. Together, this data links the transient modulation of individual neurons by IEDs to specific declarative memory deficits in specific cell types, thereby revealing a mechanism by which IEDs disrupt MTL-dependent declarative memory retrieval processes.

Significance statement

Interictal epileptiform discharges (IEDs) are thought to be a cause of memory deficits in chronic epilepsy patients, but the underlying mechanisms are not understood. Utilizing single-neuron recordings in epilepsy patients, we found that hippocampal IEDs transiently change firing of hippocampal neurons and disrupted selectively the retrieval, but not encoding, of declarative memories. The extent of the modulation of the individual firing of hippocampal neurons by an IED predicted the extent of reduction of subjective retrieval confidence. Together, this data reveal a specific kind of transient cognitive impairment caused by IEDs and link this impairment

to the modulation of the activity of individual neurons. Understanding the mechanisms by which IEDs impact memory is critical for understanding memory impairments in epilepsy patients.

Introduction

Cognitive deficits are common in chronic epilepsy patients. The exact mechanism underlying these deficits is unclear, and may be due to structural damage, ongoing abnormal electrical activation, medication side effects, or a combination of these processes. Interictal discharges (IEDs) are brief high-amplitude pathological discharges commonly seen in-between seizures in some epilepsy patients (Cohen et al. 2002; de Curtis et al. 1999; de Curtis and Avanzini 2001). These discharges typically occur within or around the seizure onset zone. Although IEDs are typically considered to be asymptomatic, there is some evidence that they are related to brief lapses in cognition (Aarts et al. 1984; Aldenkamp et al. 2004; Aldenkamp and Arends 2004; Horak et al. 2017; Ung et al. 2017).

Most prior work on the relationship between epileptic IEDs and cognition has been performed using scalp EEG (Aarts et al. 1984; Rausch et al. 1978; Schwab 1939). Because the extent to which IEDs originating from the hippocampus and other deep structures can be captured using scalp EEG is limited, it remains unclear how hippocampal memory processes are modulated by IEDs. More recently, work utilizing intracranial EEG (implanted depth or subdural grid electrodes) in epilepsy patients has started to reveal a better understanding of the relationship between neural activity, cognitive processes, and their impairment by IEDs (Horak et al. 2017; Kleen et al. 2013; Ung et al. 2017). Several studies have found that the occurrence of IEDs recorded with intracranial electrodes correlates with impaired behavioral performance in working memory (Kleen et al. 2013; Krauss et al. 1997) and delayed free recall tasks (Horak et al. 2017; Kleen et al. 2013). Moreover, it was found that IEDs outside a left-hemispheric seizure onset zone impacted memory encoding, recall and retrieval, while those inside the seizure onset zone did not (Ung et al. 2017). While these studies reveal correlations between the occurrence of IEDs and behavioral effects, it remains unknown why IEDs are indicative of such impairment and what specific neuronal processes they disrupt. In particular, the temporal specificity between the occurrence of an IED and the disruption of the observed memory deficits is unclear.

IEDs are thought to be the result of large synchronous bursts of neuronal activity. In humans, this view is supported by a small number of pioneering single-neuron studies that have revealed that a subset of up to ~30% of neurons increase or decrease their firing transiently prior or during an IED (Alarcon et al. 2012; Alvarado-Rojas et al. 2013). The sparse and highly variable involvement of ~30-40% of neurons during an IED makes it difficult to study its exact role in this abnormal network activity. While these studies reveal prominent modulation of single-neuron activity by IEDs, it remains unknown whether such modulation is detrimental to memory performance or whether, alternatively, the neurons engaged in a particular task are not influenced by IEDs.

We utilized hybrid depth electrodes in human epilepsy patients to study the relationship between single neuron activity and hippocampal IEDs during a hippocampal memory-dependent new/old recognition memory task that is frequently utilized to study aspects of human declarative memory. In this task, subjects were first shown a series of novel images ("encoding"). Later, subjects were again shown the same images randomly intermixed with novel images not seen before ("retrieval"). During retrieval patients were asked to indicate if a displayed image was new or old, and how confident they were in their decision. This allowed us to study the effects of IEDs during both encoding and retrieval. This task has been widely studied in humans using a variety of techniques, including scalp EEG, single-neuron activity and functional MRI (fMRI) (Fried I. 2014; Guerin and Miller 2009; Rugg and Curran 2007), making it well suited to study the effects of hippocampal IEDs in patients with medically refractory epilepsy undergoing depth electrode invasive intracranial monitoring to localize seizures.

Materials and Methods

Subjects

Nineteen patients (Table 1) with intractable epilepsy underwent depth electrode monitoring for localization of the seizure focus as part of their pre-surgical plan for resection. Of the nineteen patients, we excluded two from analysis because they had no IEDs during the task and five because they had a seizure less than an hour prior to, or after testing. In total twenty-three behavioral testing sessions were analyzed. Two patients had 3 sessions of the task, and the rest had only one session. We also excluded one patient (P32) that only had generalized spike and

wave discharges, leaving eleven patients (13 sessions) with hippocampal IEDs for the final analysis. The study was approved by the Cedars-Sinai Institutional Review Board (IRB #13369) and all patients provided written informed consent. Electrode localization was based on clinical criteria only.

Experimental Design:

Memory Task

The task used has been previously described (Faraut et al. 2018; Rutishauser et al. 2015). There are three versions of the task, which are all identical, except for the images shown. Each stimulus set contains images chosen from five different visual categories, (cars, food, people, landscape, animals), with an equal number of instances chosen from each. The experiment consisted of two parts: a learning block and a recognition block (Fig. 1C). During the learning block, subjects were shown 100 new images. Each image was only shown once for 1 second. During the recognition block, a random subset of 50 of these images was shown again ('old'), and randomly mixed with a set of 50 new images. After each image, subjects were asked whether they had seen this identical image before ('old') or not ('new') and with what confidence. Subjects provided their answer on a 1–6 confidence scale as following: 1=new, very sure; 2=new, sure; 3=new, guess; 4=old, guess; 5=old, sure; 6=old, very sure. Patients provided their answers by pressing buttons on an external response box (RB-740, Cedrus Inc.). The task was implemented in MATLAB using the Psychophysics toolbox.

Electrode and Data acquisition

All recordings were performed with hybrid (macro-micro) depth electrodes (BF08R-SP05X-000 Behnke-Fried and WB09R-SP00X-0B6; AdTech Medical Inc). Each electrode contained an inner bundle of eight 40 µm diameter microwires that protruded 4-5 mm from the distal end of the clinical electrode and could record single neuron extracellular action potentials (single-units) (Fried et al. 1999). The signal from each microwire was locally referenced to one of the eight microwires, thus allowing the recording of activity from seven microwires in each area. Data was recorded broadband (0.1–9,000 Hz filter) sampled at 32 kHz using either an Atlas or Cheetah (Neuralynx Inc) system.

All patients were implanted in the hippocampus, amygdala, presupplementary motor area (pre-SMA), anterior cingulate and orbitofrontal cortex. Throughout the manuscript, medial temporal

lobe refers to amygdala and hippocampus together. Similarly, we refer to all cortical recording sites together as medial frontal cortex (MFC). One patient was implanted with additional electrodes in the insular cortex, and one had additional electrodes placed in the lateral anterior temporal neocortical areas identified as a possible epileptogenic zone with Magnetoencephalogram (MEG). We only performed single-neuron recordings from amygdala, hippocampus, dACC, pre-SMA, and OFC; thus, our focus here is only on these brain areas.

Statistical Analysis:

Action potential ("Spike detection") and sorting

For each channel, the raw signal was band pass filtered 300-3,000 Hz. Activity was sorted to identify putative individual neurons using the semiautomatic template-matching algorithm OSort, that is available as open source (Rutishauser et al. 2006a). This method has been described in detail (Faraut et al. 2018).

Identification of Interictal discharges (IEDs)

Given the poor inter-rater reliability of automatic IED detection (Gaspard et al. 2014), we used visual inspection of the macro and micro channels to detect IEDs. Each identified IED was manually validated by a board certified epileptologist (C.R.). Discharges on hippocampal micro and macroelectrode recording showing a biphasic or triphasic morphology with an initial fast phase of 200 msec or less were chosen (Fig.2A). These discharges may or may not have been followed by an after-going slow wave. Time zero was defined as the first change from the baseline of the fast component (Fig. 2A; Vertical line). Note that others sometimes use the peak of the fast component as time zero (Keller et al. 2010). Recordings were bilateral and we marked right and left IEDs independently. Thus, in the few patients that had hippocampal IEDs occurring bilaterally, not simultaneously, we designated these as separate events. For the purpose of this study, we identified IEDs only on the hippocampal contacts. However, we found that ~99% of these IEDs were also visible on the amygdala micro-electrode contacts in the amygdala and could thus be designated as medial temporal IEDs. However, given that the time stamps were generated from the hippocampal micro-electrode contact, we refer to them here as hippocampal IEDs throughout.

One patient had both independent hippocampal and generalized spike and wave discharges. For this patient, the generalized and hippocampal IEDs were marked separately. IEDs were selected during the entire new/old task on the microelectrode recording and confirmed with the macroelectrode recording. Since we wanted to avoid peri-ictal or ictal related discharges (Gotman and Koffler 1989; Karoly et al. 2016) we eliminated sessions in which an ictal event occurred less than an hour prior to start of the task. IEDs were inspected and marked in EEGLAB with the VisEd plugin (Delorme and Makeig 2004). The median rate of IEDs across all subjects were 0.0863 per second (0.007-0.442/second, SD ± 0.1419).

Electrode localization

For each patient the microelectrode positions were localized from MRI scans performed after implantation of electrodes. These scans were registered to pre-operative MRI scans using Freesurfer's MRI_robust_register as described previously (Faraut et al. 2018) (Fig.1).

Data analysis of modulation of single-neuron firing by IEDs

We examined in total 728 isolated single units across 11 patients. To quantify the time course of IED-related modulation of single-neuron activity, time zero ("start of the IED") was identified as the first change from the baseline of the fast component of the IED, not the peak of the fast component as mentioned by Keller et al. (Keller et al. 2010) (see * in Fig. 2a). We defined a neuron to be modulated by an IED if the neurons firing rate during the 0-50 msec time period following the start of the IED was significantly different from that of the firing rate within 50ms before the IED (-50-0 ms), evaluated using a two-tailed ttest at $p<0.05$. We further quantified the modulation of the activity of a neuron by an IED using a modulation index (MI), defined as MI= (mean firing rate after IED) – (mean firing rate before IED)/ (mean firing rate after IED+mean firing rate before IED). Here, the mean firing rate was again quantified in 50ms bins before/after t=0 of IED onset. An MI of 0 indicated no modulation. A negative MI indicates a decrease in the neuronal firing rate due to the IED, and a positive MI indicates an increase in firing rate due to the IED. We in addition also calculated Cohen'd, defined as score = (mean firing rate after IED) – (mean firing rate before IED)/ standard deviation, to further characterize the strength of modulation. Here as above, the mean firing rate was quantified in 50ms bins before/after t=0 of IED onset.

To visualize the IED-related modulation in firing rate for each neuron, we plotted the normalized PSTHs of the neurons as a heatmap (e.g. Figure 3b). In these plots, each row represents a neuron, each column is a time bin (25 ms), and the color indicates the change in firing rate from baseline (e.g. a value of 3 indicates the firing rate is 3 time higher than baseline). Neurons are sorted in descending order by the strength of their firing rate modulation.

Extracellular spike waveform analysis

We used the extracellular waveform width to differentiate between different putative neuronal types (Bartho et al. 2004; Mitchell et al. 2007; Rutishauser et al. 2015; Takahashi et al. 2015). For each neuron we calculated the trough-to-peak width of the average extracellular action potential. The trough was identified as the timepoint when the waveform was largest, and the peak is the first local maximum after the trough. The distribution of spike widths was bimodal (Fig. 4A), as often observed in extracellular recordings. We classified cells as being narrow or wide spiking by performing k-means clustering on the trough-to-peak width of the spikes, selecting for two k-means groups.

Visualization

For plotting purposes, we binned each neuron's firing rate into 50 msec bins and averaged the firing rate over all neurons in order to calculate the peri-stimulus time histogram (PSTH) (Koch 1999).

Identification of selective cells

We characterized subsets of MTL cells according to their response to the visual category and novelty/familiarity of the presented visual stimuli as previously described. Briefly, a cell was characterized as visually selective (VS) if its response in a 1.5s window starting 200ms after stimulus onset was significantly modulated by the visual category of the stimulus (one-way ANOVA, $p<0.05$) (Faraut et al. 2018; Rutishauser et al. 2015). A cell was classified as memory selective (MS) if its response in the same time window differed significantly as a function of whether the presented stimulus was novel or familiar (bootstrap test, $p<0.05$) (Faraut et al. 2018; Rutishauser et al. 2015). Cells whose firing rate after stimulus onset across all trials differed significantly relative to baseline were classified as visually response (VR) cells). Some cells qualified as multiple types. Cells that were not classified as neither VS, MS, or VR cells were categorized as Non-significant cells (NS).

Testing influence of IEDs on Behavior

We used a GLM to test whether the likelihood that an image was correctly recognized or encoded varied as a function of whether an IED occurred within a given period of time in a given trial. For each trial of interest, we first determined the number of IEDs E (>=0) that occurred within the time window of interest (a 3s window, advanced from -3s to +5s relative to image onset) and whether the trial was correctly recognized or encoded C (0 or 1). We then fit the generalized linear model (GLM) 'C ~ 1 + E + (1|ID)', where ID is a random factor that specifies the session ID. We fit this GLM to the data using a binomial response distribution function using *fitglme* in Matlab.

To compare how well this model explained the data for different types of trials (recognition old, recognition new, learning trials) we used two approaches: i) we compared the size of the weight for variable E between different models (each fit to one the three trial types), and ii) we compared, for each model, whether it explained more variance compared to a null model. We compared the size of the estimated weight α_E of the model parameter E using its exponential, i.e. $\exp(\alpha_E)$. This way, a weight of 0 is equivalent to an odds ratio of 1 (indicating no influence on the outcome). To estimate the significance of α_E, we estimated the null distribution of α_E at every point of time using a permutation test (10,000 iterations). During every iteration, we first scrambled the order of the variable C (within each session), thereby preserving the average behavioral performance of each subject but destroying the trial-by-trial relationship. Using this null distribution, we then estimated the significance of α_E. To estimate whether IEDs contributed significantly to explaining the data, we compared the fit to a null model without the model parameter E (null model specification 'C ~ 1 + (1|ID)'. We compared the full and null model using the log likelihood ratio. In addition to odds and log likelihood ratio we confirmed the results also using Akaike information criterion (AIC) to compare two models.

Testing influence of IED-mediated neuronal modulation on behavior

We used a generalized linear model (GLM) to test whether the degree to which the activity of individual neurons was modulated by the occurrence of an IED was predictive of impairments of memory retrieval, here assessed by the confidence reported by the subject for each trial. The model we used was 'Conf ~ 1 + A + E + (1|CellID) + (1|SessionID)', where A is the number of spikes that a neuron fired during a given IED, E is the number of IEDs that occurred in this trial

(here E≥1), Conf is the confidence reported for this trial (high=1 or low=0), and CellID and SessionID are random factors to account for differences across neurons and patients. For this analysis, only neurons in the MTL significantly modulated by IEDs were included. Also, only trials during which at least one IED occurred were included (because the firing rate relative to an IED is undefined if there was no IED in a trial). The number of IEDs in each trial were counted in a 3s time window, starting at -500ms prior to IED onset (see Fig. 6C). To assess whether knowing the level of neuronal activity increased predictability, we compared this model to two different null models. Null model 1 was 'Conf ~ 1 + E + (1|CellID) + (1|SessionID)', which is identical to the full model except the term A, thereby examining whether knowing the activity of neurons increases predictability beyond that already provided by the number of IEDs in a trial. Null model 2 was 'Conf ~ 1 + A + (1|CellID) + (1|SessionID)', thereby examining whether knowing the number of IEDs in addition to neural activity provides additional explanatory power. The number of spikes fired by a neuron A was counted in a window of size 100ms. For the time course (Fig. 6D), the position of this window was moved from -200ms to +200ms relative to IED onset (which was at t=0) in steps of 5 ms. For the fixed time window analysis (Fig. 6C), spikes were counted in the window -130 to 30ms relative to IED onset (this window was picked because of the timecourse shown in Fig. 6D shows). For the model confidence was computed as a binary index (high or low), and not a 6-point scale.

Results

Clinical characteristics of patients

The mean age of the patients was 49 ± 17.14 years (SD) (minimum 24, maximum 70). The most common etiology of the patients' epilepsy was medial temporal sclerosis. One patient had insular onset of unclear etiology, and two had bitemporal onset of their seizures. Resection was offered to 8 of these patients.

Hippocampal IEDs preferentially modulate single neurons in the MTL

A total of 1871 hippocampal IEDs (Fig. 2A, 40% Right hippocampal, 60% Left hippocampal) were identified from 11 patients (Table 1). 728 single units and 1871 IEDs were analyzed across 13 sessions. We first tested, for every neuron, whether its activity was significantly modulated by the occurrence of a hippocampal IED (two-tailed ttest, $p<0.05$, of firing rate quantified in bins of

50ms before vs. after the IED). An example of a significantly modulated unit in the right hippocampus is shown in Figure 2. We found that across all brain areas and patients, a small proportion of neurons (6.8 %, N=50/728, Binomial, P=0.016) were modulated by hippocampal IEDs. The extent of modulation differed significantly as a function of brain area (χ^2 test of association between brain areas Amygdala, Hippocampus, and Cortex and proportion of modulated cells: $\chi^2(2)=9.6$, p=0.008; also see Table 2). Post-hoc comparisons revealed that the proportion of neurons modulated in the hippocampus was significantly larger compared to both amygdala ($\chi^2(1)=6.90$, p=0.009) and cortex ($\chi^2(1)=6.94$, p=0.008). For all recorded MTL neurons, a significant proportion were modulated (33/416, Binomial, p=0.007). Comparing between different hemispheres, modulation was significantly higher for neurons recorded from the right compared to the left hippocampus ($\chi^2(1)=5.93$, p=0.015; 20% (N=12/58) vs. 7.6% (N=8/105), respectively). The proportion of modulated cells was not significantly different from that expected by chance in the amygdala (right: 5.21%, N=6/115, Binomial, p=0.52; left: 5%, N=7/138, Binomial, P=0.54) and did not differ significantly between the left vs. right side ($\chi^2(1)=0.001$, p=0.97). In the medial temporal lobe, the majority of modulated neurons (75.75%, n=25/33) were contralateral to the seizure-onset zone. Additionally, a majority of the right temporal lobe neurons modulated by IEDs (88.8%, n=16/18) were contralateral to a left hemispheric seizure onset zone. We next tested whether neurons recorded in the cortex are modulated by hippocampal IEDs. Across all cortical areas recorded from, a relatively small and not significant proportion of cells showed such remote modulation (17/312, 5.4%; see Table 2). This was also true when considering brain areas individually, with no significant differences between areas in the propensity to be modulated by hippocampal IEDs (χ^2 test of association between brain areas preSMA, ACC, and OFC vs. proportion of modulated cells: $\chi^2(2)=1.09$, p=0.58). Together, this shows that the neurons which were most modulated by hippocampal IEDs were those recorded in the hippocampus, with no significant modulation of neurons in the other recorded brain areas.

In the medial temporal lobe, cells can be characterized into different functional categories based on their response to the visual stimulus shown during the recognition memory task (Table 3) (Faraut et al. 2018; Rutishauser et al. 2015). Here, as done previously, we characterized MTL cells based on their response pattern as either visually selective (VS; meaning their response differs as a function of the category of the visual image), memory selective (MS; response differs

according to whether the image is new or old) or neither. We then evaluated separately for each of the groups of cells what proportion was modulated by IEDs. While the proportions varied somewhat between the different cell types, there was no significant difference between the different functional cell types in their propensity of being modulated by IEDs (χ^2 test of association between brain cell types MS, VS and other: $\chi^2(2)=1.00$, $p=0.61$; see Table 3). This shows that IEDs tend to modulate differentially tuned cells indiscriminately.

Temporal pattern of modulation by IEDs

We next compared the pattern of modulation across all IED-modulated neurons. For this, we determined for each modulated neuron whether the modulation was positive or negative as indicated by the sign of the modulation index (MI), which compares the firing rate of neurons between a 50ms wide window before vs. after the onset of an IED (see methods). If the MI was negative it indicated an IED-modulated decrease in firing rate comparing before vs. after IED onset. In contrast, if the MI was positive this indicated an IED-modulated increase in firing rate relative to the firing rate immediately before IED onset. Across all brain areas, thirty-five modulated single units had a positive MI (mean=0.43, SD±0.17), while fifteen had a negative MI (mean= -0.18, SD±0.70). In the right MTL, the MI of all IED modulated single units was positive (mean= 0.40 +/- 0.03 SEM, Cohen's d score = 0.24 +/- 0.02 SEM). The left temporal lobe did not show this preferential distribution of MI; with eight units being positive (mean=0.42 +/- 0.05 SEM, Cohen's d score = 0.23 +/- 0.04 SEM) and seven being negative (mean= 0.54 +/- 0.09 SEM, Cohen's d score = -0.30 +/- 0.06 SEM). The negative or positive MI values can result from several different patterns, including changes only before or after but also more complex pattern such as inhibition of firing after relative to before IED onset. To further investigate these differences, we plotted a group peristimulus time histogram (PSTH) centered around the IED separately for units with positive and negative MI. This revealed that the n=18 positively modulated cells (none negative) in the right temporal lobe transiently increased their firing rate in the 50ms window following IED onset at t=0, with no modulation extending beyond ~100ms after IED onset (on average; see Fig.3A-B). In the left temporal lobe (Fig. 3C-F), on the other hand, there were two temporal patterns of modulation: while both groups exhibited (on average) an increase in firing rates due to IEDs, this increase either followed (Fig. 3C) or preceded (Fig. 3E) the IED onset by ~100ms. The neurons with negative MI, on the other hand, exhibited little

modulation on average, indicating that such modulation is either heterogenous or weak (Fig. 3E-F).

IEDs preferentially increase firing of putative inhibitory neurons in the right temporal lobe

We next asked whether different electrophysiological types of cells are differentially affected by IEDs. To achieve this, we characterized the neurons that were significantly modulated by IEDs based on the trough to the peak width of their extracellular waveform (i.e. the action potential). Neurons with narrow action potentials are thought to be GABAergic interneurons, while those with wider action potential (>0.5 ms) are thought to be excitatory neurons (Bartho et al. 2004; Mitchell et al. 2007; Rutishauser et al. 2015; Takahashi et al. 2015).

As expected (Fu et al. 2019; Rutishauser et al. 2015), pooling neurons across all the brain areas we studied, the distribution of neurons was bimodal with the cutoff between the two groups equal to 0.52 ms (Fig. 4A-B). The majority of cells had wide action potentials (71%, n=571), compared to narrow waveform neurons (21.5%, n=157) (Table 4). Fig. 4C shows the average waveform of the two groups. This is compatible with earlier work (Rutishauser et al. 2015), and indicates that the majority of neurons recorded are putatively excitatory pyramidal cells. We next tested separately for narrow-and wide waveform neurons whether their activity was modulated by IEDs. This revealed that neurons with narrow waveforms were significantly more likely to be modulated by IEDs compared to neurons with wide waveforms (19/157 vs. 31/571; 12.1% vs. 5.4%; significantly different, p=0.0034, χ^2 test). In addition, the modulated units with narrow waveforms, which are putative interneurons, were significantly more likely to increase rather than decrease their firing in response to the IEDs (14/19 increase vs. 5/19 decrease; p=0.0035, χ^2 test). This was also true for wide-waveform neurons (see Table 5). In conclusion, IEDs were more likely to modulate narrow-waveform neurons and this modulation was more likely to be an increase rather than decrease of firing rate (Fig. 4D).

We next repeated the above analysis for only MTL neurons (above, all neurons across all brain areas were pooled). Most MTL neurons had wide waveforms (81%, N= 339/418), of which only 6.5% (n=22) were modulated by IEDs. Of the narrow waveform neurons (19%, N=79/418), 13.9% (11/79) were modulated by IEDs (see Table 7), a proportion significantly larger than that for wide-waveform neurons (p=4.5e-4, χ^2 test). We did not find a significant difference in the proportion of narrow-waveform neurons between right and left temporal lobes (Table 6). The

neurons modulated by IEDs in the MTL contralateral to the seizure focus showed a slightly higher proportion of narrow-waveforms (81% N=9/11), compared to wide-waveform neurons (73%, N=16/22), and both types of cells were equally likely to increase their firing during IEDs. This result shows cell-type specificity of modulation by IEDs.

IEDs that appear within 2 seconds of image presentation predict disruption of retrieval of old memories

We next tested whether the occurrence of an IED had an effect on behavior by testing whether accuracy in the recognition memory task was affected by whether an IED occurred or not in a given trial. We were particularly interested in the temporal sensitivity of this effect and thus evaluated this effect separately for different points of time between IED onset and stimulus onset. For this, we used GLM models to assess whether the probability of correctly retrieving (or later remembering for encoding trials) was correlated with the presence of IEDs (see methods). We fit one model each to all old trials during recognition, all new trials during recognition, and all learning trials. We then compared these models with a null model that was equivalent except for the IED variable, which was removed. We quantified the significance of these model comparisons using both the log likelihood ratio and AIC.

We found that when IEDs occurred during a retrieval trial in which an old image was shown, the old images were more likely to be forgotten (i.e. subjects were more likely to say it was new, thus a false negative; Odds ratio= 0.63, p=0.004; Fig. 5A, left). A model comparison revealed that the model with access to IEDs was significantly more likely than a null model without access to this variable (Fig. 5B, left; log likelihood ratio =8.32, p=0.01; also confirmed using AIC= 747.98 < 752.57). Fitting the same model to new trials during recognition revealed that the probability of correctly identifying a new trial (i.e. a true negative) was not significantly correlated with the presence or absence of IEDs (Fig. 5A, middle, Odds ratio=1, p=0.96). This impression was confirmed by a model comparison with a null model without access to IEDs, which showed no significant difference (log likelihood ratio =0.003, p=0.96; AIC = 667.91>665.91).). Lastly, we tested whether the presence or absence of IEDs affected the probability that a memory was successfully formed during encoding. To evaluate this, we tested whether the probability that a new image shown during the learning phase would later be

correctly recognized as old was influenced by the presence or absence of an IED during encoding of that particular image. We found no significant relationship (Fig. 5A, right; Odds ratio = 1.1, p=0.64; model comparison shown in Fig. 5B, right, log likelihood ratio =0.25, p=0.62, AIC = 576.34 > 574.59). This thus indicates that the presence of IEDs did not disrupt the encoding process.

To provide further intuition into the result of these model comparisons we also visualized the difference in behavioral performance between trials with and without IEDs, separately for the three different trial types investigated above (Fig. 5C-E). Note, however, that this is for illustration only because this univariate interpretation does not account for factors such as repeated measures of multiple neurons in the same subject and between-subject variability in firing rates that the multivariate analysis performed above using GLMs takes into account. Nevertheless, these univariate analysis confirmed the impression given by the GLMs: performance differed significantly between trials with and without IEDs for recognition old (Fig. 5C, paired t-test, p=0.02) but not for recognition new (Fig. 5D, paired t-test, p=0.26) and learning trials (Fig. 5E, paired t-test, p=0.36).

We next tested whether the effect of the occurrence of IEDs during the retrieval of old images varied as a function of time. For this, we evaluated above model (on recognition old trials) separately for different points of time relative to stimulus onset, counting only IEDs that occurred within a window of ±1.5s around the center of the bin (3 s time window; plotted point is center of window in Fig. 5F). This revealed that the effect of the IED on correct retrieval of an old image was strongest if the IED occurred approximately at stimulus onset (Fig. 5F). IEDs that appeared up to 2s before stimulus onset also significantly impaired retrieval. In contrast, as expected, IEDs that occur more than 1.5 second after stimulus onset did not influence retrieval (Fig. 5F). Together, this correlation between behavior and IED timing shows high temporal specificity of IEDs, with the strongest effect observed if an IED occurred simultaneously with stimulus onset.

Modulation of neuronal activity by IEDs predicts reduced confidence

The above results reveal a relationship between the occurrence of IEDs and behavior as well as modulation of the activity of individual neurons. However, it remains unclear whether the two phenomena are related. Examining individual neurons that were significantly modulated by IEDs

453 on average revealed substantial IED-by-IED variability in this modulation (Fig. 6A-B). We thus
454 hypothesized that the variable degree of modulation of neurons by a given IED would provide a
455 tool to examine correlations of IED-modulated neuronal modulation with behavior. Here, we
456 used the subjective confidence reported by the subject (the declarative aspect of this recognition
457 memory task) as a sensitive behavioral readout of the retrieval process. We used a GLM to
458 assess the extent to which the subjective confidence provided by a patient for a given recognition
459 trial (regardless of whether it was new or old) was related to the degree by which neurons
460 changed their activity around the onset of IEDs. This population-level model consisted of the
461 pooled activity of all IED-modulated neurons in the MTL and all trials in which at least one IED
462 occurred (see methods). We first compared the full GLM model with access to both the firing
463 rate of neurons around an IED and the number of IEDs that occurred (see methods) with one that
464 only had access to the number of IEDs. This revealed that the full model with access to neuronal
465 activity explained significantly more variance in the confidence judgments provided by the
466 subjects (Fig. 6C, left; $p=0.005$; note the effect size of approximately an 8-fold increase). In
467 contrast, comparing a model that has only access to the number of IEDs with one that has no
468 such access was not able to explain significantly more variance than the null model (Fig. 6C,
469 middle; $p=0.07$). Also, comparing the full model with one where only the number of IED term
470 was dropped (providing the model with only access to neuronal firing rates) also did not reveal a
471 significant drop in ability to explain variance in confidence judgments (Fig. 6C, right; $p=0.08$).
472 Together, these model comparisons indicate that firing rate around IEDs was the best predictor.
473 We next examined the full model more closely. The weight of the firing rate parameter was
474 significantly different from zero and negative (-0.046, $p=0.0053$, confidence interval -0.078...-
475 0.014). Since the coding for confidence was such that a higher value equals higher confidence,
476 this indicates that higher firing rates of neurons around IEDs lower recognition confidence. We
477 confirmed this impression by performing a univariate analysis for visualization only (Fig 6E-F,
478 see legend for statistics).
479 Lastly, we tested if the effect on confidence of recognition by the modulation of IEDs
480 varied as a function of time. For this we evaluated the same full GLM model as discussed above,
481 but at different time points relative to IED onset (binsize 100ms, stepsize 5ms). This revealed
482 that the effect of modulation of a single-neuron activity on confidence of recognition was
483 strongest for spikes occurring in a window from -130 to 30ms prior to the onset of IEDs (Fig.

6D). This shows that the effect of IED-modulated firing rate changes on memory retrieval (as assessed by confidence) has high temporal specificity, with respect to onset of the IED, with the strongest effect observed prior to onset on intracranial EEG.

Discussion

We found that hippocampal IEDs are associated with a decrease in the likelihood of correctly retrieving an existing memory. In contrast, we found no effect on the encoding of new memories, a finding that is different from a previous studies that suggested that IEDs impair encoding of new memories (Kleen et al. 2013). Note, however, that we used a hippocampal-dependent recognition memory task whereas this previous work used a working memory task (Kleen et al. 2013). It is thus possible that selective impairment of retrieval is specific to long-term memory. We also provide the first single unit analysis of firing modulation by IEDs during a recognition memory task, which shows that neurons are modulated during active performance of a task. Note that, in contrast, previous work has evaluated modulation of IEDs during rest (Alvarado-Rojas et al. 2013; Creutzfeldt 1993; Keller et al. 2010). IEDs can differ markedly between rest and active task performance (J. Y. Matsumoto et al. 2013), making it important to study IED-related modulation during performance of a task. We also found that modulation of single-neuron activity by IEDs was more pronounced in the right MTL. Additionally, a greater proportion of right medial temporal neurons modulated by IEDs were contralateral to a left hemispheric seizure onset zone. It is possible that these areas were healthier hence more likely to respond to IEDs.

The occurrence of IEDs has been shown to predict decreases in performance during encoding and retrieval in a free-recall task (Ung et al. 2017). Similarly, a second study found that increased rates of IEDs in neocortical and left hemispheric areas were correlated with impaired encoding and recall to a greater extent (Horak et al. 2017) compared to right hemispheric IEDs. We found that hippocampal IEDs impacted recognition but not encoding. Note that the odds ratio we observed was similar to that obtained in the previous study (Horak et al. 2017). Note also that, in our experiment, we were able to differentiate between effects related to the presentation of novel (“new”) images, the effects of task demands (learning vs. retrieval), and effects related to specific images themselves. This is because we repeated the same images that

were new during learning during retrieval, intermixed again with new images. We found the behavioral effects of IEDs were specific to old images during recognition, but not the recognition of new images during recognition, nor their encoding during learning.

In humans, single-neuron studies have revealed that a subset of ~30% of neurons modulate their firing transiently prior or during an IED (Alarcon et al. 2012; Alvarado-Rojas et al. 2013). The modulation of single unit firing at the start of the IED is thought to be due to paroxysmal depolarization shift (PDS). The initial depolarization phase of an IED is thought to represent glutamate receptor-, mainly AMPA and NMDA- mediated calcium conductance (Traub and Wong 1982; Trevelyan et al. 2006). The increase in neuronal firing around the IED is followed by decrease in firing in the post-IED period (Alvarado-Rojas et al. 2013; Keller et al. 2010; Wyler et al. 1982). The ensuing hyperpolarization phase is thought to represent GABA-mediated inhibition (Cohen et al. 2002), and is also accompanied by decreased rate of neuronal firing (Altafullah et al. 1986; Alvarado-Rojas et al. 2013; Ulbert et al. 2004). This period of suppression is longer and has been shown to be accompanied by large current sources in middle cortical layers (Trevelyan et al. 2007). The modulation of single unit firing in our study showed significant changes in firing compared to the baseline firing rate in the 50 ms prior to the onset of the IED. Our MI is a more sensitive measure of IED induced changes in firings rates than simply comparing changes in single-unit firing probability (Alvarado-Rojas et al. 2013), since it incorporates information about baseline firing rates immediately prior to IED onset.

The proportion of neurons modulated in our study were smaller than in previous studies. In contrast to the 20% we found to be modulated in the right medial temporal lobe (hippocampus and amygdala), earlier studies found that during sleep 30% of hippocampal neurons (Alvarado-Rojas et al. 2013) and during quiet wakefulness 48% of all neurons (Keller et al. 2010) are modulated by IEDs. The IED rates in our and these previous studies are similar (0.0863 /second versus 0.057/second (Keller et al. 2010). However, note that in general cognitive load is believed to lower IED rates (Aarts et al. 1984; J. Y. Matsumoto et al. 2013), leaving open the possibility that at rest the IED rates in our patient would have been higher. The lower modulation rates in our vs. previous studies supports the hypothesis that performance of a recognition-memory task lowers the effect of IED on single-neuron activity. If so this would indicate that engagement of

neurons by IEDs can be changed flexibly based on task demands, a feature that could possibly be used for new strategies to reduce the impact of IEDs.

We found that the occurrence of IEDs during retrieval, but not encoding, was predictive of impaired performance. This disruption was temporally specific. This is compatible with earlier work, which showed that hippocampal IEDs that occurred during retrieval, but not during the maintenance phase of a Sternberg working memory task, predicted a decrease in response accuracy (Kleen et al. 2013). Prior work in children with a short-term memory test, presented as an engaging television game, found that right-sided discharges caused impairment of the spatial version of the task, while left-sided with impairments on the verbal version (Binnie et al. 1987). These effects were also temporally specific. Thus, the timing of IEDs relative to ongoing task effects is critical to their behavioral impact, arguing for a highly specific and transient mechanism rather than more general and long-lasting impairment.

Linking the neuronal and behavioral effects of IEDs, we found that the degree to which single-neuron activity in the MTL was modified by IEDs was predictive of decreases in retrieval confidence. The timing of this was specific, with the most predictive power being the activity of neurons during the period of -130-30ms before the onset of the marked onset time of the IED. An IED is thought to represents the extracellular correlate of the synchronous and excessive discharge of a group of neurons, and is believed to be preceded by a paroxysmal depolarizing shift (PDS) (de Curtis et al. 1999; de Curtis and Avanzini 2001; Dichter and Spencer 1969; H. Matsumoto and Ajmonemarsan 1964; Wong and Traub 1983). Thus it would be expected that changes in the activity of individual neurons would be observed before the onset of the IED itself and that these changes would be most reflective of synchronous synaptic input. Our finding that activity changes shortly before IED onset are most predictive of changes in retrieval confidence is compatible with this interpretation. Together, this result reveals a first direct link between the degree by which an individual IED modulates the activity of neurons in the MTL and a behaviorally measured impairment in declarative memory, here assessed by confidence.

To put our findings in perspective, consider that there are approximately 48 and 12 million neurons in each hippocampus and amydala, respectively (Simic et al. 1997)(Schumann and

Amaral 2005). Our finding that on average 8% of neurons were significantly modulated thus implies that ~9 million neurons per hemisphere changed their firing rate due to an IED. This large-scale modulation likely explains our ability to correlate the modulation strength of individual neurons around an IED with behavior.

Our results call to attention the phenomenon of transient cognitive impairment (TCI), which is believed to be related to IEDs (Aarts et al. 1984; Binnie 2003). The main feature of TCI is the time-locked nature of the IED with the disruption. To our knowledge ours is the first study to investigate a putative mechanism for TCI. The increased firing of a greater proportion of inhibitory interneurons compared to the excitatory neurons, especially in the right medial temporal lobe could signify a possible mechanistic link to the behavior we see when retrieving old images and the disruption of confidence of recognition (i.e. retrieving an existing memory). Mechanistically, a transient and disproportionate increased in inhibitory interneuron firing could block local network and intra-areal transmission of information within the medial temporal lobe, therefore impacting recall of learned information.

In conclusion, this study provides critical new insights into the mechanisms by which IEDs impair human cognition. The task used here is a recognition memory task with the explicit declarative component of confidence ratings, which are a highly sensitive behavioral measure of memory strength (Rutishauser et al. 2006b; Squire et al. 2007). In this task, hippocampal IEDs preferentially and transiently impaired retrieval of familiar images, preferentially modulated the activity of putative inhibitory neurons in the MTL, and the engagement of neurons shortly before IED onset predicted reductions of retrieval confidence. More broadly, this study demonstrates that examining the effects of IEDs at the single-neuron level provides a way to start understanding why and how specifically IEDs impair human cognition.

Author contributions

C.R., C.M., N.C., and U.R., analyzed data
C.R., A.M., and U.R., wrote the paper
J.C. patient care

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711

712

Tables

Table 1. List of the 12 subjects analyzed. Each subject contributed one session except P54, which contributed 3 sessions.

Patient ID	Type of IEDs during NO	Seizure onset zone
P32	Generalized Spike and wave	Undetermined
P34	Left hippocampal	Bitemporal
P35	Left hippocampal	Left temporo-neocortical
P36	Right hippocampal	Right medial temporal
P38	Bitemporal	Right medial temporal
P39	Bitemporal	Right insular
P47	Bitemporal	Left medial temporal
P48	Bitemporal	Left neocortical
P49	Bitemporal	Left amygdala
P54 (x3)	Bitemporal and generalized spike and wave	Right medial temporal
P55	Right hippocampal	Right medial temporal
P56	Left hippocampal	Bitemporal

Table 2 Number and percentage of modulated single units for all the sessions during the new-Old task

Brain Area	Number of modulated cells/Total cells	Percentage of modulated cells (%)
Left anterior cingulate	2/20	10
Left pre-supplementary motor area (SMA)	6/107	5.6
Left amygdala	7/138	5
Left hippocampus	8/105	7.6
Left orbitofrontal	1/19	5
Right anterior cingulate	2/50	4
Right pre-supplementary motor area (SMA)	3/85	3.52
Right amygdala	6/115	5.21
Right hippocampus	12/58*	20
Right orbitofrontal	3/31	9.6
Medial bitemporal	33/418*	8.0

Significance (**=significant $p<0.05$) marks result of Binomial test vs. chance of proportion of identified neurons, SOZ= seizure onset zone.

Table 3 Number of modulated single units based on the characteristic type

	Number of modulated cells/Total cells			
Brain Area	**MS**	**VS**	**VR**	**NS**

Left amygdala	0/11	1/24	2/38	4/65
Left hippocampus	1/8	1/23	3/32	3/42
Right amygdala	1/7	1/23	0/27	4/58
Right hippocampus	1/3	1/6	3/22	7/27
Medial temporal left + right (%)	10	5	6	9

Table 4. Number of IED-modulated narrow and wide-waveform cells across all brain areas.

Type	IED modulated	IED non-modulated	Total
Narrow waveforms	19	138	157
Wide waveforms	31	540	571

Table 5. Number of modulated single-units in the entire brain based on their firing pattern.

Type of modulation	**Narrow waveforms**	**Wide waveforms**	**Total**
Increased firing of units	14*	21*	35
Decreased firing of units	5*	10*	15
Total	19	31	50

Significance (*=significant $p<0.05$) marks result of Binomial test vs. chance of proportion of identified neurons.

Table 6. Number of modulated single-units in the right and left medial temporal lobe (hippocampus and amygdala) based on their firing pattern.

Area	**Narrow waveforms (Modulated by IED/Total)**	**Wide waveforms (Modulated by IED/Total)**	**Total**
Right temporal	6/40*	12/138*	178
Left temporal	5/39*	10/201	240

Significance (*=significant $p<0.05$) marks result of Binomial test vs. chance of proportion of identified neurons.

Table 7. Number of modulated single-units in the right and left medial temporal lobe (hippocampus and amygdala) based on their firing pattern.

Type of modulation	**Narrow waveforms**	**Wide waveforms**
Increased firing of units	7*	19*
Decreased firing of units	4	3

Total	11	22

Significance (*=significant p<0.05) marks result of Binomial test vs. chance of proportion of identified neurons.

Figure legends

Figure 1: Electrode placement and the recognition memory task. (A) Electrode locations across all patients, projected onto an axial (z=-16) and (B) sagittal (x=22.1) view. All electrode locations for which at least one usable electrode was recorded are shown (yellow=hippocampus, pink=amygdala). (C) The task is composed of a learning phase during which 100 new images are shown to the subjects. During the recognition test phase, they are shown both new and old images and have to report whether they have seen each image before by reporting a new/old decision together with a confidence level on a 1-6 scale.

Figure 2: Relationship between IEDs in the intracranial EEG and single-neuron activity. (A) Example IED. Shown is the raw iEEG recording from a right hippocampal macroelectrode (top) and microelectrode (bottom) of p48. (*=peak of the IED) (B) The waveform of the action potential of a modulated unit recorded from the same microwire as shown in (A). (C) Raster plot of the unit shown in (B), aligned to the IED onset at t=0. Each row is a different IED. Red lines indicate the ±500ms around the IED. (D) Heatmap of the average firing rate of the neuron shown in (B-C) in a window ±500ms around the IED. Each datapoint is the mean firing rate in a 25ms bin. Scale of the normalized response shown on right, with the color indicating the change in firing rate from baseline (e.g. a value of 3 indicates the firing rate is 3 time higher than baseline). (E) PSTH of the data shown in (C) in a window ±500ms around the IED. Each datapoint is the mean firing rate in 50ms bin. Error bars indicate SEM of the mean firing rate. Note different time scale in panels C and D+E. (F) The mean firing rate for the unit shown in (B-E) shows an ~100% increase in firing of the unit during the IED relative to baseline. Error bar indicates SEM of the mean firing rate.

Figure 3: Time-course of modulation of single-neuron activity by IEDs. Peristimulus time histogram (PSTH) of the modulation of the firing averaged across modulated neurons, split according to right (A, B), and left temporal region (C-F). (A) PSTH of all modulated neurons in

765 the right medial temporal lobe. All had positive MIs. (B) Heatmap showing firing rate
766 modulation of all neurons averaged in (A). (C) PSTH of all left medial temporal lobe single
767 neurons with positive MIs. (E) PSTH of all left MTL single neurons with negative MIs. (D,F)
768 Heatmap of firing rate modulation of all left medial temporal lobe neurons with increased (D)
769 and decreased (F) firing in response to an IED. (B,D,F) Each row is a neuron. Scale of the
770 normalized response is shown on right. The color indicates the proportional change relative to
771 baseline (e.g. a value of 3 indicates the firing rate is 3 time higher than baseline). Neurons are
772 sorted in descending order by the strength of their firing rate modulation. Horizontal line (A, C,
773 E) separates the hippocampus (top) from amygdala (bottom). Red dashed line (A, C and E)
774 indicates ± standard error across neurons. Bin size of PSTH = 50 ms, binsize for heatmap=25 ms.
775 Note time scale is different for heatmaps and PSTH.

776 **Figure 4: Cell-type specific modulation by IEDs.** (A) Histogram of the distribution of spike
777 widths of all single units analyzed. The two peaks indicate the presence of two distinct
778 populations of neurons with the cut-off around 0.5 ms. (B) Distribution of spike widths of all the
779 single units after splitting them into two groups: wide waveform cells (mean spike width of 0.81
780 +/- 0.17) and narrow waveform cells (mean spike width of 0.31 +/- 0.044 ms). (C) Average
781 waveforms of the two groups shown in (B). (D) Group average PSTH of all modulated wide (left
782 panel) and narrow width (right panel) single units across all the brain areas shows that neurons
783 modulated with narrow waveforms on average increase their firing rate during IEDs, whereas the
784 modulation of wide waveform neurons is more heterogenous, resulting in little on-average
785 modulation. Red dashed line indicates standard error across neurons.

786 **Figure 5: Behavioral effects of IEDs during different task phases.** (A) Results of different
787 GLM models to assess the impact of IEDs on behavior during different types of trials. During the
788 recognition phase of the task, the presence of IEDs during a given trial significantly reduced the
789 likelihood that an image will be remembered correctly. In contrast, there was no significant
790 change in the likelihood of a new image being recognized as such during recognition nor in the
791 likelihood that a new image during learning (right) was later remembered correctly. Each bar
792 shown represents an independent GLM model fit to the indicated subset of trials. Error bars
793 indicate confidence intervals (odds-ratio 0.63, ***p=0.004). (B) Model comparison vs. a null
794 model without access to when IEDs occurred. Compared to the null model, the model that takes

into account when IEDs occurred was significantly more likely given the behavioral data (**p=0.01) for recognition old trials. No multiple comparison was performed as each bar is the result of a different model on an independent subset of trials. (C-D) Difference in behavioral performance for each subject between trials with none vs. at least one IED. This revealed a significant difference in the proportion of correctly remembered old images (C, shift to the right-C, paired t-test, p=0.02), with no difference in the proportion of correctly identified new trials (D). (E) Same as (C,D), but for learning trials. Shown is the difference in the proportion of later correctly remembered learning trials between trials in which there was no vs. at least 1 IED. There was no significant difference (* p<0.05, NS= not significant). (F) Time course (blue line) of the odds ratio for the variable shown in (A) of the model, for recognition old trials. Stimulus onset is at t=1s (red line). The largest effect of IEDs was around stimulus onset. Bin size =3000ms (plotted points are the center of this bin). Black line is the null model. Standard Error is the dashed line in F. In F, * p<0.01, after correcting for multiple comparisons with FDR across all time-points shown. Null distribution was established using a bootstrap, scrambling the order of trials within each subject, repeated 10000 times for each time-point.

Figure 6: Extent of modulation of the activity of individual neurons by IEDs predicts reduction in behaviorally declared memory retrieval strength (confidence). (A-B) Raster plots of two example neurons that are modulated by IEDs. Each row is a different IED (t=0 is onset of the IED). Rasters are rank ordered by the number of spikes fired in a window -100…0ms relative to IED onset. Note the substantial trial-by-trial variability in modulation. (A) Same unit as show in Fig. 2A-C (B) Example unit from p49. (C) Model comparisons between different models that predict the confidence (high or low) of a recognition trial as a function of the firing rate of recorded neurons and the number of IEDs observed in a given trial. The model with access to both neuronal activity around IEDs (time window -130 to -30ms relative to IED onset) and the number of IEDs performs significantly better than a model with only access to the number of IEDs (left; p=0.005, middle; p=0.07, right; p=0.08). (D) Time course of the model comparison shown on the left in (C), quantified by the log likelihood ratio between the full model and the model with only access to the number of IEDs (binsize=100ms, stepsize=5ms, plotted datapoint is center of the bin). The firing rate of neurons was most informative about whether a trial would be rated as high or low confidence ~100ms before IED onset (t=0). *p<0.05 (uncorrected). (E) Neuron-by-Neuron comparison of mean firing rate at the time of IED

occurrence, shown separately for low and high confidence trials. This shows that the greater the increase in firing rate, the lower the confidence (left vs. right, Ks-test, p= 0.03). Each line is a neuron. (F) Summary of (E). Histogram of difference in the firing rate of neurons around IEDs between low and high confidence trials for all the neurons in the MTL modulated by IEDs. This shows that the difference was shifted to the right for low confidence trials.

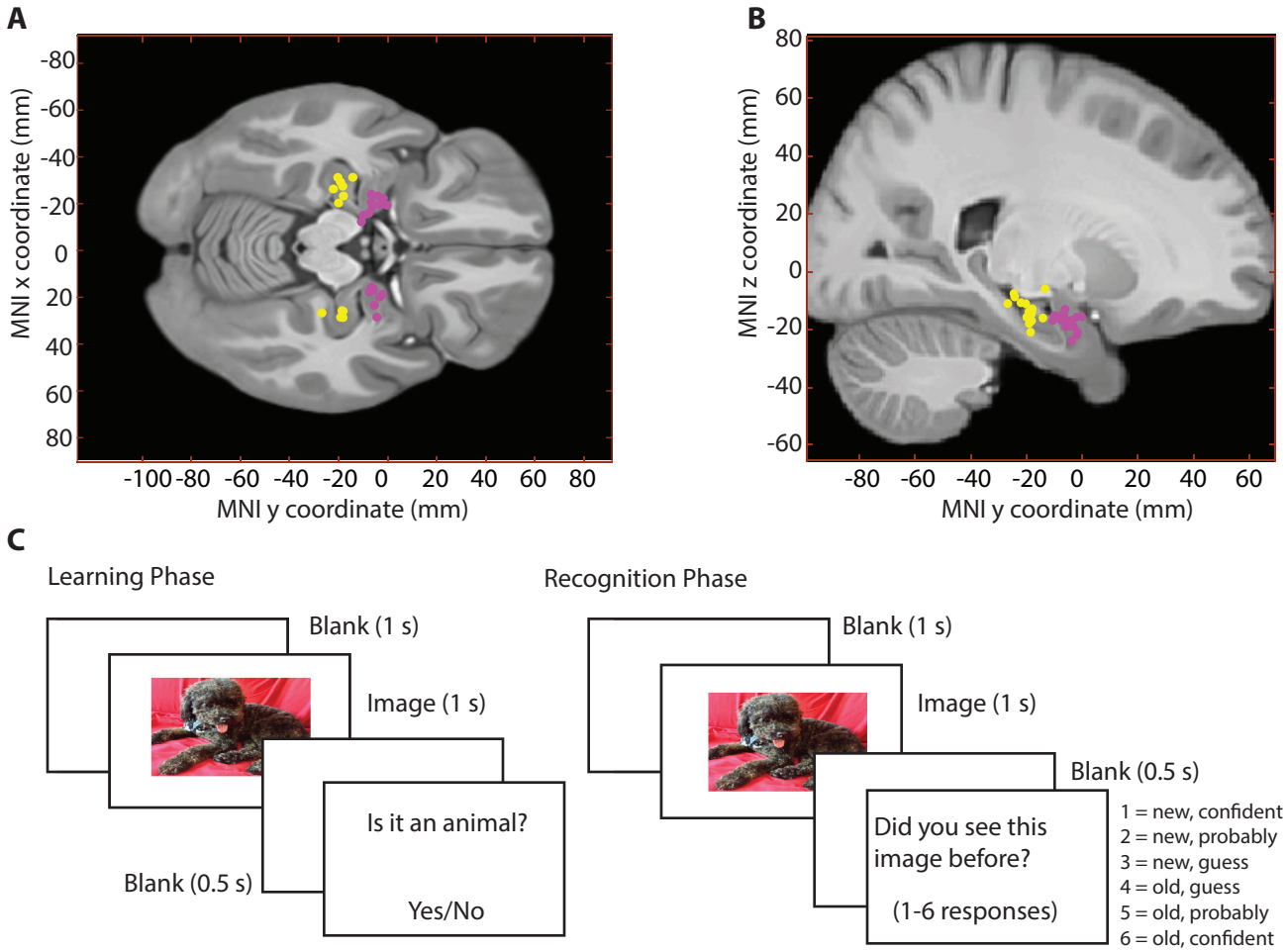

Figure 1